Türkiye Klinikleri

ADOPTING ORPHAN DISEASES
RARE INTERSTITIAL LUNG DISEASES

ÖKSÜZ HASTALIKLARI SAHİPLENMEK: NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARI



Editors/Editörler
Prof. Dr. Göksel Altınışık Ergur
Prof. Dr. Francis X. McCormack

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CONTENTS / İÇİNDEKİLER

Praface / Ön Söz v-vi
Prof. Dr. Göksel ALTINIŞIK ERGUR
Prof. Dr. Francis X. MCCORMACK

Authors and Contributors / Yazarlar ve Katkıda Bulunanlar vii-viii

01 | **An Overview of Rare Interstitial Lung Diseases** **1**
Nadir İnterstisyel Akciğer Hastalıklarına Genel Bir Bakış
Göksel ALTINIŞIK, Francis X. MCCORMACK

02 | **Differential Diagnosis in Rare Interstitial Lung Diseases Through Radiological Hints** **9**
Nadir İnterstisyel Akciğer Hastalıklarında Radyolojik İpuçlarıyla Ayırıcı Tanı
Furkan UFUK

03 | **Pulmonary Alveolar Proteinosis** **25**
Pulmoner Alveoler Proteinozis
Nazlı ÇETİN

04 | **Pulmonary Alveolar Microlitiasis** **45**
Pulmoner Alveoler Mikrolitiazis
Nilüfer YİĞİT

05 | **Acute Silicosis/Silicoproteinosis** **61**
Akut Silikoz/Silikoproteinoz
Metin AKGÜN

06 | Birt-Hogg-Dubé Syndrome **75**
Birt-Hogg-Dubé Sendromu
Orkun Eray TERZİ, Elif Yelda ÖZGÜN NİKSARLIOĞLU

07 | Lymphangioleiomyomatosis **91**
Lenfanjiyoleyomiyomatozis
Lauren A. HIPP, Nishant GUPTA

08 | Pulmonary Langerhans Cell Histiocytosis **107**
Pulmoner Langerhans Hücre Histiyositozu
Nilüfer YİĞİT, Erhan UĞURLU

09 | Hermansky-Pudlak Syndrome **123**
Hermansky-Pudlak Sendromu
Merve ERÇELİK

10 | Familial Interstitial Pneumonias (SP-C/Telomere Shortening/ABCA3) **135**
Ailevi İnterstisyel Pnömoniler (SP-C/Telomer Kisalmasi/ABCA3)
Demet POLAT YULUĞ, Eylem SERCAN ÖZGÜR

11 | Pulmonary Amyloidosis **147**
Pulmoner Amiloidoz
Yonca SEKİBAĞ, Şermin BÖREKÇİ

12 | Pleuroparenchymal Fibroelastosis **159**
Plöroparenkimal Fibroelastoz
Özlem ÖZDEMİR KUMBASAR

13 | Thoracic Involvement in IgG4-Related Diseases **171**
IgG4 ile İlişkili Hastalıklarda Toraks Tutulumu
Merve Sinem OĞUZ, Züleyha BİNGÖL

14 | Rare Interstitial Lung Diseases in Medical and Postgraduate Education **187**
Tip Eğitimi ve Mezuniyet Sonrası Eğitimde Nadir İnterstisyel Akciğer Hastalıkları
Ilgım VARDALOĞLU, Göksel ALTINIŞIK

15 | Patient Perspective in Rare Interstitial Lung Diseases **197**
Nadir İnterstisyel Akciğer Hastalıklarında Hastanın Bakış Açısı
Aycan YÜKSEL

16 | The LAM Story: **209**
From Grass Roots Patient Advocacy to an Effective Treatment
LAM Hikayesi:
Hasta Savunuculuğundan Etkin Tedaviye
Sue BYRNES, Francis X. MCCORMACK

17 | End-of-Life Care in Rare Interstitial Lung Diseases **219**
Nadir İnterstisiyel Akciğer Hastalıklarında Yaşam Sonu Bakımı
Burcu ÖZALP, Meltem UYAR

18 | Telemedicine Opportunities for Rare Interstitial Lung Diseases **233**
Nadir İnterstisyel Akciğer Hastalıkları için Tele-Tıbbın Sağladığı Fırsatlar
Nazlı ÇETİN, Gülfem ÖZDUYGU

19 | Lung Transplantation in Rare Interstitial Lung Diseases **245**
Nadir İnterstisyel Akciğer Hastalıklarında Akciğer Nakli
Ayşe Nigar İZGİ, Sevinç ÇITAK

20 | Pulmoner Rehabilitation in Rare Interstitial Lung Diseases **257**
Nadir İnterstisiyel Akciğer Hastalıklarında Pulmoner Rehabilitasyon
Ayşenur YILMAZ

21 | Future Perspective on Rare Interstitial Lung Diseases **269**
Nadir İnterstisiyel Akciğer Hastalıklarına Gelecek Perspektifi
Maria MOLINA MOLINA



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Adopting Orphan Diseases: Rare Interstitial Lung Diseases was conceived and brought to life to meet a pressing need in the field of respiratory medicine. These conditions, encountered only rarely—and in some cases, exceedingly rarely—remain insufficiently understood in their biopsychosocial dimensions. Opportunities for research are often constrained by the limited number of patients or by the lack of interest from industry. Against this background, we aimed to bring together up-to-date theoretical knowledge with the realities of medical practice.

Within this practice, we sought to address a broad spectrum—from the role of these diseases in undergraduate and postgraduate education to the patient perspective, from advocacy efforts to visions for the future. It has been a particular source of joy for us to see this book, with international reach and contributions from some of the foremost experts in the field, completed in a spirit of collective wisdom and in what could be considered a record time. The invaluable contributions of each author have allowed us to create a resource designed to support physicians eager to deepen their understanding of these diseases and to better serve their patients. We wished to provide a reference to which a physician faced with a rare interstitial lung disease might turn, enabling them to navigate the process in the most appropriate way.

Another distinctive feature of this book is its attention to the social dimensions of rare interstitial lung diseases. One chapter, enriched by the history of the LAM Foundation and LAMposium, shares a real story that brings forward both the patient and caregiver perspective—an inspiring example of patient advocacy. We sincerely hope this will encourage similar efforts and serve as a source of inspiration for the active participation of patients and their families in these journeys.

We owe our gratitude to all our contributing authors, to the publication team, and to the dedicated scientists who, long before us, devoted themselves to adopting orphan diseases and laid the groundwork for this book. However rare a disease may be, for the patient who receives the diagnosis and for their loved ones, and for the physicians striving to provide the best possible care, we hope this book will offer both knowledge and breath.

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ÖN SÖZ



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Öksüz Hastalıkları Sahiplenmek: Nadir İnterstisyel Akciğer Hastalıkları başlıklı bu kitap, göğüs hastalıkları alanında önemli bir gereksinimi karşılamak amacıyla kurgulandı ve gerçekleştirildi. Az, hatta bazıları çok az rastlanmaları nedeniyle haklarındaki bilginin (biyopsikososyal açılardan) kısıtlı olduğu, araştırma olanağının hasta sayısı ya da endüstrinin ilgisindeki azlık nedeniyle yeterli olamadığı bu hastalıklarda güncel teorik bilgiyi hekimlik pratiği ile birleştirmeyi hedefledik. Bu pratiğin içinde, mezuniyet öncesi ve sonrası eğitimdeki konumlarından hasta perspektifine, hasta savunuculuğundan gelecek perspektifine geniş bir yelpazeyi ele aldık.

Uluslararası erişimi olan bir kitabı, alanının önde gelen uluslararası isimlerinin de yazarlarımız arasında yer aldığı bir ekiple, ortak akıl ve rekor denebilecek sürede tamamlamış olmak ayrı bir mutluluk kaynağı. Her bir yazarın değerli katkıları, hastalıkları derinlemesine öğrenmek ve hastalarına yardımcı olmak isteyen hekimlere destek kitabı oluşturmamıza olanak sağladı. Nadir bir interstisyel akciğer hastalığı ile karşılaşan bir hekimin, başvuracağı ve bu sayede süreci en uygun şekilde yürütebileceği bir kaynak olmasını istedik. Ayrıca konunun sosyal yönlerini, üstelik hasta savunuculuğunun özgün bir örneği olan LAM Vakfı ve LAM sempozyumu tarihçesiyle hasta ve hasta yakını perspektifini gerçek bir öyküden aktaran bir bölümün yer alması, bu kitabın fark yaratan yönünü oluşturmaktadır. Bunun, benzer örnekleri çoğaltmasını, hasta ve hasta yakınlarının süreçlere katılması için ilham kaynağı olmasını yürekten umuyoruz.

Kitabımızın okurlarına ulaşmasında emeği geçen yazarlarımıza, yayın ekibine, yazında yer alan değerli bilgileri elde etmek için bizden önce de öksüz hastalıkları sahiplenen ve bu kitabın oluşmasını mümkün kılan bilim insanlarına teşekkürü bir borç biliriz. Ne denli nadir olursa olsun o tanıyı alan hasta ve onun yakınları için, tanı ya da tedavi sürecinde karşılaşarak hastasına en iyi sağlık bakımını sunmak isteyen hekimler için kitabımızın hem bilgi sunması hem nefes olması dileğimizle.

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CHAPTER 01

AN OVERVIEW OF RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARINA GENEL BİR BAKIŞ

Prof. Dr. Göksel Altınışık
Prof. Dr. Francis X. McCormack

AN OVERVIEW OF RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARINA GENEL BİR BAKIŞ

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ABSTRACT

While ILDs represent a heterogeneous group of over 200 disorders, rare forms are often grouped under the ambiguous "others" category in classification systems, making them difficult to identify. In today's era of personalized medicine, it is increasingly important to reflect individualized approaches within disease classifications as well. This book aims to provide a comprehensive approach to rare interstitial lung diseases (rare ILDs), exploring their diagnosis, treatment options, integration into medical education, and the patient perspective.

By focusing on the concepts of rare and "orphan" diseases, conditions that have low prevalence and often suffer from a lack of clinical or research interest, this book seeks to systematically increase awareness and recognition. Delays and difficulties in diagnosis are common in rare ILDs, often due to insufficient knowledge. Thus, integrating these diseases into undergraduate medical education and strengthening their presence in postgraduate training is essential, the methods should be enriched.

Given the key role of imaging in diagnosis, an early chapter of the book is devoted to radiological clues specific to rare ILDs, offering a foundational perspective before exploring individual disease groups. The book categorizes rare ILDs into four major groups: alveolar filling disorders, cystic lung diseases, familial ILDs, and other uncommon conditions. Each chapter begins with a case vignette to highlight the clinical relevance of the topic, followed by theoretical content and concludes with a case analysis and a few reflective questions to reinforce understanding.

Beyond its scientific content, the book also emphasizes other important dimensions: the patient experience, educational gaps and recommendations, end-of-life management, telemedicine opportunities, and an example of social and scientific collaboration (LAM Foundation). Pulmonary rehabilitation, a modality often overlooked yet potentially impactful, and lung transplantation are also discussed, highlighting the need to both improve current practice and shape future directions.

Ultimately, this book is designed as the seed of a snowball, small but powerful, aiming not only to address rare ILDs from a scientific standpoint but also to embrace patients, caregivers, and physicians as part of a shared human context, fostering a sense of 'adopting' these orphan conditions.

Keywords: *Interstitial lung diseases; Rare interstitial lung diseases; Orphan diseases; Computerized tomography; Patient perspective; Education; Lung transplantation; End of life management; Future perspective*

ÖZET

Bu kitap, nadir interstisyel akciğer hastalıkları (nadir İAH) özelinde tanı, tedavi seçenekleri, eğitimdeki yerleri, hasta perspektifi gibi farklı başlıklar altında konuya bütüncül bir yaklaşım sınmayı amaçlamaktadır.

İnterstisyel Akciğer Hastalıkları, genellikle 200'den fazla hastalığı kapsayan heterojen bir grup olarak tanımlanırken, sınıflama sistemlerinde nadir formlar genellikle "diğer" başlığı altında yer almakta ve bu durum söz konusu hastalıkların tanınmasını zorlaştırmaktadır. Günümüzün kişiselleştirilmiş tıp bakışını, hastalık sınıflamalarına da yansıtmak önemli bir gereksinim olarak karşımıza çıkmaktadır.

Nadir ve "öksüz" hastalıklar kavramları üzerinden, düşük prevalanslı ama aynı zamanda çoğunlukla klinik ve araştırma ilgisinden yoksun ya da az sayıda hasta olması nedeniyle bu açıdan kısıtlılıklara sahip hastalıkları sistematik biçimde ele alarak bilinirliklerini artırmak önem taşımaktadır.

Nadir İAH tanılarında çeşitli nedenlerle hem gecikmeler hem de zorluklar genellikle yaşanmaktadır. Bir tanıdan kuşkulanmak için hakkında bilgi sahibi olma gerekliliğinden hareketle, nadir İAH'larının mezuniyet öncesi tıp eğitimi müfredatında yer bulması, özellikle de uzmanlık eğitimi düzeyinde daha fazla ve kapsamlı biçimde yer almaları gereklidir.

Bu hastalıkların tanısında görüntüleme bulgularını kilit rol oynaması nedeniyle, tek tek tartışılmalarından önce nadir İAH bağlamında radyolojik ipuçları üzerine bir bölümün, henüz kitabın başında aydınlatıcı bir temel oluşturması amaçlanmıştır. Ardından, nadir İAH'ları dört temel grupta incelenmektedir: alveoler dolum hastalıkları, kistik hastalıklar, ailesel İAH'ları ve diğer nadir durumlar. Her bölümün bir olgu sunumu ile başlaması, ardından gelecek teorik bilgisinin kullanım alanlarını vurgulamayı amaçlarken, pratik-teorik bilgi bütünleşmesini, bölüm sonundaki olgu analizi ve akılda kalıcılığı artıracak birkaç soru sağlayacaktır.

Bilimsel içeriğinin zengin olması yanında, bu kitabın başka bazı yönleriyle de öne çıkması amaçlanmıştır. Hasta perspektifi, eğitimde mevcut durum ve öneriler, yaşam sonu bakımı, tele-tıp olanakları, sosyal ve bilimsel organizasyon örnekleri bu amaçla kitabın kapsamına alınmıştır. Pulmoner rehabilitasyona tedavide göz ardı edilmesi; ancak etkili olma potansiyeli taşıması nedeniyle, deneyimin artırılmasına gereksinim duyulan akciğer nakli uygulamasına güncel durumunu bilip gelecekteki yerini hazırlamak gerekliliği açısından yer verilmiştir.

Sonuçta, bu kitap bir kartopunun çekirdeğini oluşturmak üzere kurgulanarak, nadir İAH'larını yalnızca bilimsel yönleriyle ele almakla kalmayıp hasta, hasta yakını ve hekimleri insan bağlamında kucaklamayı, bir anlamda sahiplenmeyi öne çıkarmaktadır.

Anahtar Kelimeler: *Ağrı; İnterstisyel akciğer hastalıkları; Nadir interstisyel akciğer hastalıkları; Öksüz hastalıklar; Bilgisayarlı tomografi; Hasta perspektifi; Eğitim; Akciğer transplantasyonu; Yaşam sonu yaklaşımı; Gelecek perspektifi*

INTRODUCTION

Interstitial Lung Diseases (ILDs) are defined in the first sentence of almost all related articles as "a heterogeneous group of more than 200 entities that affect the alveolar-capillary unit and, in some cases, the small airways and pulmonary vasculature." Updates to the classification of ILDs are infrequent but consistently implemented.[1,2] These classifications typically include an "other" category for lesser-known and less prevalent ILDs. These rare diseases are often unnamed in the lists thus have a risk to be underestimated due to their rarity. A recent classification differs from previous ones by explicitly naming diseases such as Pulmonary Alveolar Proteinosis (PAP), Lymphangioleiomyomatosis (LAM), and Pulmonary Langerhans Cell Histiocytosis (PLCH), in addition to a subgroup called "other rare ILDs" under the fifth category: ILDs with cysts and/or airspace filling.[3] In their review, Ryerson and Collard proposed a future classification approach based on genetic, molecular, and environmental phenotypes, grouped according to disease pathobiology. They advocated for a personalized medicine framework aimed at providing clinicians with more accurate prognostic information and targeted therapies tailored to the underlying biology of each disease.[4] Despite these developments, recent overviews of ILDs continue to focus primarily on more common diagnoses, with rare diseases still consolidated into generalized groups.[5] Despite two decades of progress, a persistent need remains to allocate greater attention and representation to rare ILDs in classification systems. These insights underscore the importance of adopting a new perspective in future updates- one that prioritizes the awareness and recognition of rare ILDs.

In a recent narrative review, the importance and specific characteristics of rare ILDs were emphasized to support their accurate identification -distinguishing them from other diseases with similar clinical or radiological presentations- and to highlight the implications of correct diagnosis for management and prognostic outcomes.[6] In the *ERS Monograph on Orphan Lung Diseases*, Cordier described their objective as "to develop efficient care, especially through more appropriate diagnosis and research, including drug development and a more humanistic consideration of the patients".[7] In this monograph, rare ILDs among orphan lung diseases are discussed in several chapters, as part of groups of diseases such as multiple cystic lung diseases, alveolar lipoproteinosis syndromes, and rare interstitial lung diseases of environmental origin. In another comprehensive book titled *Orphan Lung Diseases: A Clinical Guide to Rare Lung Diseases*, a broad range of conditions is covered with the stated aim "to provide synthesized and easily accessible information about the main orphan lung diseases." The editors intend to support clinicians in answering the practical questions they encounter in patient care in a timely and effective manner.[8] This textbook covers many orphan lung diseases, including some relatively common rare ILDs, from a medical perspective.

A decade later, there remains a need to publish a handbook that not only addresses recent advances in rare ILDs from a medical standpoint but also integrates integrative and future perspectives across a

broad spectrum with a central focus on the patient, to whom all efforts should ultimately be dedicated. Therefore, the title of this book (*Adopting Orphan Diseases: Rare Interstitial Lung Diseases*) was chosen to emphasize the commitment to embracing this group of diseases by exploring rare ILDs across a broad spectrum, from medical to social aspects.

DEFINITION OF RARENESS

It would be appropriate to begin by defining certain terms, both in terms of their frequency, such as rare diseases in general, rare lung diseases, and rare ILDs, and their functional use, such as the concept of orphan diseases.

Rare diseases and *orphan diseases* are terms often used interchangeably, but their distinctions warrant clarification—particularly in a book intended as a reference guide. Jeff Aronson has clearly defined these terms, including their ontological origins: the word *rare* comes from the Latin *rarus* (meaning loosely spaced or sparse), and *orphan* originates from the Greek *orphanos* (referring to a child deprived of one or both parents, or an adult deprived of a child).[9] In medical contexts, *rare* generally refers to the low prevalence of a disease, whereas *orphan disease* is used to describe neglected diseases. Furthermore, orphan diseases convey the sense that affected patients feel abandoned-that no one cares about their disorder and that little, if any, research is conducted to improve diagnosis and management.[10]

A rare disease is defined in Europe as one that affects fewer than one person in every 2,000.[7] Orphan diseases are those that are not widely researched, lack specific treatments, or attract limited interest from scientists and clinicians. In the United States, a rare disease is defined as one affecting fewer than 200,000 individuals.[11] Approximately 30 million people in the U.S. are living with a rare disease, a figure that translates to about 1 in 10 people.[10] In Japan and Australia, a disease is considered rare if it affects fewer than 50,000 and 2,000 people, respectively. These thresholds correspond to a prevalence of 1 to 8 in 10,000 people. The European Union defines rare diseases as those affecting fewer than 5 in 10,000, while the World Health Organization uses a range of less than 6.5 to 10 in 10,000 people.[9] Therefore, a disease considered rare in one region may not be classified as rare in another.

Specific, coordinated initiatives in the field of rare diseases are essential to ensure equity in care delivery, the development of best practices, and the availability of reliable information for healthcare professionals and the broader public.[12] It is widely acknowledged that rarer conditions are too often neglected by health services, resulting in reduced quality of life for affected individuals and increased costs to national healthcare systems, welfare programs, employers, and patients themselves.[13] When barriers stand in the way of providing the best care for patients and their families in the field of rare diseases, rare lung diseases are also affected by this disadvantageous situation. Considerable variability in the prevalence and incidence of ILDs has been observed, depending on the specific diagnosis, which in turn is influenced by factors such as gender, age, geographic region, and ethnicity.[5] Rare ILDs can be approached from a similar perspective.

HOLISTIC APPROACH TO RARE ILDS

The rarer the disorder, the more tests and healthcare visits are usually required to achieve a correct diagnosis. This often results in increased costs, unnecessary procedures, and missed opportunities for early intervention.[10] Unfortunately, the lack of interest stems from limited medical knowledge about these diseases and the unsatisfactory financial incentives from the industry's perspective. Lesser-studied ILDs represent a diagnostic and therapeutic challenge and are frequently misdiagnosed. Recently, the need for more global and accessible educational methods for rare diseases has been emphasized.[10] Since diagnostic work-ups begin with clinical suspicion and involve a broad differential diagnosis, an optimal level of basic knowledge about these diseases should be ensured through medical education, both at the undergraduate level and during pulmonary medicine training, alignment with current curricula.[5] From this perspective, a chapter titled "**Rare ILDs in Medical and Postgraduate Education**" aims to highlight the current situation and propose alternative educational approaches.

Radiological investigation is the primary tool for both guiding the development of an appropriate list of differential diagnoses and determining the diagnostic work-up needed to reach a correct diagnosis. The following chapter, titled "**Differential Diagnosis in Rare ILDs Through Radiological Hints**," provides a radiology-focused overview of all these conditions, highlighting their characteristic imaging features often the first step in raising clinical suspicion and guid-

ing differential diagnosis. Differentiating cystic lung diseases within the group of rare ILDs is essential, as these diseases have distinct clinical features and therapeutic approaches. Radiological guidance plays a crucial role in recognizing the underlying pathology and planning an appropriate diagnostic approach. To reach an accurate final diagnosis, similarities and distinguishing imaging findings must be carefully evaluated, especially when attempting to avoid the need for histopathological confirmation. However, in some cases, a radiologist with expertise in rare ILDs may not be available to support clinicians. Therefore, physicians should be able to recognize key radiological features, at least to ensure timely referral to an expert center. The radiology chapter is designed to support pulmonary medicine specialists in such circumstances by providing a wide range of radiological images and a structured diagnostic workflow.

According to a biomedical approach, this book on rare ILDs is organized into four main categories: alveolar filling diseases [**Pulmonary Alveolar Microlithiasis (PAM), Pulmonary Alveolar Proteinosis (PAP), Acute Silicosis/Silicoproteinosis**), cystic lung diseases (**Birt-Hogg-Dube Syndrome (BHD), Lymphangioleiomyomatosis (LAM), Pulmonary Langerhans Cell Histiocytosis (PLCH)**], **Familial Interstitial Pneumonias (SP-C, ABCA3, telomere-related disorders)**, and other conditions such as **Pleuroparenchymal Fibroelastosis (PPFE), Pulmonary Amyloidosis, Hermansky-Pudlak Syndrome, and Thoracic Involvement in IgG4-related ILD**. These represent the key diseases included under the umbrella of rare ILDs.

Each topic is presented in a structured format designed to provide the reader with a systematic approach and practical understanding of the aforementioned diseases. The format follows a flow that begins with a concise and illustrative clinical case to introduce the topic and engage the reader. After the initial steps, presentation, clinical evaluation, physical examination, and preliminary diagnosis, the chapter proceeds to the next section. Details regarding the final part of the case report are withheld until the end, while the theoretical background is conveyed in an organized manner. This is followed by a case analysis. At the end of each chapter, sample questions and take-home messages are included to help apply the information in practical settings. This format may enhance the impact of the book by making it a useful handbook for daily medical practice, in addition to its educational value in the context of rare ILDs.

A holistic approach would not be complete without the chapters on "**Patient Perspective in Rare ILDs**", "**End-of-Life Management in Rare ILDs**" and "**The LAM Story: From Grass Roots Patient Advocacy to an Effective Treatment**". Even though treatment options are generally limited for rare ILDs, non-pharmacological approaches such as "**Telemedicine Opportunities for Rare ILDs**," which explores remote healthcare delivery, and "**Pulmonary Rehabilitation in Rare ILDs**" are addressed in related chapters. Additionally, a discussion on lung transplantation in rare ILDs is essential due to the importance of careful benefit-risk evaluation.

The future of patients with orphan lung diseases depends not only on equitable access to a definitive diagnosis and optimal current care, but also on advancements in both clinical and basic research. Standard randomized, double-blind, placebo-controlled trials for evaluating new drugs in very rare diseases are often hindered by challenges in patient recruitment. As a result, researchers frequently resort to alternative, suboptimal study designs, methods, and clinically meaningful endpoints.[8] Consequently, due to the lack of randomized controlled trials, there are still no well-established therapeutic options available.[6] Unfortunately, there has been hardly any progress so far. This topic could be addressed in a chapter titled "**Future Perspectives on Rare ILDs.**"

CONCLUSION

It has been more than a decade since Jean-François Cordier, in the introduction to the *ERS Monograph on Orphan Lung Diseases*, wrote: "For too long, orphan diseases have been a matter of curiosity to the public and to doctors, rather than an obligation of solicitude to the affected patients. The time has come to develop efficient care, especially through more appropriate diagnosis and research, including drug development and a more humanistic consideration of the patients who should no longer be made to feel like an 'orphan.'".[7] Furthermore, four decades have passed since the enactment of the Orphan Drug Act in the United States, which stated: "There is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to pro-

vide financial incentives to develop such drugs; and it is in the public interest to provide such changes and incentives for the development of orphan drugs."[11] In a recently published book on rare and interstitial lung diseases, only PAM, PAP, PPFE, IgG4-related diseases, and PLCH took place through a certain case report for each chapter to demonstrate real life experiences.[14]

While review articles and occasional case reports continue to be published, there remains a significant need to compile, analyze, and extract new insights from them to improve our understanding of rare ILDs. Early consultation with, or referral to, experts has been recommended to "diagnose, optimally treat, and support patients with rare ILDs, as well as advance the field," and the *European Reference Network on Rare Respiratory Diseases* (ERN-LUNG) has been identified as a key platform for clinical and research collaboration to improve care for patients with rare ILDs across Europe.[15] However, an optimal level of knowledge is essential for the continuation of this process, and local solutions are critical components of real-life medical practice. This underscores the need for collaborative efforts on each of the topics discussed in this book.

With the impact of this book in raising awareness and fostering enthusiasm for addressing rare ILDs, we can remain hopeful about achieving broader global recognition and commitment to orphan diseases-metaphorically speaking, adopting them with the care and responsibility they deserve.

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CHAPTER 02

DIFFERENTIAL DIAGNOSIS IN RARE INTERSTITIAL LUNG DISEASES THROUGH RADIOLOGICAL HINTS

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARINDA RADYOLOJİK İPUÇLARIYLA AYIRICI TANI

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DIFFERENTIAL DIAGNOSIS IN RARE INTERSTITIAL LUNG DISEASES THROUGH RADIOLOGICAL HINTS

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ABSTRACT

Thin-slice computed tomography (CT) has become the cornerstone for diagnosing in interstitial lung diseases (ILDs), allowing radiologists to triage patients by pattern, distribution, and ancillary systemic clues long before histology is available. Thin-section volumetric acquisitions <1.25 mm recommended by the Society of Thoracic Radiology and recent Fleischner updates maximise conspicuity of subtle cysts, nodules, and septal thickening while standardising terminology across centres. Among cystic disorders, pulmonary Langerhans-cell histiocytosis typically shows upper- and mid-zone centrilobular nodules that cavitate into irregular cysts with relative costophrenic sparing, strongly associated with cigarette smoking; lymphangioleiomyomatosis demonstrates innumerable uniformly thin-walled cysts scattered throughout enlarged lungs that often spare pericostophrenic angles and may coexist with chylous effusion or renal angiomyolipoma; and Birt-Hogg-Dubé syndrome produces fewer, variably shaped lentiform cysts clustered in basal-medial regions, frequently heralded by spontaneous pneumothorax. The "crazy-paving" pattern is a mosaic of ground-glass opacities (GGOs) with superimposed inter- and intralobular septal thickening remains the signature of pulmonary alveolar proteinosis (PAP), although it is recognised as a non-specific pattern shared with infection and acute lung injury. Smooth septal thickening with background GGOs in a child or young adult, particularly when accompanied by hepatosplenomegaly, should raise concern for Niemann-Pick disease type B or other lysosomal storage disorders. Diffuse hyperdense calcific micronodules generating the "black pleura sign" and "sandstorm appearance" are virtually diagnostic of pulmonary alveolar microlithiasis (PAM). Integrating these imaging signatures with clinical context accelerates multidisciplinary consensus, reduces unnecessary biopsies, and positions radiology at the forefront of precision therapeutics for these uncommon but morbid entities.

Keywords: *Interstitial lung disease; Computed tomography; Langerhans-cell histiocytosis; Lymphangioleiomyomatosis; Birt-Hogg-Dubé syndrome; Cystic lung disease*

ÖZET

İnce kesitli bilgisayarlı tomografi (BT), interstisyel akciğer hastalıklarının (İAH) tanısında temel yöntem haline gelmiş olup, radyologların histopatoloji sonuçları olmadan önce hastaları patern, dağılım ve sistemik ipuçlarına göre sınıflandırmasına olanak tanır. Society of Thoracic Radiology (STR) ve güncel Fleischner kılavuzları tarafından önerilen <1,25 mm ince kesitli volumetrik taramalar, ince duvarli kistlerin, nodüllerin ve septal kalınlaşmaların daha belirgin hale gelmesini sağlayarak farklı merkezler arasında terminolojinin standartlaşmasına katkıda bulunur. Kistik hastalıklar arasında pulmoner Langerhans hücreli histiyositoz genellikle üst ve orta akciğer zonlarında sentrilobüler nodüllerle başlar ve zamanla düzensiz kistlere dönüşür; kostofrenik sinüsler genellikle korunur ve tablo sigara kullanımıyla güçlü ilişkilidir. Lenfanjiyoleyomiyomatozis, genellikle tüm akciğerlere yayılmış, homojen, ince cidarlı sayısız kistle karakterizedir; perikostofrenik açı sıklıkla korunur ve kistlere şilöz efüzyon veya böbrek anjiyomiyolipomu eşlik edebilir. Birt-Hogg-Dubé sendromunda daha az sayıda, şekil olarak değişken lentiform kistler bazal ve mediyal alanlarda kümelenir ve çoğu zaman spontan pnömotoraks ilk bulgu olabilir. Arnavut kaldırımı (Crazy-paving) paterni, buzlu-cam opasiteler üzerine binen inter- ve intralobüler septal kalınlaşmanın mozaik görünümüdür ve en çok pulmoner alveoler proteinozis (PAP) ile ilişkilidir; ancak enfeksiyon ve akut akciğer hasarı gibi diğer durumlarda da gözlenebilir. Çocuk veya genç erişkinlerde düzgün septal kalınlaşma ve eşlik eden buzlu-cam opasiteleri, özellikle

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hepatosplenomegali de varsa, Niemann-Pick hastalığı tip B veya diğer lizozomal depo hastalıkları ayırıcı tanıda düşünülmelidir. Yaygın hiperdens kalsifik mikronodüllerle oluşan "siyah plevra işareti" ve "kum fırtınası görünümü" pulmoner alveoler mikrolitiyazis (PAM) için neredeyse tanısaldır. Bu görüntüleme bulgularının klinik bağlamla birleştirilmesi, multidisipliner karar süreçlerini hızlandırır, gereksiz biyopsileri azaltır ve radyolojiyi bu nadir fakat ciddi hastalıkların tanı ve tedavisinde önemli bir konuma taşır.

Anahtar Kelimeler: *İntertisyel akciğer hastalığı; Bilgisayarlı tomografi; Langerhans hücreli histiyositoz; Lenfanjiyoleyomiyomatozis; Birt-Hogg-Dubé sendromu; Kistik akciğer hastalığı*

INTRODUCTION

Interstitial lung diseases (ILDs) encompass a heterogeneous group of disorders characterized by varying degrees of inflammation and fibrosis of the pulmonary interstitium and alveoli, often leading to respiratory failure and impaired gas exchange.[1-3] While common forms like idiopathic pulmonary fibrosis (IPF) are well-studied, rare ILDs pose unique diagnostic challenges due to their low prevalence, diverse etiologies, and overlapping radiological features.[4] Radiological evaluation, particularly thin slice chest computed tomography (CT) with ILD protocol, serves as a cornerstone in the ILD diagnostic pathway. Chest CT enables detailed visualization of ILD patterns, such as ground-glass opacities (GGOs), cysts, nodules, mosaicism, traction bronchiectasis, architectural distortion, and reticulation, which are essential for shaping differential diagnoses and guiding multidisciplinary discussions.[5] Through integration with clinical history, pulmonary function tests (PFTs), and, when necessary, histopathology, radiologists play a critical role in narrowing down the possible causes of ILD. However, differentiating rare ILDs remains fraught with difficulties. Most important challenges include atypical radiological manifestations and mimicry of more common diseases. These factors often contribute to diagnostic delays, misclassification, and suboptimal patient management.[4,5] This section is aimed to equip clinicians and radiologists with a structured radiological framework to recognize and differentiate rare ILDs, ensuring that even subtle or atypical presentations are systematically evaluated. It also aimed to emphasize distinct imaging features across a spectrum of uncommon conditions, highlighting patterns that may mimic more prevalent diseases. Finally, it aimed to explore the role of emerging technologies, such as artificial intelligence (AI)-driven tools, quantitative CT techniques, and advanced modalities like photon-counting CT.

ROLE OF THIN-SLICE CT (CT) TECHNICAL PROTOCOLS

Thin-slice CT is essential in ILD evaluation because it substantially improves the visualization of fine lung details, such as subtle reticulation, small nodules, interlobular septal thickening, and early honeycombing. A comprehensive ILD CT protocol includes full-inspiratory thin-slice imaging, with prone or expiratory series as needed to uncover dependent changes and air-trapping. The American College of Radiology (ACR) and Society of Thoracic Radiology (STR) recommend thin-slice CT acquisition with the following parameters for ILD evaluation:[6]

1. Volumetric expiratory and inspiratory scans performed supine at full inspiration, with patient arms raised to reduce beam hardening and motion artifacts.
2. Thin collimation of ≤1.25 mm (typically 1 mm) using high-resolution (sharp) reconstruction kernels ensures optimal lung parenchymal detail.
3. A dedicated prone inspiratory series (restricted to the dependent lung bases) is recommended when dependent opacities are seen supine; this helps differentiate true pathology from gravitational atelectasis.
4. Expiratory imaging in supine position may be acquired to assess for air-trapping in airway-dominant disorders.

Even with robust protocols, thin-slice CT is susceptible to motion artifacts, suboptimal inspiration, and beam-hardening, particularly near the diaphragm or chest wall. Inadequate breath-hold or improper positioning can degrade image quality; thus, technologists should immediately review images and repeat acquisitions as necessary. Utilizing volumetric acquisition allows post-processing into coronal and sagittal reformats, which not only aids diagnosis but also helps mitigate the impact of artifacts.[7]

ANCILLARY IMAGING TOOLS IN RARE ILD

Lung Ultrasound (LUS)

Lung ultrasound (LUS) is emerging as a bedside screening tool for ILD, especially in rheumatologic conditions.[8] The presence and count of B-lines, along with pleural irregularities and subpleural nodules, show high sensitivity (83%) and specificity (81.2%) compared to high-resolution CT (HRCT).[9] LUS also outperforms symptom-based screening in detecting subclinical ILD among rheumatoid arthritis.[10] Advanced techniques such as lung surface-wave elastography promise non-invasive assessment of superficial parenchymal stiffness.[11] However, ultrasound remains limited to superficial lung zones and cannot visualize deeper structures obstructed by air.

Magnetic Resonance Imaging (MRI)

Lung MRI is increasingly recognized as a radiation-free, multimodal imaging alternative for ILDs.[7] Its strengths include superior tissue characterization, where inflammation highlights on high T2-weighted images with early contrast uptake, while fibrosis remains hypointense with delayed enhancement. Ultrashort echo time (UTE) sequences have demonstrated strong correlations with HRCT for detecting fibrosis patterns such as reticulation, honeycombing, and traction bronchiectasis in idiopathic pulmonary fibrosis, with sensitivity up to 97.1% and a correlation coefficient of r=0.72.[12] Building on this, zero echo time (ZTE) MRI has shown excellent agreement with thin-slice CT for quantifying ILD extent in systemic sclerosis, with an intermodality correlation of r=0.986 and high interobserver reliability (ICC up to 0.969), making it a promising tool for serial monitoring without ionizing radiation.[13] Additionally, hyperpolarized gas MRI using ^{3}He or ^{129}Xe offers functional maps of ventilation and gas exchange, enabling sensitive detection of regional abnormalities that correlate with PFTs.[14] Despite these advancements, MRI lags HRCT in spatial resolution, remains susceptible to motion artifacts, and demands specialized protocols, respiratory control, and proprietary hardware that limit widespread adoption.[15] Nonetheless, with continuous technological improvements and increased accessibility, MRI offering a safer, no-radiation approach to diagnosing and managing rare ILDs.

Positron Emission Tomography-CT (PET-CT)

PET-CT provides functional insight by mapping metabolic activity onto anatomical CT images. Standard FDG-PET has demonstrated utility in identifying active inflammation and early fibrotic changes, particularly in connective tissue disease (CTD)-related ILDs.[16] Additionally, ^{68}Ga-FAPI PET-CT-targeting fibroblast activation protein has recently emerged as a sensitive tool for quantifying fibrotic burden in ILDs.[17] Although promising, PET-CT use in rare ILDs remains investigational and requires more prospective validation for routine clinical integration.

MULTIDISCIPLINARY APPROACH

Integrating clinical and pathologic data through a multidisciplinary approach is essential for accurate and timely diagnosis of rare ILDs.[18] Regular meetings involving pulmonologists, rheumatologists, thoracic radiologists, and ILD-trained pathologists form the diagnostic gold standard, improving inter-observer agreement, boosting diagnostic confidence, and reducing the number of unclassifiable cases. Such collaborative synthesis not only enhances diagnostic precision but also guides procedural choices, informs prognosis, and reduces the need for unnecessary invasive testing.[18]

RADIOLOGICAL PATTERNS OF RARE ILDs

Rare ILDs often display distinct radiologic patterns that are critical for differential diagnosis.[4] The crazy-paving pattern, combining GGOs with septal thickening, is first described in pulmonary alveolar proteinosis but also occurs in many disorders, including alveolar microlithiasis, acute silicoproteinosis, Langerhans cell histiocytosis, and pulmonary hemorrhage. Cystic changes are typical of lymphangioleiomyomatosis and Birt-Hogg-Dubé syndrome, while nodular patterns commonly appear in Langerhans cell histiocytosis, amyloidosis, sarcoidosis, and pneumoconioses. Finally, fibrotic features with reticulation, traction bronchiectasis, and honeycombing, as seen in pleuroparenchymal fibroelastosis and familial interstitial pneumonias, can resemble usual interstitial pneumonia (UIP) but often show apical pleural thickening or familial clustering.[4-6] Recognizing these imaging signatures and their nuances is essential to avoid misdiagnosis and guide targeted clinical and genetic evaluation.

Pulmonary Alveolar Proteinosis (PAP)

Pulmonary alveolar proteinosis (PAP) classically presents on chest radiographs with bilateral, symmetric alveolar opacities with mid-to-lower lung zone predominance, often described as a bat-wing pattern. These radiographic findings reflect filling of the alveoli with surfactant-rich material, giving a homogenous, cloud-like appearance.[19] On chest CT, PAP is most notably characterized by the crazy-paving pattern, where GGOs are intersected by smooth interlobular and intralobular septal thickening.[5,19,20] These GGOs are frequently patchy or geographic with sharply demarcated borders from adjacent unaffected lung, which often appears relatively clear, a helpful clue for identifying involved zones (Figure 1). These imaging features, when recognized in the appropriate clinical context, strongly suggest PAP and help distinguish it from other causes of diffuse lung opacities.[19,20]

Differential considerations to bear in mind include *Pneumocystis jirovecii* pneumonia (PCP), pulmonary edema, and alveolar hemorrhage. PCP should be a prime consideration in immunocompromised patients presenting with upper lung zone predominant diffuse GGOs or crazy-paving pattern on CT.[21] Pulmonary edema also mimics this pattern and characterized by smooth septal thickening combined with GGOs in dependent lung regions, often alongside cardiomegaly and pleural effusions. Lastly, alveolar hemorrhage can present a similar CT appearance, particularly in acutely symptomatic patients with concurrent clinical or laboratory evidence of bleeding.[5,21]

Pulmonary Alveolar Microlithiasis (PAM)

Pulmonary alveolar microlithiasis (PAM) is a rare, genetic disorder marked by widespread intra-alveolar calcium phosphate microliths.[22] On chest radiographs, PAM displays the characteristic "sandstorm" appearance—diffuse, bilateral micronodular calcifications that obscure the cardiac borders and diaphragms—most prominently in the mid to lower lung zones.[23] A classic CT pattern includes innumerable tiny, high-density microliths superimposed on GGOs and septal thickening, often accompanied by calcification of the pleura and interlobular septa (Figure 2). An important diagnostic clue is the "black pleura sign," a thin, lucent subpleural line created by spared peripheral lung immediately beneath dense calcified parenchyma. Subpleural cysts may also be seen in advanced cases.[22,23] Importantly, these radiographic findings starkly contrast the typically mild clinical presentation, and patients often remain asymptomatic or mildly symptomatic despite pronounced imaging abnor-

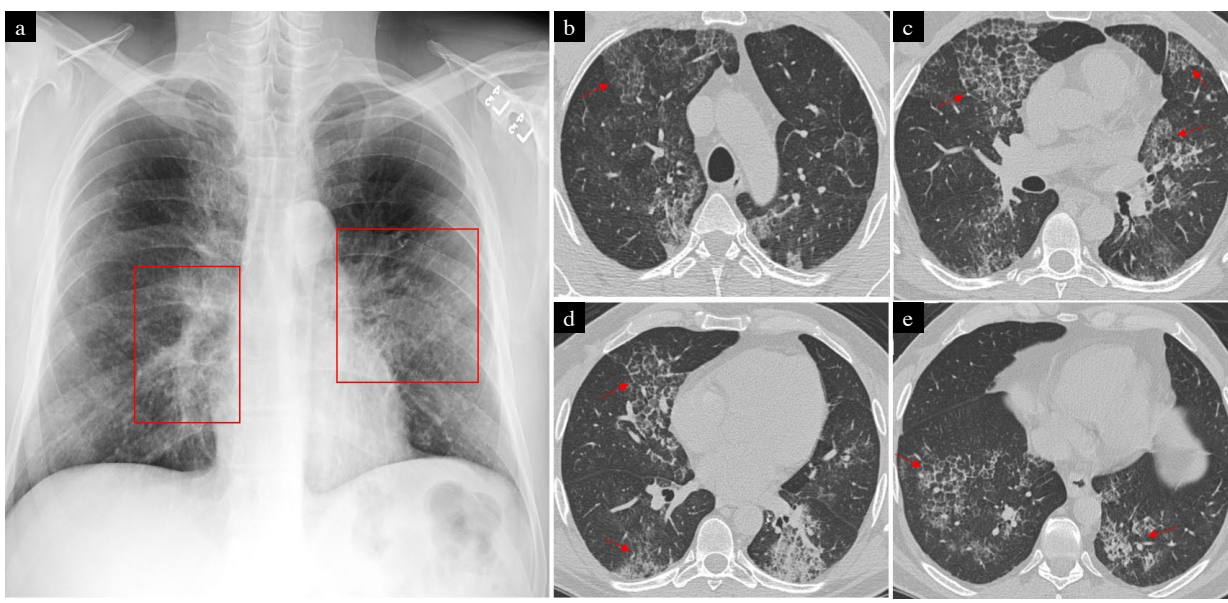


Figure 1. A 59-year-old male with pulmonary alveolar proteinosis. **a)** Frontal chest radiograph demonstrates bilateral, predominantly perihilar interstitial opacities (rectangles). **b-e)** Axial chest CT images show patchy ground-glass opacities with smooth interlobular and intralobular septal thickening, consistent with a crazy-paving pattern (arrows).

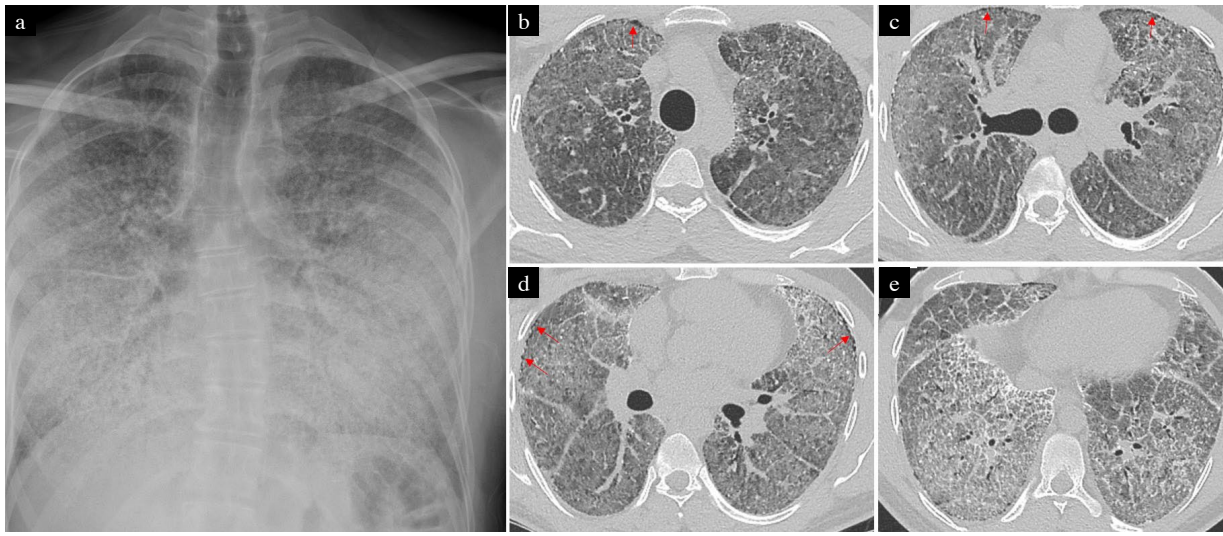


Figure 2. A 34-year-old male with pulmonary alveolar microlithiasis. **a)** Frontal chest radiograph shows the characteristic "sandstorm" appearance, with diffuse, bilateral micronodular calcifications obscuring the cardiac borders and diaphragms, most prominent in the mid to lower lung zones. **b-e)** Axial chest CT images demonstrate innumerable tiny, high-density microliths superimposed on ground-glass opacities and septal thickening. Calcification of the pleura and interlobular septa is also present, along with subpleural cysts (arrows).

malities. Differential diagnoses include PAP, silicosis, amyloidosis, pulmonary hemosiderosis, sarcoidosis, and metastatic calcification; however, the presence of dense micronodular calcifications with pleural or septal involvement, absence of cardiomegaly or lymphadenopathy, and the sandstorm and black-pleura signs are generally distinguish PAM from these mimics.[5,22,23]

Acute Silicosis

Acute silicosis, also known as silicoproteinosis, is a fulminant form of silicosis that typically develops within months to a few years after intense silica exposure.[24] Chest CT often shows bilateral, posterior-predominant consolidation with GGOs, and in many cases, centrilobular nodules, some with calcification, reflecting inhalational injury (Figure 3).[25] Unlike idiopathic PAP, the classic crazy-paving pattern may be present but is less consistent, and fibrosis is usually minimal or absent. Additional distinguishing findings include ill-defined centrilobular nodules in over 80% of cases, patchy consolidation, and septal lines; calcified mediastinal or hilar lymph nodes are common.[26] Chest radiographs often reveal diffuse alveolar filling with air-space consolidation, resembling pulmonary edema or pneumonia. Given the rapid clinical progression, history of silica exposure is critical for diagnosis and differentiation from other causes of GGO and consolidation.[24-26]

Birt-Hogg-Dubé (BHD) Syndrome

Pulmonary cysts are the defining radiological feature of BHD syndrome, an autosomal dominant condition marked by lower-lobe, medial, and subpleural distribution of multiple variably sized, thin-walled cysts on chest CT.[27,28] Unlike other cystic lung diseases, BHD cysts are fewer, fusiform or lenticular in shape, and abut interlobular septa or mediastinal pleura (Figure 4). These cysts also tend to cluster basally and medially, with frequent involvement of costophrenic recesses. The surrounding lung parenchyma remains typically normal, and cyst size and number remain relatively stable over time.[29] Clinically, these distinctive imaging findings—particularly when accompanied by spontaneous pneumothorax and skin or renal tumors—raise strong suspicion for BHD syndrome. Their recognition can prompt genetic testing for the folliculin (FLCN) mutation and guide focused surveillance for associated renal neoplasms.[27-29]

Lymphangioleiomyomatosis (LAM)

Lymphangioleiomyomatosis (LAM) characterized by numerous thin-walled, round or oval cysts, typically

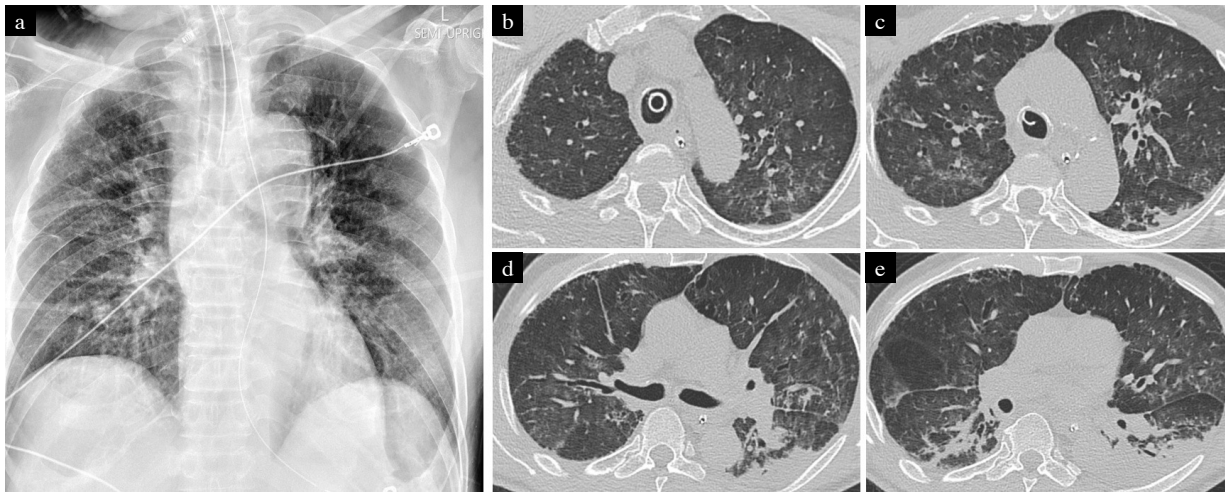


Figure 3. A 53-year-old male with silicoproteinosis. **a)** Frontal chest radiograph shows nonspecific patchy pulmonary opacities. **b-e)** Axial chest CT images demonstrate bilateral, posterior-predominant consolidation and ground-glass opacities with scattered centrilobular nodules, consistent with inhalational injury. An endotracheal tube is present.

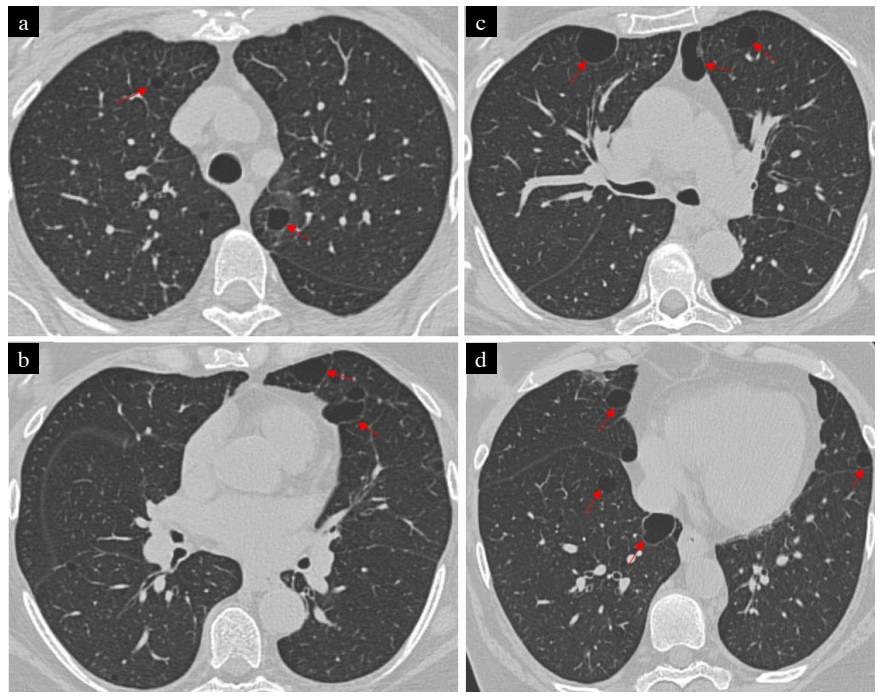


Figure 4. A 62-year-old female with Birt-Hogg-Dubé (BHD) syndrome. **a-d)** Axial chest CT images demonstrate multiple bilateral, subpleural-predominant, thin-walled cysts of varying sizes (arrows). Most cysts are lenticular in shape and abut the mediastinal pleura.

uniform in size and diffusely distributed throughout both lungs, and cysts often spare the extreme lung bases on CT (Figure 5).[30] Unlike the basal-predominant cysts seen in Birt-Hogg-Dubé syndrome, LAM's cysts appear evenly across all zones and may be accompanied by interlobular septal thickening, ground-glass opacities, spontaneous pneumothorax, or chylous pleural effusions.[29] Chest radiographs are often normal ear-

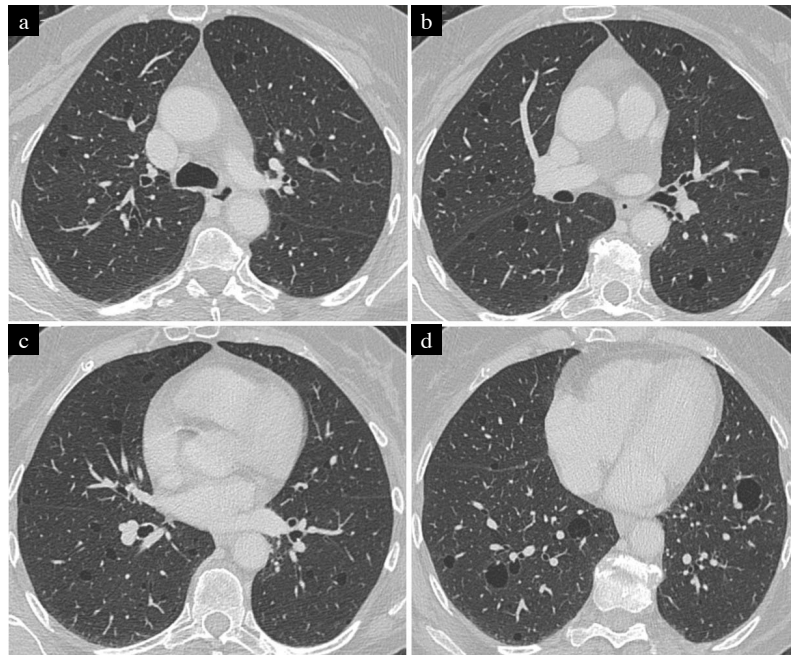


Figure 5. A 65-year-old female with lymphangioleiomyomatosis. **a-d)** Axial chest CT images show numerous thin-walled, round cysts that are relatively uniform in size and diffusely distributed throughout both lungs.

ly in the disease but may later show bilateral reticular or cystic changes and hyperinflation, while maintaining normal lung volumes. The consistent cyst distribution, context of a woman in her reproductive years, and possible correlates like renal angiomyolipomas or elevated serum vascular endothelial growth factor-D (VEGF-D) strongly support a LAM diagnosis and help differentiate it from other cystic lung diseases.[29,30]

Pulmonary Langerhans Cell Histiocytosis (PLCH)

Pulmonary Langerhans cell histiocytosis (PLCH) typically presents on chest CT with a striking combination of centrilobular nodules, cavitating nodules, and irregularly shaped cysts, predominantly affecting the upper and mid-lung zones while sparing the costophrenic angles.[31] In the early stages, small, poorly defined nodules measuring 1-10 mm predominate; as the disease progresses, some of these nodules cavitate and merge, gradually transforming into thick- or thin-walled cysts with irregular, often bizarre shapes. Advanced disease may result in confluent cystic destruction mimicking emphysema (Figure 6).[29,31] A distinguishing feature is the upper-lobe predominance with relative basal sparing, which helps separate PLCH from other diffuse cystic lung diseases.[31] Chest radiographs often initially reveal nodular or reticulonodular patterns, progressing to cystic changes as the disease advances. Key diagnostic clues include a history of smoking, spontaneous pneumothorax, and the characteristic nodular-to-cystic transformation on CT.[29,31]

Hermansky-Pudlak Syndrome (HPS)

Hermansky-Pudlak syndrome (HPS)-associated ILD typically characterized by diffuse, basal-predominant reticular pattern, traction bronchiectasis, and GGOs. As fibrosis advances, honeycombing becomes evident in the lower lobes, while apical regions are often relatively spared (Figure 7).[32] Unlike idiopathic UIP, however, HPS occurs in younger patients and is associated with oculocutaneous albinism and bleeding diathesis, which serve as critical diagnostic clues.[33] Chest radiographs typically show lower-zone reticular opacities and volume loss in more advanced stages. The combination of progressive fibrotic changes on imaging, systemic features, and a history of easy bruising or bleeding strongly supports HPS and helps distinguish it from sporadic UIP or other fibrosing ILDs.[32,33]

Familial Interstitial Pneumonias (FIP)

Familial interstitial pneumonias (FIP) encompass a

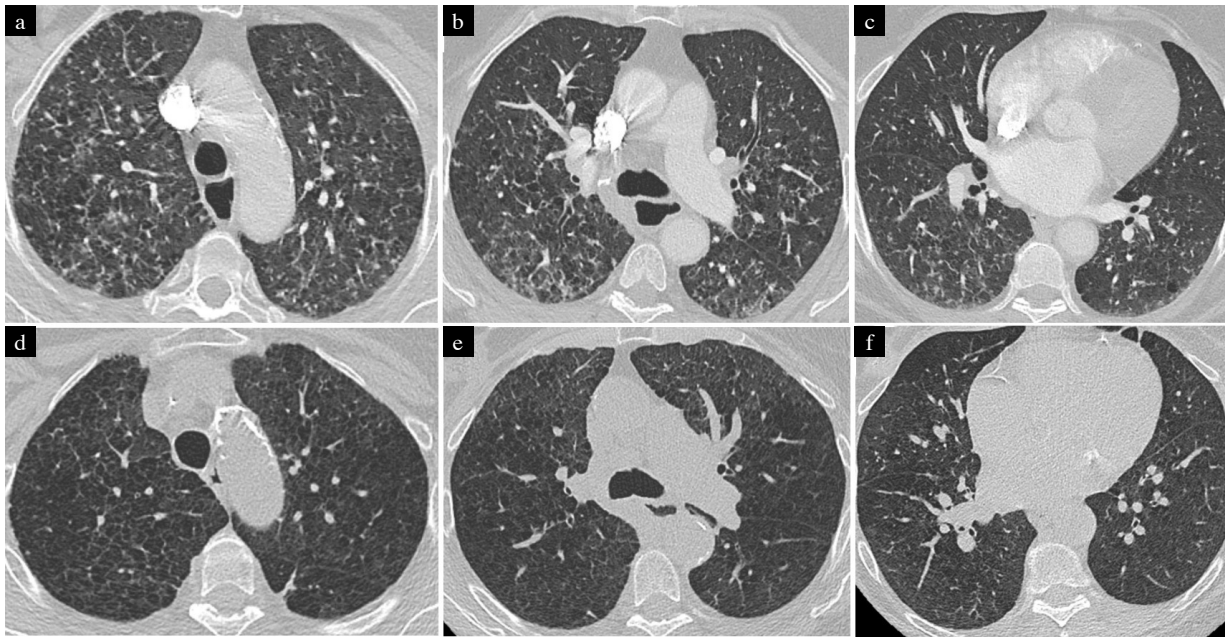


Figure 6. A 57-year-old female with pulmonary Langerhans cell histiocytosis. **a-c)** Initial axial chest CT images demonstrate a combination of centrilobular nodules, cavitating nodules, and irregularly shaped cysts, predominantly involving the upper and mid-lung zones. **d-f)** Axial chest CT images obtained seven years later show numerous thin-walled cysts with irregular and bizarre shapes, along with advanced, upper lung–predominant confluent cystic destruction mimicking emphysema.

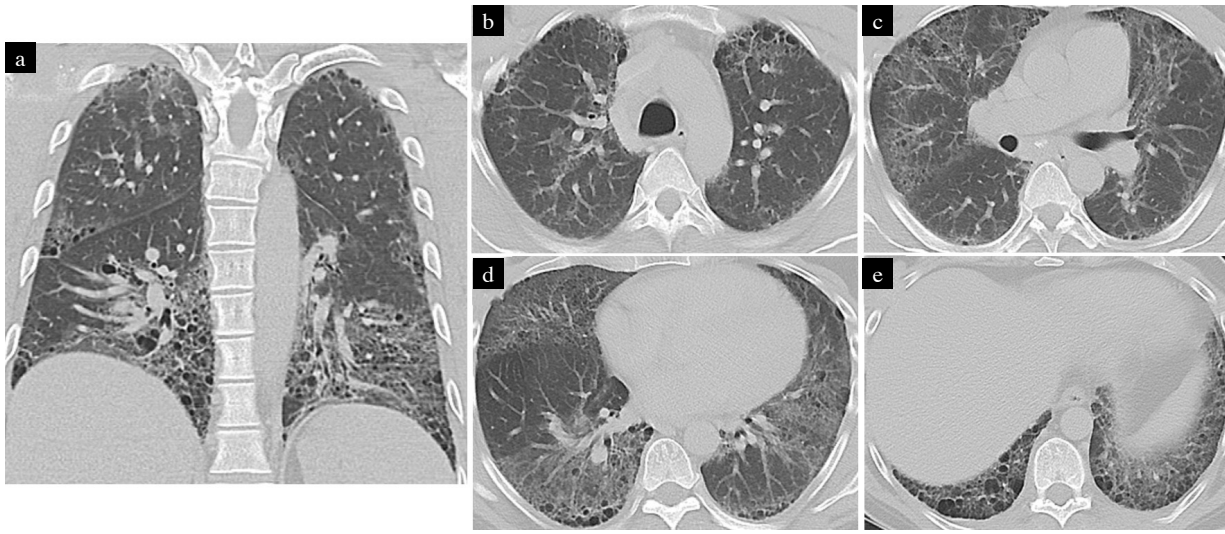


Figure 7. A 35-year-old male with Hermansky-Pudlak syndrome. **a)** Coronal and **b-e)** axial chest CT images demonstrate a diffuse, basal-predominant reticular pattern, traction bronchiectasis, and ground-glass opacities, along with bibasilar honeycombing.

heterogeneous group of fibrosing lung diseases occurring in two or more family members, often linked to genetic mutations in surfactant protein C (SFTPC), ATP-binding cassette transporter A3 (ABCA3), and telomere-related genes such as TERT and TERC.[33] Chest CT findings frequently overlap with sporadic IPF, showing basal-predominant reticulation, traction bronchiectasis, and honeycombing consistent with

a UIP pattern. However, FIP may also demonstrate nonspecific interstitial pneumonia (NSIP) features, including ground-glass opacities and subpleural sparing, particularly in younger individuals or those with surfactant-related mutations. Imaging alone rarely differentiates familial from sporadic disease; thus, a combination of radiologic findings, family history of ILD or premature hair graying, extrapulmonary features (such as liver disease or bone marrow failure in telomeropathies), and genetic testing is essential for diagnosis (Figure 8). Serial CT imaging is often used to monitor disease progression, as FIP can progress more rapidly than nonfamilial forms.[33,34]

Pulmonary Amyloidosis

Pulmonary amyloidosis can manifest on CT in three patterns: nodular, tracheobronchial, and diffuse interstitial involvement.[35] The nodular form appears as well-defined, often calcified parenchymal nodules, which may be solitary or multiple and can occasionally cavitate. The tracheobronchial pattern is characterized by irregular, nodular and circumferential thickening of the tracheal and bronchial walls, sometimes with luminal narrowing and calcification.[35,36] The diffuse interstitial form mimics other chronic infiltrative processes, showing reticulation, septal thickening, and GGOs, occasionally progressing to fibrotic distortion (Figure 9).[35] On chest radiographs, nodular amyloidosis may present as multiple bilateral opacities, while tracheobronchial involvement can be suggested by airway narrowing or calcified plaques.[35,36] Recognizing these imaging patterns in the appropriate clinical context is essential to prompt histologic confirmation and exclude systemic amyloidosis, which frequently coexists.

IgG4-Related Disease (IgG4-RD)

Thoracic IgG4-related disease (IgG4-RD) is both common and notably heterogeneous on imaging.[37] High-resolution CT reveals multiple overlapping patterns: peribronchovascular thickening, mediastinal lymphadenopathy, parenchymal solid and ground-glass nodules, interstitial changes, and pleural abnormalities (Figure 10). Specifically, peribronchovascular involvement is seen in over half of cases, often presenting alongside bronchial wall thickening

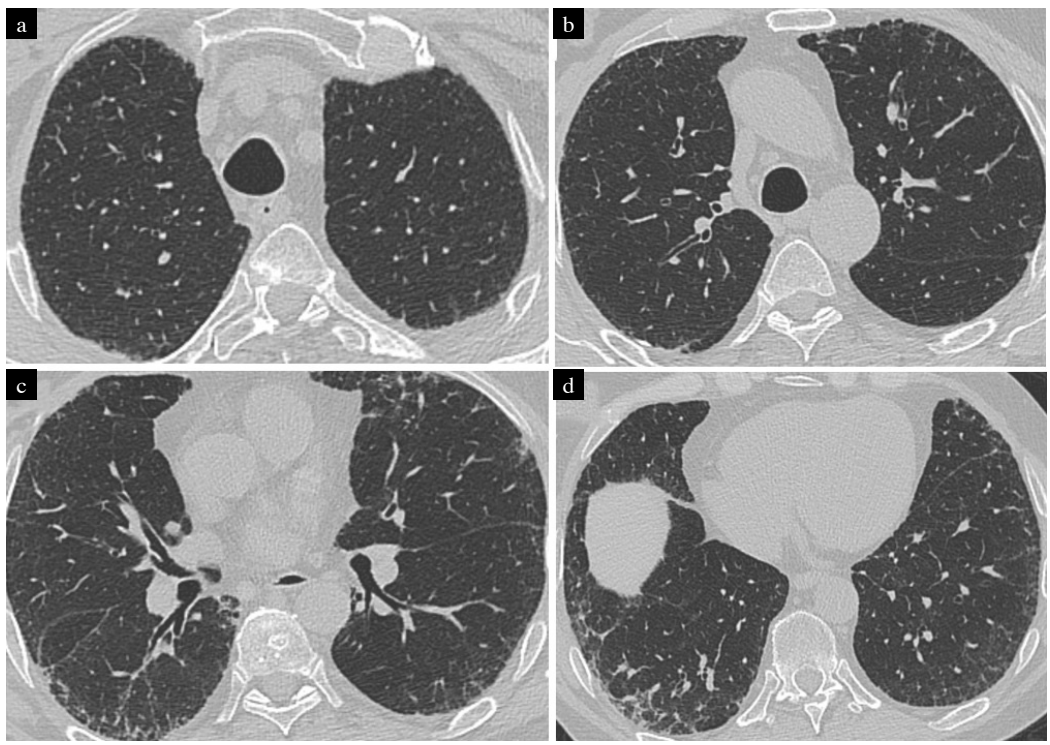


Figure 8. A 49-year-old male with short telomere syndrome. **a-d)** Axial chest CT images demonstrate basal-predominant subpleural reticulation and traction bronchiectasis.

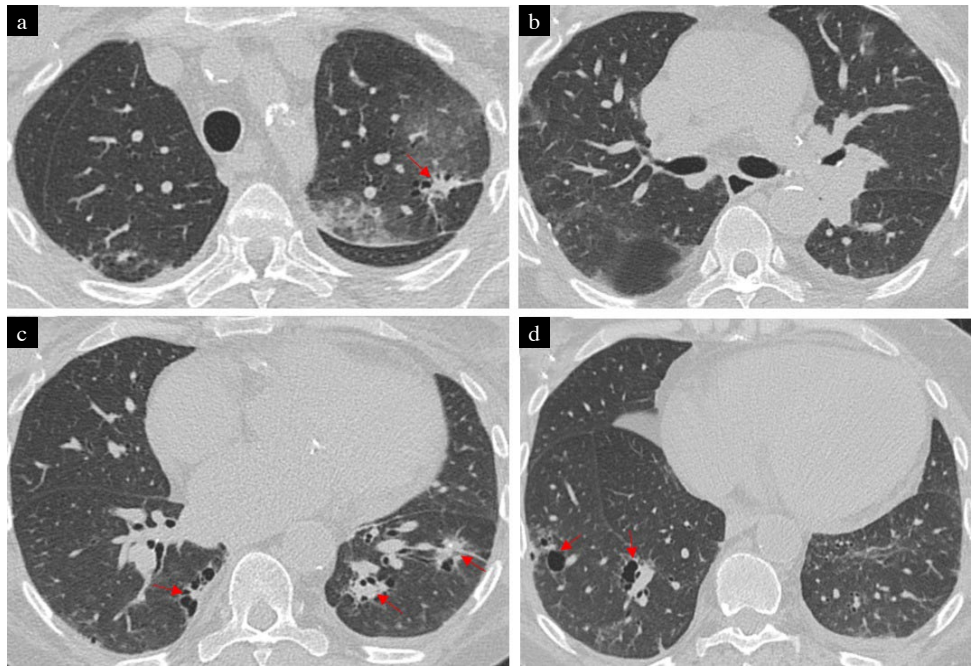


Figure 9. A 58-year-old female with pulmonary amyloidosis. **a-d)** Axial chest CT images show multifocal irregular pulmonary nodules with adjacent architectural distortion and cystic changes (arrows). Note the accompanying patchy ground-glass opacities and reticulations.

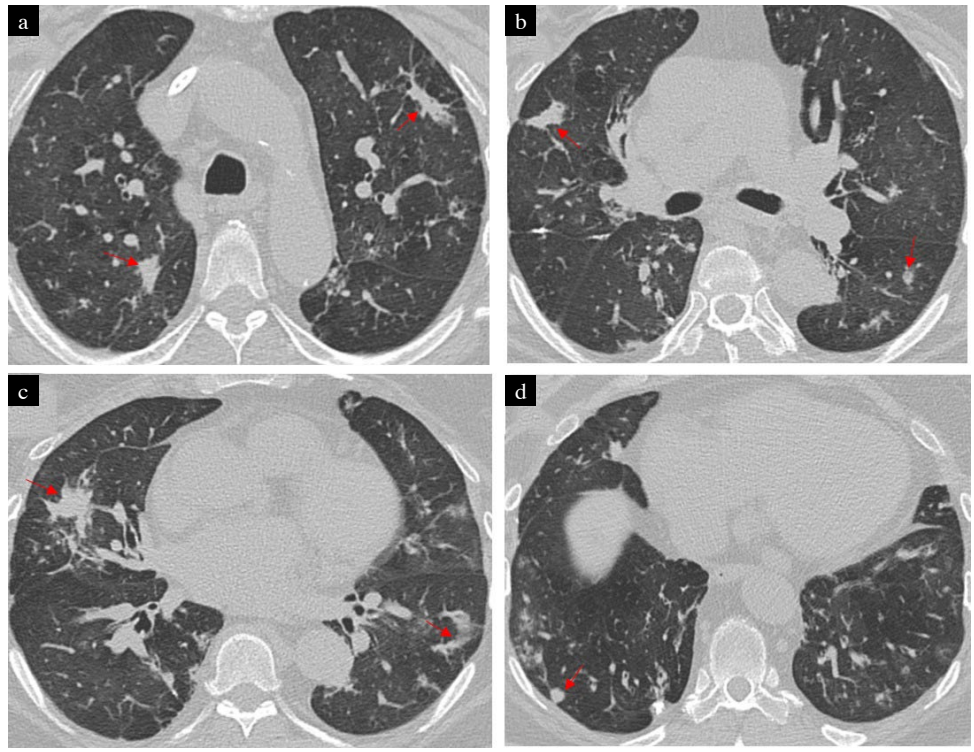


Figure 10. A 60-year-old female with IgG4-related lung disease. **a-d)** Axial chest CT images demonstrate multifocal irregular solid pulmonary nodules (arrows), diffuse bronchial wall thickening, scattered patchy ground-glass opacities, and diffuse pulmonary mosaicism.

and traction bronchiectasis.[37] Other notable findings include multifocal solid nodules, sometimes with spiculated or lobulated margins mimicking malignancy, as well as round GGOs and diffuse ground-glass patterns.[37-39] A less frequent but distinctive manifestation is fibrosing mediastinitis, where periaortic or paravertebral mediastinal soft tissue thickening may extend into structures like the pleura or pericardium.[39] Chest radiographs are often normal or reveal nonspecific findings. The key to accurate diagnosis lies in the combination of imaging patterns and histological confirmation of storiform fibrosis with IgG4 plasma cells.[37-39] Recognizing this radiological mosaic, especially in patients with appropriate serology or multisystem involvement, is critical to differentiate IgG4-RD from neoplastic, infectious, or fibrotic diseases.

Other Rare Causes of ILD

Rare multisystem diseases like Niemann-Pick disease (especially type B) can involve the lungs, manifesting on chest radiograph as a reticulonodular interstitial pattern and on chest CT as smooth interlobular and intralobular septal thickening, patchy GGOs, and occasionally crazy-paving pattern in lower lobes.[40,41] Niemann-Pick syndrome should be considered in children or young adults when smooth septal thickening is present in conjunction with hepatosplenomegaly. Differential considerations include Gaucher disease, which typically shows more prominent bone-marrow infiltration, hepatosplenomegaly, GGOs and reticulonodular opacities, and Erdheim-Chester disease, characterized by peri-aortic soft tissue encasement ("coated aorta" appearance).[42,43]

Desquamative interstitial pneumonia (DIP) variants, often linked to smoking or environmental exposures, are radiologically characterized by diffuse GGOs, usually in a basal and peripheral distribution. These can include subtle reticulation and small cysts in about one-third of cases; chest radiographs typically show faint hazy opacities.[7,44]

FUTURE PERSPECTIVES: ARTIFICIAL INTELLIGENCE (AI) AND LARGE LANGUAGE MODELS (LLMs)

Artificial intelligence (AI) is transforming diagnostic assessments in (ILD), with FDA-cleared tools (such as Brainomix's e-Lung and Imvaria's ScreenDx) now approved to quantify ILD extent on chest CT and flag suspected disease.[45,46] While these machine-learning models show promising correlations between lesion volume and pulmonary function decline, and can assist in prognosis stratification, current approvals remain limited to specific quantitative and screening functions. Many such systems are FDA-cleared under 510(k) or DeNovo pathways and are intended for adjunctive use only, not autonomous diagnosis. Moreover, maintenance of regulatory compliance involves rigorous pre-market validation and ongoing post-market oversight, such as FDA-mandated predetermined change control plans for evolving algorithms.[47] Deep learning techniques, ranging from convolutional neural networks to radiomics, can extract subtle imaging biomarkers beyond visual detection. Zero-shot or multimodal networks offer resistance against limited annotated datasets by generalizing across underrepresented ILD subtypes.[48,49] Yet, most are still in research phases and lack clearance for clinical deployment.

Large language models (LLMs) like GPT-4 can streamline report generation, extract structured findings, and suggest guideline-based follow-up. However, they are not FDA-cleared for diagnostic interpretation. Their use in clinical workflows remains predominantly for administrative and documentation support. Integration challenges include explainability, potential biases, data privacy concerns (e.g., HIPAA compliance), and the absence of robust regulatory pathways governing diagnostic decision-making AI systems.[50]

In summary, while AI and LLM tools offer considerable promise in enhancing radiologist efficiency and consistency in ILD assessment, they should currently be viewed as adjunctive aids, not replacements for clinical judgment. Their deployment demands careful navigation of regulatory constraints, validation requirements, and ethical considerations.

CONCLUSION

In conclusion, this section highlights key imaging features across rare ILDs and shows how these findings can help guide accurate diagnosis (Table 1). Looking ahead, future research should aim to validate advanced imaging biomarkers, apply AI tools to less common diseases, and combine genetic and molecular information into decision-support systems. These efforts will improve our understanding, reduce uncertainty, and support more personalized approaches to managing rare ILDs.

Table 1. The summary of key radiological findings in rare interstitial lung diseases.

Disease	Key Radiologic Features	Diagnostic Clues
Pulmonary Alveolar Proteinosis	Crazy-paving pattern (ground-glass opacities + septal thickening), sharply demarcated areas with adjacent clear lung	Mid-lower zone bat-wing opacities, minimal air bronchograms, preserved lung volumes
Pulmonary Alveolar Microlithiasis	Diffuse, dense micronodular calcifications ("sandstorm" appearance), septal and pleural calcifications, black pleura sign, subpleural cysts	Striking radiographic findings despite mild symptoms
Acute Silicosis (Silicoproteinosis)	Diffuse or posterior-predominant ground-glass opacities, centrilobular nodules (some calcified), patchy consolidation, crazy-paving (less consistent), mediastinal lymph node calcification	Rapid progression after silica exposure, history of intense occupational inhalation
Birt-Hogg-Dubé Syndrome	Multiple thin-walled cysts, basally and medially predominant, fusiform or lenticular shape, cysts abutting septa or mediastinum	Fewer cysts (<50), spontaneous pneumothorax, associated renal tumors and skin lesions
Lymphangioleiomyomatosis	Numerous, diffusely distributed thin-walled cysts of uniform size, preserved parenchyma, chylous effusions, mild GGO	Women of reproductive age, renal angiomyolipomas, elevated VEGF-D
Langerhans Cell Histiocytosis	Upper/mid-lung centrilobular nodules evolving to cavitated nodules and bizarre cysts, sparing of costophrenic recesses	Nodular-to-cystic progression, smoking history, spontaneous pneumothorax
Hermansky-Pudlak Syndrome	Basal-predominant reticulation, traction bronchiectasis, GGO, late-stage honeycombing	Oculocutaneous albinism, bleeding diathesis, young age
Familial Interstitial Pneumonias	UIP pattern (reticulation, honeycombing, traction bronchiectasis), possible NSIP features (GGO, subpleural sparing)	Family history, telomere syndromes, premature hair graying, liver/bone marrow dysfunction
Pulmonary Amyloidosis	Nodular (calcified nodules), tracheobronchial wall thickening/calcification, diffuse interstitial pattern (reticulation, septal thickening, GGO)	Known systemic amyloidosis, airway narrowing, histologic confirmation
IgG4-Related Disease	Peribronchovascular thickening, bronchial wall thickening, solid nodules, diffuse GGO, fibrosing mediastinitis	Elevated IgG4, multisystem involvement, storiform fibrosis
Niemann-Pick Disease (Type B)	Smooth septal thickening, patchy GGO, lower lobe crazy-paving	Hepatosplenomegaly, lipid storage disorder
Gaucher Disease	Diffuse GGO, septal thickening, small interstitial nodules, mosaic attenuation	Splenomegaly, bone involvement, enzyme deficiency
Desquamative Interstitial Pneumonia	Diffuse basal and peripheral GGO, subtle reticulation, occasional small cysts	Smoking history, macrophage-rich alveolar filling, mild symptoms

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CHAPTER 03

PULMONARY ALVEOLAR PROTEINOSIS

PULMONER ALVEOLER PROTEİNOZİS

Dr. Nazlı Çetin

PULMONARY ALVEOLAR PROTEINOSIS

PULMONER ALVEOLER PROTEİNOZİS

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ABSTRACT

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by surfactant accumulation within the alveoli, leading to impaired gas exchange and, in severe cases, respiratory failure. Once regarded as idiopathic, PAP is now classified into autoimmune, secondary, hereditary, and congenital forms based on distinct underlying mechanisms. Autoimmune PAP (aPAP), the most common type, is mediated by GM-CSF autoantibodies that impair macrophage-mediated surfactant clearance. Secondary PAP is typically associated with hematologic malignancies or environmental exposures, while hereditary and congenital types result from genetic defects affecting surfactant metabolism or GM-CSF receptor function.

Despite a shared histopathological hallmark, clinical manifestations are heterogeneous, ranging from asymptomatic cases to progressive dyspnea and hypoxemic respiratory failure. Diagnosis relies on clinical suspicion supported by characteristic radiological findings, bronchoalveolar lavage (BAL) cytology, and GM-CSF autoantibody testing. High-resolution CT often reveals the classic "crazy paving" pattern, while milky BAL fluid with PAS-positive material is considered diagnostic in the appropriate clinical context.

Whole lung lavage (WLL) remains the cornerstone of treatment, particularly for symptomatic patients, and is strongly recommended in current guidelines. Inhaled GM-CSF has emerged as an effective and noninvasive alternative for aPAP, with support from randomized controlled trials. Other options, such as rituximab, plasmapheresis, or lung transplantation, may be considered in refractory cases. For secondary and congenital PAP, no standardized treatment exists, and management primarily focuses on treating the underlying condition and providing supportive care.

Prognosis varies depending on PAP subtype, disease severity, and treatment response. While spontaneous remission can occur, close follow-up is essential due to the risks of respiratory failure, infections, and, in rare cases, fibrosis. Advances at the molecular level, novel therapies targeting cholesterol homeostasis and macrophage function, and the expansion of international registries and PAP centers are expected to improve diagnosis, treatment, and outcomes for this complex disease, while also enhancing patient access to specialized care.

Keywords: *Autoimmune PAP; Crazy paving; GM-CSF; Pulmonary alveolar proteinosis; Surfactant; Whole lung lavage*

ÖZET

Pulmoner alveoler proteinozis (PAP), alveoller içinde sürfaktan birikimi ile karakterize nadir bir sendromdur. Surfaktan metabolizmasındaki bozukluklar ya da artmış sürfaktan üretimi sonucu gelişen bu durum gaz değişimini bozar ve ileri vakalarda solunum yetmezliğine yol açabilir. Başlangıçta idiopatik olarak tanımlanan PAP, günümüzde altta yatan mekanizmalara göre primer (otoimmün ve kalıtsal), sekonder ve konjenital formlar olarak sınıflandırılmaktadır. En yaygın form olan otoimmün PAP (aPAP), makrofaj aracılı surfaktan temizliğini bozan GM-CSF otoantikorları aracılığıyla gelişir. Sekonder PAP genellikle hematolojik maligniteler veya çevresel maruziyetlerle ilişkilidirken, kalıtsal ve konjenital formlar surfaktan metabolizması ya da GM-CSF reseptör fonksiyonunu etkileyen genetik bozukluklara bağlıdır.

Histopatolojik özellikler benzer olsa da klinik bulgular oldukça değişkendir. Hastalar asemptomatik

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olabileceği gibi ilerleyici dispne ve hipoksemik solunum yetmezliği ile başvurabilirler. Tanı, klinik şüpheye ek olarak karakteristik radyolojik bulgular, bronkoalveoler lavaj (BAL) sitolojisi ve GM-CSF otoantikor testleriyle konur. Yüksek çözünürlüklü BT'de tipik olarak alveoler dolum ile ilişkili buzlu cam dansitelerine intralobüler ve interlobüler septaların eşlik ettiği "çılgın kaldırım taşı" (crazy paving) paterni görülür. PAS pozitif materyal içeren sütlü BAL sıvısı, uygun klinik bağlamda tanısal kabul edilir.

Belirgin semptomları olan hastalarda, güncel kılavuzların da güçlü önerisiyle, tüm akciğer lavajı (TAL) temel tedavi yöntemidir. Otoimmün PAP'ta, randomize kontrollü çalışmalarla desteklenen inhaler GM-CSF, etkili ve invaziv olmayan bir tedavi seçeneği olarak öne çıkmaktadır. Rituksimab, plazmaferez veya akciğer nakli gibi diğer tedaviler, dirençli olgularda düşünülmektedir. Sekonder veya konjenital PAP için standart bir tedavi bulunmamaktadır. Bu nedenle yönetim, gerektiğinde TAL ile altta yatan nedenin tedavisi ve destekleyici bakıma odaklanır.

PAP'ın prognozu alt tip, hastalık şiddeti ve tedavi yanıtına göre değişkenlik gösterir. Bazı olgularda spontan remisyon görülebilir; ancak solunum yetmezliği, enfeksiyonlar ve nadiren de olsa fibrozis riski nedeniyle yakından izlem önemlidir. Moleküler düzeydeki gelişmeler, kolesterol homeostazı ve makrofaj fonksiyonunu hedefleyen yeni tedaviler, uluslararası kayıtların ve PAP merkezlerinin yaygınlaşması karmaşık hastalığın tanı, tedavi ve sonuçlarını iyileştirmeye, hastaların uzmana ulaşımını artırmaya katkı sağlayacaktır.

Anahtar Kelimeler: *GM-CSF; Otoimmun PAP; Pulmoner alveoler proteinozis; Sürfaktan; Total akciğer lavajı*

CASE PRESENTATION

A 47-year-old woman presented to the outpatient clinic in respiratory distress. She had no known chronic medical conditions but reported progressively worsening shortness of breath over the past six months. Initially, dyspnea occurred only during long walks or while climbing inclines, but more recently it had begun to occur indoors and even during conversation. A newly developed productive cough with sticky sputum was also noted. She had initially sought care at a local health center where she was treated for presumed acute bronchitis. Later, she was diagnosed with asthma and prescribed inhaler therapy. However, her symptoms persisted, and a thoracic computed tomography (CT) performed at another facility revealed abnormalities that prompted referral to a tertiary center.

The patient, with no significant history of occupational exposure, had been engaged in embroidery work at home for the past year. She had a history of smoking 22.5 pack.years, which she quit two months prior to presentation. On physical examination, she was visibly dyspneic, with peripheral cyanosis and digital clubbing. Inspiratory crackles were audible beneath the left scapula on auscultation. Her oxygen saturation on room air was 81%, and her pulse was 110 bpm. Recent chest CT imaging showed a diffuse alveolar pattern (Figure 1). Flexible bronchoscopy was performed, and bronchoalveolar lavage fluid (BALF) had a characteristic milky appearance. Cytological examination demonstrated strong periodic acid–Schiff (PAS) positivity, consistent with a diagnosis of pulmonary alveolar proteinosis (PAP). Despite supplemental oxygen, her saturation could only be maintained at 90%, and her respiratory distress persisted. Whole-lung lavage (WLL) was indicated; however, the nearest center where the procedure could be performed was 470 km away. The patient, unwilling to travel, insisted on receiving treatment locally.

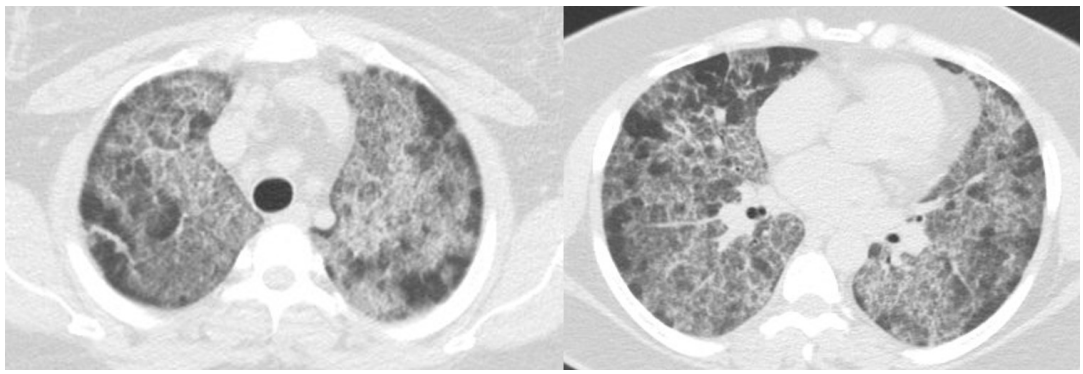


Figure 1. High-resolution computed tomography (HRCT) image demonstrating widespread interlobular septal thickening accompanied by diffuse ground-glass opacities in both lungs, resulting in the characteristic "crazy paving" pattern.

"I wasn't disturbed when I was first diagnosed with asthma as an explanation for the shortness of breath I was experiencing. Asthma was a condition I had heard about, something I roughly understood. But then I was told that I actually had alveolar proteinosis, and my world fell apart. Learning that I had a disease I had never even heard of was far more unsettling than having asthma. Especially because of all the uncertainties…"

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a syndrome characterized by the accumulation of surfactant within the alveoli, which can progress to respiratory failure.[1,2] The term syndrome is preferred over disease because of the substantial heterogeneity in its underlying mechanisms, clinical manifestations, and natural history.

In 1958, Rosen, Castleman, and Liebow published a report describing 27 cases in which periodic acid-Schiff (PAS)-positive lipoproteinaceous material was found within the alveoli. This seminal work defined PAP as a clinicopathological entity for the first time. While the authors described typical findings of progressive dyspnea and radiographic alveolar infiltrates, they were unable to identify a clear underlying mechanism, as no evidence of inflammation, fibrosis, or neoplasia could be demonstrated.[1] Although hypotheses related to infections, lipid metabolism disorders, and environmental exposures were later proposed, the etiology remained elusive for decades. In the 1990s, experimental models mimicking PAP led to a major breakthrough in our understanding of the disease. These studies identified the crucial role of granulocyte–macrophage colony-stimulating factor (GM-CSF) in surfactant homeostasis and clearance, providing the first mechanistic insights into PAP pathogenesis.[3]

In the early 2000s, what had previously been considered idiopathic PAP was reclassified as autoimmune PAP (aPAP) following the identification of GM-CSF autoantibodies in bronchoalveolar lavage fluid (BALF) from affected individuals, but not in healthy controls or patients with other respiratory diseases.[4] Although autoimmune PAP is now known to account for the majority of cases, other PAP subtypes have been described in association with hematologic malignancies (especially myelodysplastic syndromes), inhalational exposures (such as silica, titanium, and aluminum dust), and immunosuppressive therapies.[5-12] The increasing availability of genetic studies in the 2000s also led to the identification of mutations affecting surfactant homeostasis. These discoveries enabled recognition of two distinct hereditary forms of PAP: one due to impaired surfactant clearance and another due to abnormal surfactant production, now classified as congenital PAP.[13-15] Today, PAP is no longer regarded as a single disease, but rather as a syndrome defined by a shared histopathological hallmark, alveolar surfactant accumulation, with diverse etiologies. Based on underlying mechanisms, PAP is broadly classified into primary (autoimmune and hereditary), secondary, and congenital forms.[16]

In this chapter, PAP will be reviewed in light of current evidence, with an emphasis on evolving pathophysiological insights and corresponding therapeutic approaches. The case presented at the beginning of the chapter will be revisited to illustrate key diagnostic and management principles.

EPIDEMIOLOGY

As with many rare diseases, epidemiological data on PAP are limited. In the 1990s, the estimated prevalence was 1-3 cases per million, whereas more recent cohort studies have reported a prevalence of 6-7 cases per million individuals.[17-19] Although numerous publications have addressed PAP since its initial description, the majority of earlier reports consisted of case presentations or small case series.[2] Recent cohort studies from the United States and Japan have contributed to the understanding of PAP epidemiology, though it has been emphasized that diagnostic delays may limit the accuracy of frequency estimates.[18,19] To date, no significant global or sociodemographic differences have been identified in the prevalence of the disease. PAP affects both children and adults across all ages, ethnicities, and geographical regions. The disease appears to occur independently of socioeconomic status.[16] However, a recent population-based study from Korea reported a PAP prevalence of 4.4 per million, with a higher mean age at diagnosis and a lower male-to-female ratio compared to Western populations. These findings suggest that ethnicity may influence certain demographic features of PAP.[20] Among environmental risk factors, cigarette smoking and silica dust exposure are the most commonly reported associations. Additional exposures include biomass smoke, nitro-

gen dioxide, organic and inorganic dusts, aluminum, cellulose fibers, titanium dioxide, and indium-tin oxide. However, most of these exposures have been reported in isolated case reports or small series.[2,12,21-23] Following the recognition of anti-GM-CSF autoantibodies and the classification of aPAP, it has become clear that aPAP accounts for more than 90% of all PAP cases.[18,19] Secondary PAP accounts for 5-10% of cases, while hereditary PAP is responsible for less than 1%.[19,24,25] In a U.S. cohort study, congenital PAP due to mutations in surfactant production genes was reported in approximately 1.5% of patients, whereas no such cases were identified in the Japanese cohort.[18,19]

Studies investigating mutations associated with congenital PAP have reported widely varying estimates. For example, ABCA3 (ATP-binding cassette subfamily A member 3) deficiency is estimated to occur in approximately 1 in 3,000 live births annually, whereas SP-B (surfactant protein B) deficiency is estimated at 1 in 1.7 million.[26]

Although various disorders are thought to impair the number or function of alveolar macrophages in secondary PAP, the most common cause is hematological disease, particularly myelodysplastic syndromes.[16,24,27]

PATHOGENESIS

Surfactant plays a vital role in healthy lung function. It reduces surface tension by forming a lipid-rich film along the alveolar lining, thereby preventing alveolar collapse (atelectasis) and reducing the work of breathing. In addition, surfactant contributes to pulmonary host defense by modulating the immune response to inhaled pathogens.[28]

The substance known as lipoproteinaceous material, i.e., pulmonary surfactant, consists of approximately 80% polar phospholipids (primarily saturated phosphatidylcholine and, to a lesser extent, other phospholipids), 10% neutral lipids (including free cholesterol, triglycerides, and free fatty acids), and 10% surfactant proteins (SP-A, SP-B, SP-C, and SP-D).[29] Both deficient surfactant production and impaired surfactant clearance can result in significant lung pathology. In PAP, abnormal accumulation of surfactant in the alveoli occurs due to overproduction and/or inadequate clearance.[1,2]

Surfactant homeostasis depends on a delicate balance involving adequate production, secretion into the alveolar space, and either recycling or catabolism. Type II alveolar epithelial cells are responsible for production, secretion, and partial reuptake, while alveolar macrophages play a key role in the clearance of excess surfactant from the alveolar space.[16] Disruption of any part of this cycle can lead to PAP, and the classification of PAP is based on the underlying site and mechanism of dysfunction.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine produced by type II alveolar epithelial cells. Named for its ability to stimulate neutrophil and macrophage colony formation, GM-CSF binds to specific cell surface receptors and activates intracellular signaling pathways. These include Janus kinase 2 (JAK2) and signal transducer and activator of transcription 5 (STAT5), ultimately promoting the terminal differentiation and functional maturation of alveolar macrophages.[30-33]

GM-CSF also plays a constitutive, dose-dependent, and reversible role in regulating cholesterol efflux from alveolar macrophages. In experimental models of impaired GM-CSF signaling, the primary defect in lipid metabolism was not in surfactant phospholipid degradation, but rather in the markedly reduced ability of macrophages to efflux cholesterol, resulting in an increased cholesterol-to-phospholipid ratio in lung surfactan.[16,34] The mechanistic links between disrupted GM-CSF signaling and PAP have been extensively reviewed by Trapnell et al.[16]

In relation to pathogenesis, PAP has three cathegories, as mentioned above: Primary, secondary and congenital.

Primary PAP

Most cases of PAP are due to impaired surfactant clearance, typically resulting from defective GM-CSF signaling, which leads to functional impairment of alveolar macrophages and neutrophils. This category is collectively referred to as primary PAP.

- In aPAP**,** neutralizing autoantibodies against GM-CSF block surfactant clearance by interfering with macrophage maturation.
- In hereditary PAP, mutations in the genes encoding the alpha or beta chains of the GM-CSF receptor (CSF2RA or CSF2RB) impair GM-CSF signaling at the receptor level.

Autoimmune PAP

A landmark discovery demonstrated that injecting

GM-CSF autoantibodies isolated from PAP patients into non-human primates reproduced PAP features.[35] Subsequent studies confirmed that GM-CSF autoantibody levels are elevated in patients with autoimmune PAP but not in individuals with secondary, congenital, or hereditary PAP, nor in healthy controls.[36,37] However, since low levels of GM-CSF autoantibodies may also be detected in healthy individuals, a diagnostic cutoff of ≥10.2 μg/mL has been established, offering 100% sensitivity and specificity for the diagnosis of aPAP.[36,38-40] Importantly, no correlation has been found between antibody levels and disease severity or activity.[41]

These autoantibodies are polyclonal IgG, primarily of the IgG1 and IgG2 subclasses, and bind multiple distinct epitopes on the GM-CSF molecule. They neutralize GM-CSF effectively at concentrations exceeding physiological levels. Notably, therapeutic monoclonal anti-GM-CSF antibodies, used in the treatment of autoimmune diseases such as rheumatoid arthritis, have not been associated with the development of PAP in any patient, despite large treatment cohorts.[42] This supports the notion that the polyclonal nature of GM-CSF autoantibodies in aPAP reflects a complex and broadly targeted immune response, involving the use of multiple immunoglobulin variable region (V) genes.[16,43]

Furthermore, the targeting of multiple, non-overlapping epitopes suggests that the immune response in aPAP is not the result of cross-reactivity with a foreign antigen, but rather a primary response directed against GM-CSF itself.[44]

Hereditary PAP

Hereditary PAP is caused by mutations in the genes encoding the alpha or beta subunits of the GM-CSF receptor (CSF2RA or CSF2RB), and it is inherited in an autosomal recessive pattern.[15,45,46] Although relatively few cases have been reported in the literature, clinical presentation typically occurs during early childhood, although asymptomatic or late-onset cases have also been described. Although most patients are diagnosed in childhood, there are cases of hereditary PAP in young adults.[13,14,47-49]

In a study evaluating nine children with CSF2RA mutations from the Kids Lung Register, early-onset disease was associated with a more severe clinical phenotype. However, no clear correlation was found between initial disease severity and long-term prognosis or genotype severity.[14] Interestingly, even among family members with identical mutations, clinical presentation varied, suggesting that additional genetic or environmental modifiers may influence disease expression.[13,50]

Secondary PAP

Although the mechanisms by which surfactant accumulates in the alveoli in secondary PAP are not fully understood, the condition is believed to be associated with a reduction in the number and/or function of alveolar macrophages due to underlying diseases or exposures.[16] Supporting this, animal models in which alveolar macrophages were chemically depleted demonstrated marked surfactant accumulation in the alveoli.[51]

Since secondary PAP is rare, most data are derived from case reports and small case series.[7,8,10,52-54] In these reports, hematologic disorders, particularly myelodysplastic syndromes, are the most frequently identified underlying cause, accounting for approximately 75% of cases.[11,55] In a case series and literature review by Zhang et al. (2018), secondary PAP was attributed to hematologic malignancy in 70% of patients, followed by solid organ transplantation (10.4%), infections (7.9%; including M. tuberculosis, nontuberculous mycobacteria, HIV, and *Aspergillus*), autoimmune diseases (6.7%), non-hematologic malignancies, and dust exposure.[11]

In hematologic diseases, PAP may result from impaired phagocytic clearance due to profound leukopenia or disrupted immune function secondary to hypergammaglobulinemia.[5] A case of PAP in a patient with myelofibrosis was diagnosed following the development of respiratory symptoms shortly after initiation of ruxolitinib, with symptom improvement upon discontinuation of the drug, highlighting the potential role of medications in PAP pathogenesis in rare hematologic conditions.[56]

In malignancy, the disease process or cytotoxic chemotherapy may impair immune cell function and distribution, thereby disrupting pulmonary phagocytic clearance and promoting PAP development.[57] One report described coexisting metastatic melanoma and PAP in a surgical lung biopsy specimen, suggesting that altered macrophage function in the setting of progressive malignancy may play a role in surfactant accumulation.[8]

PAP has also been reported in association with immunosuppressive therapy. The use of mTOR inhibitors (e.g., everolimus, sirolimus), commonly prescribed after solid organ transplantation, has been implicated in PAP development, with improvement following drug withdrawal.[58,59]

Infections may also impair macrophage function and lead to secondary PAP. Tuberculosis is the most frequently reported infectious trigger.[11] However, because infections such as *M. tuberculosis*, *Nocardia*, and *Aspergillus* may develop in patients with existing PAP, distinguishing infection as a precipitating factor versus a complication can be challenging.[60] In such cases, measurement of GM-CSF autoantibody levels may help distinguish autoimmune from secondary forms.

Among environmental exposures, silica is the most well-established risk factor.[21] Experimental animal studies have shown that silica disrupts surfactant homeostasis.[61,62] Although acute silicoproteinosis may occur after intense exposure, cases have become increasingly rare due to improved awareness and occupational protection measures.[16,63] In a cohort of 70 patients, Bonella et al. reported that 90% had autoimmune PAP and 54% had a history of dust exposure, including not only silica but also aluminum and sawdust.[64] A more comprehensive discussion of this rare condition is provided in another chapter of the current book.

Due to the absence of large registries, current data remain limited, and most reports are based on individual cases. Exposures to titanium, cadmium, fiberglass insulation, and other inhaled substances have also been linked to PAP.[12,22,65,66] Although toxic inhalation is a recognized cause of secondary PAP, it may also trigger autoimmunity. For example, in one case of PAP with occupational exposure to cement and paint, elevated GM-CSF autoantibody levels suggested toxic inhalation–induced autoimmune PAP.[67]

Two workers exposed to indium–tin oxide in a manufacturing plant were diagnosed with PAP; one case was fatal, and indium was detected in lung tissue. Both patients had elevated GM-CSF autoantibody levels.[23] In a Japanese autoimmune PAP cohort, 26% of patients reported dust exposure, supporting a possible link between inhalational exposure and autoimmunity.[18] As awareness increases and GM-CSF autoantibody testing becomes more widespread, it is anticipated that the heterogeneity of secondary PAP will diminish through improved classification.[68]

Congenital PAP

Congenital PAP is associated with mutations in genes encoding surfactant proteins, SFTPB and SFTPC (encoding surfactant protein B and C, respectively), as well as genes involved in surfactant metabolism, such as ABCA3 (encoding ATP-binding cassette subfamily A member 3), and transcriptional regulators such as NKX2-1 (encoding thyroid transcription factor 1, TTF1). Histopathological examination of lung tissue from affected infants often reveals alveolar accumulation of eosinophilic, lipoproteinaceous granular material and associated fibrosis.[69-71] Although congenital PAP typically presents in infancy or early childhood with severe and sometimes fatal respiratory failure, later-onset forms with milder symptoms have also been described. The genetic basis, clinical spectrum, and molecular mechanisms of congenital PAP have been extensively reviewed by Trapnell et al.[16]

CLINICAL MANIFESTATIONS

Despite a shared histopathological hallmark, the clinical presentation of PAP is highly variable. This variability reflects differences in the underlying cause, classification subtype, and, where applicable, the specific gene mutation and its zygosity. While it is difficult to generalize the clinical features across all types of PAP, cohort studies composed mostly of aPAP cases suggest that the disease most commonly presents in adults aged 40-50 years, with a male predominance and a high prevalence of smoking history.[2,18,20]

Although some cases are diagnosed incidentally during routine health screening in asymptomatic individuals, most patients present with progressive exertional dyspnea. Accompanying symptoms may include cough**,** sputum production**,** fatigue**,** and weight loss. Cough is often dry, but gelatinous sputum may occur. Symptoms such as fever**,** chest pain**,** and hemoptysis are typically associated with superimposed infections or underlying hematologic or malignant disease. The extent of alveolar filling and overall disease severity may result in hypoxemic respiratory failure. In addition to impaired gas diffusion, intrapulmonary shunting due to blood flow through non-ventilated alveoli may contribute to refractory hypoxemia.[72]

Symptoms generally have an insidious onset, and

many patients report prolonged periods of illness before a definitive diagnosis is made.[18,25,64] In contrast, patients with congenital PAP (particularly those with deleterious mutations) or PAP secondary to hematologic diseases may present with acute respiratory deterioration, potentially progressing to respiratory failure and death.[16]

Physical examination is often unremarkable. Bilateral, nonspecific crackles may be audible on auscultation. Notably, despite extensive radiological involvement, breath sounds may appear normal. This may be attributed to reduced alveolar ventilation caused by intra-alveolar accumulation of material, which prevents the generation of pathological sounds typically originating from the alveolar regions. Digital clubbing and peripheral or central cyanosis are reported in approximately 25-30% of cases.[2,18,73]

DIAGNOSIS

Diagnosis of PAP is challenging due to its rarity, nonspecific symptoms, subtle physical findings, and variable clinical course. Limited awareness among clinicians further contributes to delayed recognition. A detailed clinical history, systematic physical examination, and appropriate radiological assessment are key to raising clinical suspicion. Routine laboratory investigations are generally unremarkable and do not provide specific diagnostic markers. Hematological abnormalities may suggest an underlying hematologic disorder and prompt further evaluation.

In patients with compatible clinical and radiological findings, bronchoalveolar lavage (BAL) can often establish the diagnosis. When typical BAL findings are absent, more invasive procedures, such as lung biopsy, may be required.[74]

Laboratory Findings

Routine blood tests in PAP are typically within normal limits. Although nonspecific, elevated lactate dehydrogenase (LDH) is found in approximately half of patients.[2] A number of nonspecific biomarkers have been explored for their potential association with disease severity, including:

- Tumor markers: Carcinoembryonic antigen (CEA), Carbohydrate antigen 19-9 (CA 19-9), CYFRA 21-1, and neuron-specific enolase (NSE)
- Lung epithelium-derived proteins: Mucin, KL-6, SP-A, SP-B, and SP-D
- Inflammatory mediators: Chemokines (e.g., CCL-2) and chitinase 3-like protein 1 (YKL-40)

Although these markers show correlation with disease severity, further research is needed to validate their diagnostic and prognostic utility.[75]

Radiological Features

Initial radiological evaluation in suspected PAP cases is typically performed with a chest X-ray, which often reveals bilateral alveolar opacities predominantly in the mid-to-lower zones with a perihilar distribution, producing the characteristic "bat-wing" appearance.[76] (Figure 2). A normal chest X-ray does not exclude the

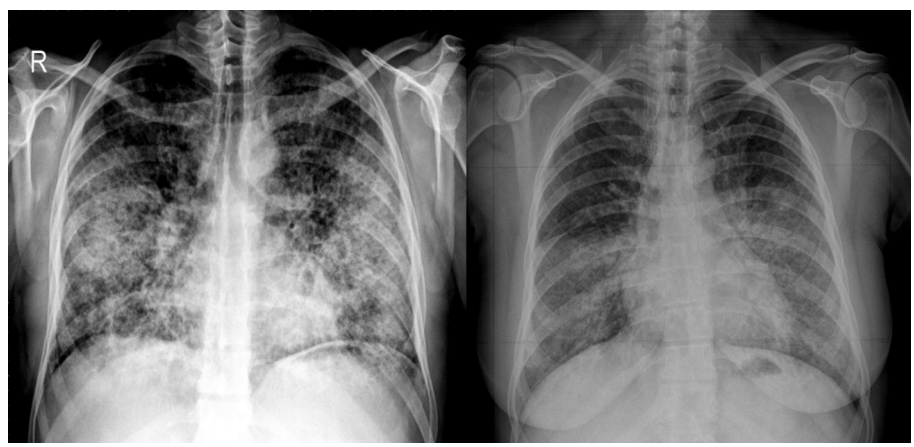


Figure 2. Bilateral alveolar opacities resembling "bat-wing" patterns are observed in both chest radiographs, predominantly in the mid-to-lower lung zones and perihilar regions, with varying degrees of involvement.

diagnosis, nor are bilateral opacities specific to PAP. Therefore, additional imaging is usually required, and high-resolution computed tomography (HRCT) frequently provides essential diagnostic clues.[16]

The hallmark finding on HRCT is ground-glass opacities resulting from alveolar filling. These are usually bilateral and often accompanied by thickened intra- and interlobular septa, forming a polygonal pattern that resembles cobblestone pavement, a radiological pattern known as "crazy paving".[76-78] Although initially described in PAP, crazy paving is not pathognomonic and may also be seen in a wide range of other pulmonary conditions.[76] Subpleural sparing, when present, is considered a supportive feature, although it is not universally observed.[76] Rarely, interstitial patterns**,** nodules**,** or fibrotic changes may be noted on imaging.[77]

In secondary PAP, isolated ground-glass opacities are more common, while the crazy paving pattern and subpleural sparing are less frequently observed.[55,79]

Despite the relatively well-characterized imaging features of PAP, they are not specific, and a comprehensive differential diagnosis should be considered. Similar findings may occur in Pneumocystis jirovecii pneumonia, mycobacterial infections, COVID-19, pulmonary edema, lipoid pneumonia, acute eosinophilic pneumonia, acute interstitial pneumonia, alveolar hemorrhage, drug-induced lung disease, and pulmonary adenocarcinoma.[80] In such cases, clinical context, supporting laboratory findings, and BALF analysis are critical for differentiation.

Radiological overlap with infectious diseases may also complicate the interpretation in patients already diagnosed with PAP, potentially leading to unnecessary infection diagnoses or precautionary measures. During the COVID-19 pandemic, radiologic similarities contributed to delays in referral and challenges in performing whole-lung lavage (WLL) for some patients.[81]

Pulmonary Function Tests

Pulmonary function tests (PFTs) may be normal in the early or mild stages of PAP. However, findings typically resemble those of other interstitial lung diseases, with a restrictive ventilatory defect characterized by reductions in forced vital capacity (FVC) and total lung capacity (TLC).[2,18] Diffusing capacity for carbon monoxide (DLco) is frequently decreased and correlates with disease severity.[2] Notably, a decline in DLco has been observed even in patients with normal spirometry.[55]

The alveolar-arterial oxygen gradient, which reflects impaired gas exchange at the alveolar level, is typically increased and is considered a reliable indicator of disease severity.[2] Resting hypoxemia and exercise-induced oxygen desaturation are also important parameters, particularly in guiding therapeutic decision-making.[1,2,24]

Bronchoalveolar Lavage (BAL)

Following clinical and radiological assessment, bronchoscopic procedures, particularly bronchoalveolar lavage (BAL), represent a key diagnostic step in patients with suspected PAP. BAL allows for sampling of the cellular and acellular components of distal airways and alveoli with relatively low risk and technical simplicity.[82]

Macroscopically, BALF often appears milky and opaque, with visible sediment, findings considered highly suggestive of PAP. Cytological examination typically reveals the following features:[16,82]

- Acellular globules that appear basophilic with May-Grünwald-Giemsa or periodic acid–Schiff (PAS) staining
- Foamy alveolar macrophages that appear red with oil-red-O staining
- Abundant cellular debris weakly staining with PAS.

When clinical and radiologic findings are consistent and accompanied by typical BALF features, a definitive diagnosis of PAP can be made.[83] Although open lung biopsy was once considered the diagnostic gold standard, its necessity has declined over time.[2]

In patients undergoing bronchoscopy, transbronchial lung biopsy (TBLB) from a different segment may provide additional diagnostic yield. However, a significant proportion of patients are diagnosed with BAL alone, estimated at 75% in a 2002 review and 83% in a 2011 cohort of 70 patients.[2,64] In a more recent study of 150 patients by Azuma et al., BAL alone was diagnostic in 90.7%, and when combined with TBLB, the yield increased to 98.8%.[84]

Beyond diagnosis, BAL plays a crucial role in detecting secondary infections, which are associated with worse prognosis and increased mortality. Oppor-

tunistic infections, including Nocardia, mycobacteria, and fungi, should be specifically investigated, and BALF should be sent for both cytological and microbiological analysis.[74,83]

In the 2024 ERS guideline, BAL is recommended as the initial diagnostic step in suspected PAP. Depending on the results, further testing, including serum GM-CSF autoantibodies**,** genetic analysis, and additional laboratory studies, may be pursued. Lung biopsy is reserved for cases with inconclusive findings and is not recommended for routine diagnosis due to its higher complication risk and limited value in patchy disease distribution.[83]

GM-CSF Autoantibody Testing

In confirmed PAP cases, or in patients with suspected PAP in whom BAL is inconclusive or cannot be performed, the next step is testing for GM-CSF autoantibodies. A serum GM-CSF autoantibody concentration of ≥10.2 μg/mL is 100% sensitive and specific for the diagnosis of aPAP.[36,83] It is critical to report the concentration, not merely the presence of the antibody.[83]

As a blood test, it is easy to perform and can eliminate the need for lung biopsy.[36,83] Understanding the role of GM-CSF in PAP pathogenesis has also led to the development of inhaled GM-CSF therapy, making this test valuable not only for diagnosis but also for guiding treatment. As a result, many experts now recommend serum GM-CSF autoantibody measurement as the first-line test in suspected PAP. However, its availability is limited to a few laboratories worldwide, which restricts its use. Establishing international collaborations with PAP centers is essential to overcoming this limitation.

Additional Diagnostic Tests

In PAP patients with negative GM-CSF autoantibody results, the next step is evaluation for secondary causes.[83] Secondary PAP has a distinct clinical profile and worse prognosis compared to primary or congenital forms. In particular, hematologic disorders associated with secondary PAP carry a higher risk of opportunistic infections and shorter survival.[11] Recognizing the underlying disease is crucial, especially when patients with hematologic disorders present with new respiratory symptoms.

If a causative condition is identified, the case is classified as secondary PAP. If no secondary cause is found, hereditary or congenital forms should be considered. In such cases, serum GM-CSF levels should be measured. Elevated serum GM-CSF, along with impaired signaling, indicates receptor dysfunction, and genetic testing for CSF2RA and CSF2RB mutations confirms hereditary PAP.[46,47,83]

In patients with normal GM-CSF levels, genetic testing for surfactant protein gene mutations (SFTPB, SFTPC, ABCA3, NKX2-1) should be performed to diagnose congenital PAP.[83]

In a small subset of patients where diagnosis remains inconclusive despite exhaustive testing, surgical lung biopsy may be considered. If the histopathology is consistent with PAP but classification remains unclear, the condition is designated as unclassifiable PAP.[83]

TREATMENT

Management of PAP varies depending on disease severity and underlying etiology. The treatment spectrum ranges from watchful waiting in asymptomatic autoimmune PAP patients, to pharmacological, genetic, or cell-based therapies targeting disease pathogenesis in some primary or secondary PAP forms, and even to lung transplantation in cases progressing to end-stage respiratory failure.

Patients who are asymptomatic or mildly symptomatic, without physiological impairment or with only mild hypoxemia, do not require urgent intervention. These patients can be managed through periodic reassessment of symptoms, oxygen saturation monitoring, pulmonary function tests, and imaging when necessary. Spontaneous remission has been reported in this group.[85,86] For patients with moderate to severe symptoms or respiratory failure, the mainstay of treatment since the disease was first described has been the WLL, which aims to physically remove the accumulated material from the alveolar space. Treatment goals include symptom control, improved oxygenation, and enhanced quality of life.[16]

All patients should receive supportive care similar to that for other chronic lung diseases, including vaccination, smoking cessation counseling, and long-term oxygen therapy when indicated.[85] While evidence on the efficacy of pulmonary rehabilitation (PR) in PAP is limited, its safety and feasibility make it a promising area for further research. A case of a PAP patient who benefited from PR is discussed in another chapter in this book, focusing on PR in rare ILDs.

Whole Lung Lavage (WLL)

Although procedural modifications and variations exist, the fundamental principle of WLL involves repetitive instillation and drainage of warmed saline until the accumulated lipoproteinaceous material is removed from the alveoli.[87,88]

Indications for WLL include moderate-to-severe symptoms, desaturation at rest, exertional dyspnea limiting daily activities, arterial hypoxemia or an alveolar-arterial oxygen gradient >40 mmHg, and progressive parenchymal abnormalities on CT.[74] Although treatment of the underlying cause is the priority in secondary PAP, WLL can be performed in all symptomatic patients, both children and adults.[14,75,83] Perioperative preparation and anticoagulant management are similar to those for bronchoscopy. General contraindications include cardiac instability and uncorrectable coagulopathy. WLL should not be performed in the presence of active pulmonary infection due to the risk of widespread infection, sepsis, and shock.[89]

The procedure is performed under general anesthesia with double-lumen intubation. While one lung is ventilated, warmed saline is instilled into the non-ventilated lung and drained passively through a closed circuit (Figure 3). The more severely affected lung is typically targeted first. Proper tube positioning must be confirmed and secured. Although various patient positions have been proposed, the supine position is most commonly used and considered safest.[40]

During the procedure, the patient's position may be slightly adjusted (e.g., Trendelenburg positioning), and percussion maneuvers are often applied, manually or using external devices like a surgical wrap or chest vest.[89,90] The lavage usually involves instilling 500-1000 mL of saline per cycle. After saline is instilled into the lung (typically visible as backflow in the endotracheal tube), passive drainage is initiated under the influence of gravity. During both the instillation and drainage phases, position adjustments and percussion maneuvers can be used to facilitate distribution and clearance. Although suctioning is not routinely employed during the drainage phase, it may be used intermittently when passive drainage is insufficient—such as in cases of fluid stagnation or suspected blockage.[91] Rapid infusion devices may reduce procedure



Figure 3. This figure presents actual images captured during the sequential stages of whole lung lavage (WLL). Under general anesthesia, a double-lumen endotracheal tube is placed, and the lumen leading to the lung designated for lavage is clamped. Tube placement is confirmed bronchoscopically. Once correct positioning is verified, warmed saline is instilled into the occluded lung. When fluid becomes visible within the tube, the saline instillation is paused, and the circuit is redirected into a collection container positioned below the patient, allowing passive drainage by gravity. During both the instillation and drainage phases, the patient bed may be repositioned, and manual percussion or mechanical vibration techniques can be employed to enhance fluid distribution and clearance.

time and improve saline distribution but carry risks of barotrauma or hydro-pneumothorax.[92] As lavage proceeds, the initially turbid, sediment-rich return fluid becomes progressively clearer (Figure 4). While there is no universally agreed volume, recommendations include 250 mL/kg or 30-50 mL/kg per lung.[40,93] The process is often continued until the effluent appears visually clear or until the optical density falls below 0.4.[93] At the end of the final instillation-drainage cycle, remaining saline may be aspirated. It is important to monitor the volume of fluid instilled and retrieved throughout the procedure. The majority of the instilled saline is expected to be recovered. A fluid loss exceeding 1000 mL may suggest leakage into the contralateral lung or pleural space.[94] Recruitment maneuvers are used when both lungs are reopened to ventilation to prevent atelectasis.[95] Switching to a single-lumen tube and aspirating residual fluid using a fiberoptic bronchoscope may also be considered.[40] In patients with advanced disease and respiratory failure, WLL can be performed under extracorporeal membrane oxygenation (ECMO) support.[40] While simultaneous bilateral WLL has been reported, the more common practice is sequential unilateral lavage, typically starting with the more affected lung, followed 1-2 weeks later by the contralateral side.[89]

Although no randomized controlled trials exist to definitively confirm its efficacy and safety, WLL is currently accepted as the standard of care. A large cohort study demonstrated a significantly higher 5-year survival rate in patients treated with WLL (94% ± 2 vs. 85% ± 5; n=146 and 85; P=0.04).[2] Numerous studies also support improvements in respiratory symptoms. The most recent ERS guideline strongly recommends WLL for patients with clinical and/or functional impairment due to PAP.[83] Though generally considered safe, WLL may be associated with complications such as hypoxemia, fever, fluid leakage, pneumothorax, hydro-pneumothorax, pneumonia, ARDS, and sepsis.[40] A multidisciplinary team, including pulmonologists, anesthesiologists, intensivists, and cardiothoracic surgeons when needed, is essential for optimal outcomes.[95]

Post-WLL clinical course is variable. Some patients achieve disease stabilization after one or a few procedures, while others may require repeated lavages. Patients who smoke tend to require more frequent WLLs compared to non-smokers.[64,85]

Pharmacological Treatments

There are a few treatment options other than WLL, though their availability and effectiveness may vary.

Exogenous GM-CSF

Following the recognition of the pathogenic role of GM-CSF autoantibodies in PAP, studies have explored the use of recombinant GM-CSF therapies. Although patient numbers are limited, both randomized controlled and numerous observational studies have highlighted the efficacy and safety of inhaled GM-CSF in confirmed aPAP cases. Subcutaneous GM-CSF has



Figure 4. In whole lung lavage (WLL), the initially turbid and sediment-rich effluent gradually becomes clearer with each instillation-drainage cycle. The procedure is typically continued until the return fluid appears macroscopically clear, ensuring effective removal of intra-alveolar material.

also shown favorable outcomes in fewer reports.[96-104] In the Pulmonary Alveolar Proteinosis GM-CSF Inhalation Efficacy (PAGE) trial, inhaled GM-CSF was administered once daily for seven days, then biweekly for 24 weeks. Improvements in the alveolar-arterial gradient and imaging findings were noted, although clinical parameters remained unchanged. Effectiveness was lower in smokers, possibly due to airway remodeling and mucus affecting drug distribution.[98] In the Inhaled Molgramostim for Autoimmune Pulmonary Alveolar Proteinosis (IMPALA) trial, patients with severe symptoms initially received daily GM-CSF, which was then continued either continuously or biweekly and compared to placebo. Similar to PAGE, significant improvements were observed in A-aO2 gradient and imaging, especially in the continuous treatment group. Symptom improvement was noted on the St. George's Respiratory Questionnaire, although there was no change in six-minute walk test (6MWT) results or WLL requirements.[97] The optimal duration of therapy remains unclear, and the long-term efficacy is currently being evaluated in the ongoing IMPALA-2 study.

Due to its noninvasive nature, ease of use, and the growing body of evidence, inhaled GM-CSF is strongly recommended in the most recent guideline.[83] It may help avoid or delay WLL, a costly intervention requiring general anesthesia and hospitalization. Especially in patients needing repeated WLLs, inhaled GM-CSF may prolong stability and offer a safer, more cost-effective alternative.[105]

Rituximab

Only a few small studies have evaluated rituximab, an anti-CD20 monoclonal antibody, in aPAP. In patients with refractory symptoms despite WLL and GM-CSF, rituximab showed improvements in DLCO and 6MWT and was generally well tolerated.[106,107] However, due to the limited and low-quality evidence, its use is conditionally recommended only in refractory aPAP.[83]

Other Interventions

Data on plasmapheresis are limited to case reports, and the level of evidence supporting its effectiveness remains low. Nevertheless, for patients with confirmed autoimmune PAP who continue to experience significant symptoms or require ongoing oxygen or repeated WLL despite GM-CSF and rituximab, it is listed as a conditional recommendation.[83]

Lung transplantation is also conditionally recommended in cases of refractory PAP, particularly when unresponsive to WLL and pharmacotherapy.[83] Given the high mortality and lifelong treatment needs in therapy-resistant PAP, lung transplantation may be a viable alternative regardless of fibrosis status.[108] Further details on this topic are provided in the relevant chapter of this book.

Emerging therapies are focusing on genetic and statin-based approaches. Gene-targeted treatments aiming to restore macrophage function may hold promise, particularly for hereditary PAP.[109] Given the recognized role of cholesterol homeostasis in PAP, research into reducing intracellular cholesterol accumulation has increased. Several reports describe improved lung function, oxygenation, and radiologic findings with statin use in autoimmune PAP.[110]

Immunosuppressive therapies, particularly corticosteroids, have been tried in aPAP but are not recommended due to lack of benefit and increased susceptibility to opportunistic infections, which may worsen outcomes.[111]

Most therapeutic studies have been conducted in aPAP. There is still no established optimal therapy for secondary, hereditary, or congenital PAP. WLL remains the primary treatment based on disease severity. Supportive care is essential, and management of the underlying cause is required in secondary PAP. Case reports describe improvement following treatment of hematologic disorders or with WLL.[112] Non-myeloablative hematopoietic stem cell transplantation (HSCT) has been combined with WLL in familial MDS and may be a therapeutic option in hereditary PAP with GM-CSF receptor defects.[112,113]

PROGNOSIS AND FOLLOW-UP

Prognosis in PAP varies according to etiology, disease severity, and response to treatment. Clinical courses include spontaneous remission, stable disease, remission/stability with WLL and/or pharmacotherapy, and refractory disease.[74] Although predictive factors for disease trajectory are not well defined, a recent global cohort study reported that patients with more severe symptoms had poorer prognoses. The overall mortality was 9.5%, with 46% of deaths related to respiratory failure and 18% to pulmonary infections. WLL

was shown to improve survival.[114] While pulmonary fibrosis is rarely reported, its presence is associated with poor outcomes.[115] Among the heterogeneous PAP subtypes, secondary PAP is linked to worse long-term survival. This is particularly true in hematologic conditions, where the risks of infection and bleeding are higher.[11,114]

In summary, careful and structured follow-up is as crucial as treatment. Monitoring for respiratory failure, infections, and fibrosis, factors associated with increased mortality, is essential. Vaccination and routine microbiological screening during WLL should not be overlooked. Smoking cessation improves both disease prognosis and response to WLL, and should be addressed at every follow-up visit.

CASE ANALYSIS

Although the patient exhibited severe symptoms and respiratory failure indicating a clear need for WLL, the nearest center capable of performing the procedure was geographically distant. Considering the patient's insistence and clinical status, preparations were initiated to perform WLL at the local hospital by the pulmonology and anesthesiology team. After undergoing relevant training, a multidisciplinary team was formed, in addition to pulmonolgist, specialists in anesthesia, intensive care, and thoracic surgery, and WLL was successfully performed without complications. A total of five WLLs were performed, and the patient has remained symptom-free for over 10 years. Following this successful experience and with more patients presenting from the region, 14 patients have since been followed at the center, and 48 WLL procedures have been conducted.

As patient numbers increased, the center initiated collaboration with an international PAP center to enable GM-CSF testing. The diagnosis of aPAP was confirmed in the index case in University of Cincinnati, with a GM-CSF autoantibody level of 289.9 mcg/mL. As with other rare diseases, limited access to expert centers for PAP poses challenges for both patients and clinicians. Strategies to increase the number of qualified centers and improve access to WLL, the current cornerstone of PAP management, should be prioritized. The story of the patient, titled "Lesson Behind Success", has been published in a book.[116]

CONCLUSION

PAP is a rare and distinct disease characterized by surfactant accumulation in the alveoli, presenting with variable symptoms and clinical courses. Over the 70 years since its first description, our understanding of PAP has significantly advanced, particularly regarding its pathogenesis and treatment options. WLL, which has long been the cornerstone of therapy, remains a successfully applied intervention, with ongoing refinements to its technique. Recognition of the role of GM-CSF in the disease mechanism has paved the way for exogenous GM-CSF therapies, which have shown promise in reducing the need for WLL. In addition, recent insights into cholesterol metabolism and genetic mutations have laid the foundation for future therapies, offering hope for novel treatment strategies. These advancements have been made possible through data sharing and the growth of registries. Further international collaborative studies and robust registries are essential to illuminate the complex landscape of PAP and take us beyond our current understanding.

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CHAPTER 04

PULMONARY ALVEOLAR MICROLITIASIS

PULMONER ALVEOLER MİKROLİTİAZİS

Assist. Prof. Dr. Nilüfer Yiğit

PULMONARY ALVEOLAR MICROLITIASIS

PULMONER ALVEOLER MİKROLİTİAZİS

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ABSTRACT

Pulmonary Alveolar Microlithiasis is a rare, slowly progressive diffuse lung disease characterized by the intra-alveolar accumulation of calcium phosphate microliths. The condition is typically inherited in an autosomal recessive manner and is caused by inactivating mutations in the SLC34A2 gene, which encodes a type IIb sodium-phosphate co-transporter primarily expressed in alveolar type II epithelial cells. The dysfunction of this transporter leads to impaired phosphate clearance from the alveolar space, resulting in the precipitation of hydroxyapatite crystals and the formation of characteristic microliths. Despite its genetic origin being elucidated in recent years, the clinical course of PAM remains unpredictable. Many patients are asymptomatic at the time of diagnosis, which is often made incidentally via chest imaging performed for unrelated reasons. However, the disease tends to progress over time, with patients eventually developing exertional dyspnea, restrictive ventilatory defects, and, in advanced stages, chronic respiratory failure and cor pulmonale. Radiologically, the condition is classically identified by a "sandstorm-like" pattern on chest X-ray, reflecting diffuse, calcified micronodules throughout the lungs. Recent advances in genetics have contributed to a better understanding of disease heterogeneity and genotype-phenotype correlations, yet no treatment has been proven effective in PAM. Empirical therapies, including corticosteroids, bisphosphonates, and whole-lung lavage, have shown limited to no benefit. Lung transplantation remains the only definitive therapeutic option for patients with advanced disease, and early referral before the onset of right heart failure is strongly recommended. This chapter will review the current knowledge on the clinical, radiological, and pathological features of PAM, explore recent insights into its genetic and molecular pathogenesis, and provide an overview of diagnostic strategies, management options, and future research perspectives. Special emphasis will be placed on the role of international registries, telemedicine in follow-up, and emerging concepts in disease monitoring and personalized care.

Keywords: *Pulmonary alveolar microlithiasis; SLC34A2 gene mutation; Rare lung disease; Alveolar microliths; Sodium-phosphate cotransporter; Clinical-radiological dissociation; Autosomal recessive disorder; Genetic heterogeneity*

ÖZET

Pulmoner Alveoler Mikrolitiazis (PAM), intra-alveoler kalsiyum fosfat mikrolitlerinin birikimi ile karakterize olan, nadir görülen ve yavaş ilerleyen difüz bir akciğer hastalığıdır. Bu hastalık genellikle otozomal resesif kalıtım gösterir ve alveoler tip II epitel hücrelerinde başlıca eksprese edilen tip IIb sodyum-fosfat kotransportörünü kodlayan SLC34A2 genindeki inaktive edici mutasyonlardan kaynaklanır. Bu transportörün işlev bozukluğu, alveoler boşluktan fosfat temizlenmesini engeller, bunun sonucunda hidroksiapatit kristalleri çökelir ve karakteristik mikrolitler oluşur. Son yıllarda genetik kökeni aydınlatılmış olmasına rağmen, PAM'ın klinik seyri öngörülemezliğini korumaktadır. Hastaların büyük bir kısmı tanı anında asemptomatiktir ve hastalık genellikle başka nedenlerle çekilen akciğer görüntülemeleri sırasında tesadüfen saptanır. Bununla birlikte, hastalık zamanla ilerleme eğilimindedir. Hastalarda eforla ortaya çıkan dispne, restriktif ventilatuvar defektler görülüp ileri evrelerde kronik solunum yetmezliği ve kor pulmonale gelişebilir. Radyolojik olarak hastalık, akciğer grafisinde tüm akciğerlere yayılmış kalsifiye mikronodüllerin oluşturduğu "kum fırtınası benzeri" görüntü ile tanınır. Genetik alandaki son gelişmeler, hastalığın heterojen yapısını ve genotip-fenotip korelasyonlarını daha iyi anlaşılmasına katkı sağlamıştır. Ancak, PAM'ın doğal seyrini değiştirebilecek etkili bir tedavi he-

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nüz bulunmamaktadır. Kortikosteroidler, bifosfonatlar ve total akciğer lavajı gibi ampirik tedavilerden elde edilen sonuçlar sınırlı ya da etkisiz kalmıştır. İleri evre hastalar için akciğer nakli, hâlen tek kesin tedavi seçeneğidir ve sağ kalp yetmezliği gelişmeden önce nakil merkezine yönlendirme önem taşımaktadır. Bu bölümde, PAM'ın klinik, radyolojik ve patolojik özelliklerine dair mevcut bilgiler gözden geçirilecek, genetik ve moleküler patogenezine ilişkin son gelişmeler tartışılacak ve tanı stratejileri, tedavi seçenekleri ile geleceğe yönelik araştırma perspektifleri sunulacaktır. Uluslararası hasta kayıtlarının önemi, tele-tıbbın hasta takibindeki rolü ve kişiselleştirilmiş izlem yöntemlerine dair yeni yaklaşımlar özellikle vurgulanacaktır.

Anahtar Kelimeler: *Pulmoner alveoler mikrolitiyazis; SLC34A2 gen mutasyonu; Nadir akciğer hastalığı; Alveoler mikrolitler; Sodyum-fosfat ko-transportörü; Klinik-radyolojik dissosiyasyon; Otozomal resesif hastalık; Genetik heterojenite*

CASE PRESENTATION

A 35-year-old male, employed as a machinery operator, was referred to our clinic nine years ago following suspicion on a routine posteroanterior (PA) chest radiograph obtained during his pre-employment screening (Figure 1). Thoracic computed tomography (CT) was performed and revealed diffuse millimetric nodules, ground-glass opacities, and focal peripheral calcifications in both lung fields (Figure 2). Based on these findings, differential diagnoses of PAM, pulmonary alveolar proteinosis (PAP), and hypersensitivity pneumonitis (HP) were considered.

As part of the diagnostic work-up, bronchoscopy was performed and transbronchial biopsy was obtained from the posterior segment of the right lower lobe. Histopathological analysis demonstrated concentrically layered calcifications filling the alveolar spaces, confirming the diagnosis of PAM (Figure 3,4). The patient was advised to stop smoking and started inhaled therapy for accompanying COPD.

INTRODUCTION

PAM is a rare autosomal recessive lung disease caused by inactivating mutations in the SLC34A2 gene, which encodes the sodium-phosphate cotransporter expressed in pulmonary epithelium.[1] This defect leads to phosphate accumulation within the alveolar spaces and the formation of hydroxyapatite microliths.

The majority of patients are asymptomatic at the time of diagnosis, and the disease is often incidentally detected during routine examinations performed for other reasons. However, in cases of PAM, a positive family history can facilitate diagnosis.[2,3] PAM may affect individuals of all ages, from early childhood to advanced age. Nevertheless, affected individuals typically become symptomatic during the third or fourth decade of life.[3,4]

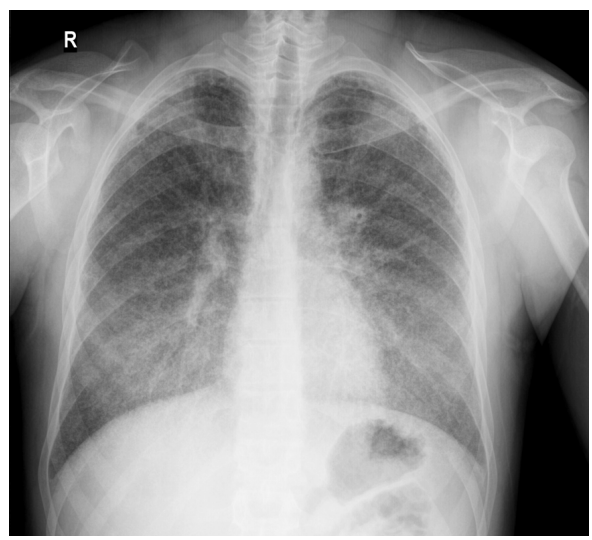


Figure 1. Posteroanterior chest radiograph of the patient from 2016. The image demonstrates prominent nodular opacities predominantly in the bilateral lower lung zones.

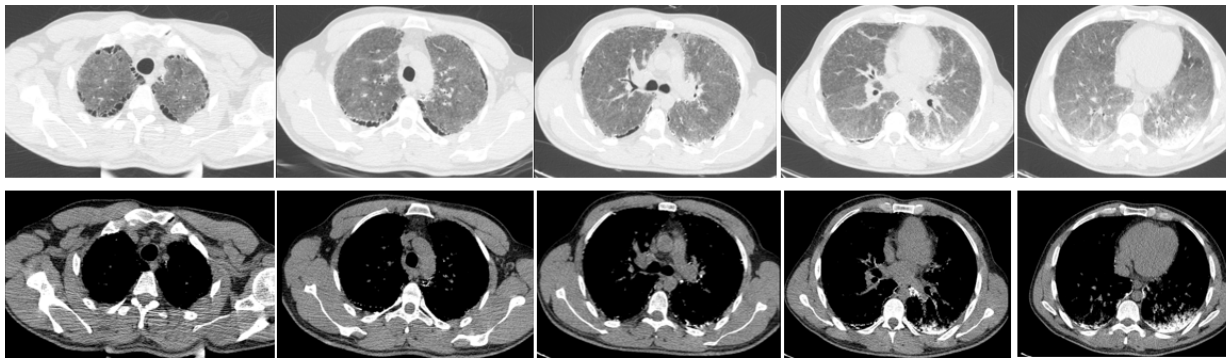


Figure 2. Widespread calcified micronodules ranging in diameter from 2 to 4 mm are observed, with more prominent calcified opacities noted particularly in the lower lung zones.

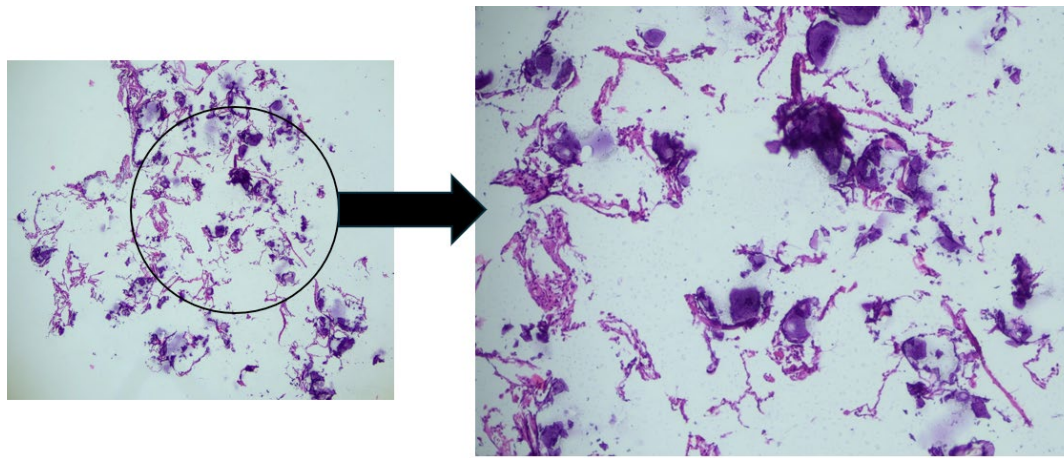


Figure 3. PAM on bronchoscopic biopsy. Punctiform calcifications were seen in alveolar spaces.

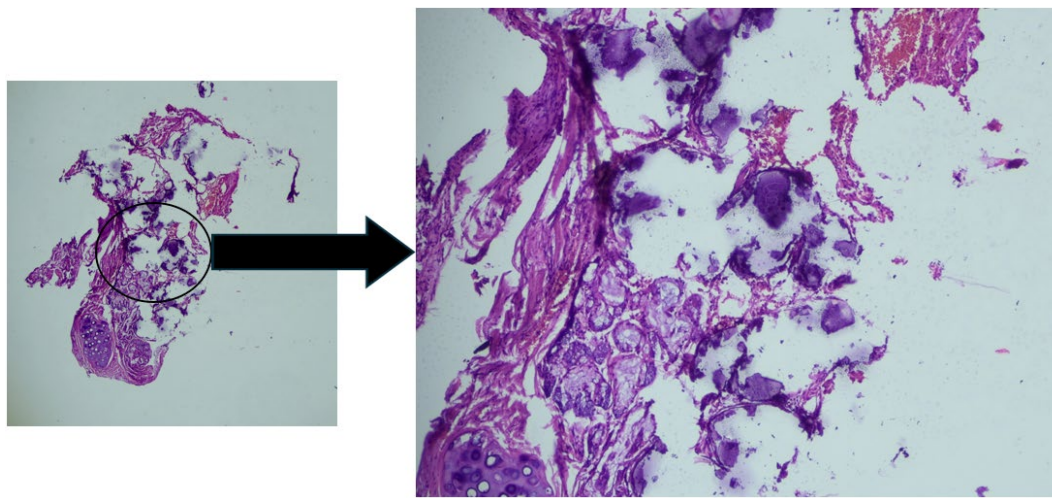


Figure 4. Numerous lamellated calcified structures within peribronchial area consistent with pulmonary microlithiasis.

Chest radiographs typically demonstrate diffuse, hyperdense micronodular infiltrates resembling a "sandstorm" pattern. In patients with a suggestive family history, this radiographic appearance may be sufficient to establish the diagnosis without the need for further invasive testing.[5]

PAM was first described in 1686 by the renowned Italian anatomist Marcello Malpighi. Although Malpighi observed calcified structures in the lung parenchyma during his microscopic examinations, the etiology or clinical presentation of the disease could not be clarified at that time. In 1918, Harbitz highlighted the presence of widespread microlith accumulation in autopsy material and characterized this finding as a distinct disease. Later, in 1933, Puhr introduced the term "pulmonary alveolar microlithiasis," thereby establishing the disease's place in the medical literature.[6,7] Since then, PAM has been recognized as a rare disease, and particularly in recent years, molecular studies have elucidated its genetic basis, confirming its association with SLC34A2 gene mutations.

Recent advances in pathogenesis and genetics have contributed to a better understanding of disease heterogeneity and genotype-phenotype correlations, yet no treatment has been proven effective in PAM. This chapter will review the current knowledge on the clinical, radiological, and pathological features of PAM, explore recent insights into its genetic and molecular pathogenesis, and provide an overview of diagnostic strategies, management options, and future research perspectives.

EPIDEMIOLOGY

PAM is a rare interstitial lung disease, and the number of reported cases worldwide remains quite limited. One of the most significant indicators of this rarity is found in a comprehensive review conducted by Castellana et al. in 2015. In that study, a total of 1,022 cases from 65 countries were identified in the literature, with Turkey, Italy, and Japan being the regions where PAM has been reported more frequently.[7] The fact that the disease is often diagnosed incidentally, the initially subtle clinical signs and symptoms, and the limited availability of genetic testing have all contributed to reduced diagnostic awareness of PAM, leading to its classification among rare diseases.

PAM is generally diagnosed between the ages of 30 and 50. Both sporadic and familial cases of PAM have been reported in the literature. Cases are defined as "familial" when two or more members of the same family (usually two or three, but in rare instances four, five, or even six) are affected by the disease, and as "sporadic" when no family history is present.[8] While no significant overall gender predominance has been observed among all reported cases, sporadic cases are more common in males, whereas familial cases are much more frequently seen in females.[7,8] Familial cases account for approximately 30% to 50% of all reported PAM cases.[9]

PATHOGENESIS AND GENETICS

PAM results from genetic variants in SLC34A2, which encodes the NaPi-IIb. SLC34A2 is located on the short arm of chromosome 4 (4p15.2) and consists of 12 coding exons. The 690-amino acid protein NaPi-IIb is a member of the SLC34 solute carrier family, which also includes NaPi-IIa (SLC34A1) and NaPi-IIc (SLC34A3). These cotransporters play essential roles in maintaining systemic phosphate homeostasis by regulating phosphate transport in the kidney (NaPi-IIa, NaPi-IIc) and the intestine (NaPi-IIb).[10]

NaPi-IIb mRNA is expressed in various organs, including the small intestine, mammary gland, kidney, and liver, and is highly expressed in type II alveolar cells in the lungs.[11] NaPi-IIb likely plays a crucial role in regulating phosphate (Pi) levels in the fluid lining the alveolar spaces.[5] Dysfunction of NaPi-IIb caused by variants in the SLC34A2 gene leads to impaired cellular uptake of Pi, resulting in elevated phosphate concentrations within the alveolar spaces. This excess phosphate subsequently precipitates with extracellular calcium, leading to crystal formation.[10,12]

To date, at least 34 allelic variants associated with PAM have been reported in approximately 68 patients in the literature.[13] These variants are located in various coding regions of the gene and consist of point mutations or deletions affecting single or multiple exons.[14] Although almost all patients in the literature who have undergone genetic evaluation have been found to carry pathogenic variants in SLC34A2, genetic testing is not yet part of routine diagnostic assessment. However, genetic investigation is increasingly being recommended.[13]

Although genetic analyses have clearly demonstrated that the disease is caused by mutations in the SLC34A2 gene, sporadic cases of PAM continue to

be reported in the literature.[7,15] Interestingly, in some of these cases, even though pathogenic variants in SLC34A2 are identified in affected individuals, the same mutations are present in family members who do not exhibit the disease. This observation suggests that the genetic penetrance of the disease may be incomplete or that certain environmental and epigenetic factors might contribute to the phenotypic expression of the disorder. Sporadic cases are often diagnosed incidentally during radiological imaging, and in the absence of a positive family history, the diagnostic process may be delayed. These features of sporadic cases provide important clinical evidence that PAM may involve a more complex pathogenic process beyond being solely a genetic disorder.

CLINICAL MANIFESTATIONS

PAM, a disease with a wide spectrum of clinical presentation, involves two main domains: pulmonary and extrapulmonary manifestations.

Pulmonary Manifestations

Most patients with PAM are asymptomatic at the time of diagnosis and are typically diagnosed incidentally during routine or unrelated chest imaging.[16] The disease generally follows a relatively slow progression, and there is usually a long latency period before clinical symptoms appear. As the disease advances, patients may develop exertional dyspnea and a dry cough; however, these symptoms often remain mild relative to the severity of the radiological findings. This phenomenon is referred to as clinical-radiological dissociation.[6]

With further progression, patients commonly experience dyspnea on exertion, and other symptoms such as cough, chest pain, hemoptysis, asthenia, and pneumothorax have also been reported. Physical examination findings may be unremarkable, particularly in mild to moderate cases. When present, peripheral or central cyanosis and digital clubbing are the most frequently observed findings; however, none of these are specific to PAM. Lung auscultation may be normal, but pathological findings such as fine crackles in both lungs or decreased breath sounds, particularly in the lower lung zones, can also be detected.[16]

Clinical suspicion plays a crucial role in establishing the diagnosis of PAM. In the presence of a family history of PAM, further diagnostic evaluation is warranted even if symptoms and clinical findings are not clearly suggestive. When compatible symptoms are present, the diagnostic work-up typically begins with chest radiography and pulmonary function testing. In the early stages of the disease, pulmonary function tests (PFTs) are often normal. However, with disease progression, impaired ventilation may develop, eventually leading to reductions in total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLco). As the disease advances, impairment in the six-minute walk test and oxygen desaturation during exertion are commonly observed.[17]

PAM is characterized by the accumulation of calcium phosphate microliths within the alveolar spaces of the lungs, ultimately leading to pulmonary hypertension, pulmonary fibrosis, and, most often in late middle age, chronic respiratory failure.[18,19]

Extrapulmonary Manifestations

In the vast majority of reported PAM cases, the disease remains confined to the lungs. However, in rare case reports, microlith accumulation has also been described in extrapulmonary sites such as the pleura, sympathetic ganglia, epididymis, seminal vesicles, and prostate.[8] Due to the rarity of PAM and the predominance of case reports in the literature, it remains challenging to establish a causal relationship between extrapulmonary calcifications and Npt2b gene mutations. Reported forms of heterotopic ossification include medullary nephrocalcinosis, nephrolithiasis, cholelithiasis, testicular microlithiasis (as well as calcifications in the seminal vesicles, epididymis, and periurethral areas), and calcifications of the aortic valve, mitral valve, and pericardium. Among these, testicular microlithiasis is of particular interest because of its reported association with testicular cancer. However, since testicular microlithiasis is relatively common in the general population (approximately 10% of males), it remains unclear whether calcifications in this organ in PAM patients are directly related to Npt2b mutations.[18]

Recent reports have demonstrated that the SLC34A2 gene is expressed not only in the alveolar epithelium but also in cardiac valve tissue. Gene expression analyses revealed significant levels of SLC34A2 mRNA in aortic valve tissue obtained from a 75-year-old male patient diagnosed with PAM, suggesting that this transporter may also play a role in the

cardiac valves.[20] In another case, advanced evaluation of a 45-year-old male presenting with cardiac symptoms revealed pulmonary hypertension and calcifications involving the tricuspid valve.[21] These findings raise the possibility that SLC34A2 mutations may not be limited to microlith accumulation in the lungs but could also be associated with cardiac pathologies such as calcific valve disease.

Additionally, several comorbid conditions have been reported in association with PAM in the literature, mostly as case reports. These include pectus excavatum, hypertrophic pulmonary osteoarthropathy, milk-alkali syndrome, diaphyseal aclasia, autosomal recessive Waardenburg anophthalmia syndrome, and lymphocytic interstitial pneumonitis.[22-27] Moreover, a case of PAM developing after varicella-zoster virus infection was reported in a patient diagnosed with antiphospholipid syndrome and discoid lupus erythematosus.[3]

PULMONARY FUNCTION TESTS

Although PFTs are often normal in the early stages of the disease, they can vary widely depending on the extent of pulmonary involvement, ranging up to severe restrictive impairment.[28] As the disease progresses, the most prominent and commonly observed functional abnormality is a decrease in diffusing capacity for carbon monoxide (DLCO). These findings typically worsen over time in parallel with disease progression. Similarly, six-minute walk tests demonstrate reduced distance and oxygen desaturation as the disease deteriorates.[6]

RADIOLOGICAL FINDINGS

Since radiological findings are key elements in raising suspicion for PAM, even in asymptomatic patients with incidental findings, these findings will be discussed separately for chest radiography and thoracic CT.

Chest Radiography

Conventional chest radiography often provides the first indication for the diagnosis of PAM. Classical findings on chest X-ray include fine, granular-appearing micronodules, or hyperdense ground glass opacity throughout both lungs, often predominating in the lower two-thirds of lung regions, which (when severe) can completely obscure the mediastinal and diaphragmatic borders.[18] These infiltrates appear as fine, sand-like opacities on chest X-rays, which has led to the description of a "sandstorm-like" pattern.[5] Notably, the pronounced radiographic findings can be strikingly discordant with the clinical presentation, as patients may be entirely asymptomatic.

A characteristic hyperlucent area known as the "black pleural line" is frequently observed on chest radiographs. This finding arises due to small, thin-walled subpleural cysts located between the lung parenchyma and the ribs. However, accurate identification and differential diagnosis of this sign require confirmation by high-resolution computed tomography (HRCT).[3]

As the disease progresses, increased lung parenchymal density may obscure cardiac borders, diaphragms, costophrenic angles, and cardiophrenic sulci, resulting in a radiographic appearance known as the "vanishing heart sign".[6]

High-Resolution Computed Tomography

HRCT is the most useful radiological modality for the diagnosis of PAM. In settings with limited diagnostic resources, radiological methods are primarily relied upon for diagnosing PAM. Typically microliths are distributed diffusely but produce widespread, hyperdense micronodular ground-glass opacities that are most prominent in the posterior segments of the lower lobes and the anterior segments of the upper lobes.[6]

When HRCT findings are characteristic, especially in individuals with a positive family history, the diagnosis can be considered definitive.[29] In such cases, diagnosis may be established based solely on HRCT without the need for invasive procedures. This approach both expedites the diagnostic process and spares patients from unnecessary invasive interventions.

A four-stage radiological progression model has been described for PAM:[6,30]

1. **Pre-calcific Stage:** The initial, pre-calcific stage is characterized by sparse, minimally calcified microliths accompanied by diffuse ground-glass opacities. This radiologic pattern has been reported primarily in asymptomatic children, and its presence in adults remains uncertain.
2. **Nodular (Sandstorm) Stage:** The radiograph has a "sandy" appearance with scattered calcified micronodules of diameters varying between 2 and 4 mm and preserved cardiac and diaphragmatic

borders. This appearance is described as "sand-storm-like" infiltrates and represents the classic radiological finding of the disease.

3. **Progressive Interstitial Stage:** Over time, interstitial thickening increases, calcified infiltrates become denser, and the cardiac and diaphragmatic borders may become obscured. The spread of opacities becomes more pronounced.
4. **Fibrocalcific (Lung Whitening) Stage:** The terminal stage is marked by widespread calcification of the interstitial tissues, often accompanied by pleural involvement, resulting in a "whitish" appearance of the lungs on imaging, with the apical areas relatively spared. In some cases, this may progress into areas of extensive calcification and consolidation. In some cases, relative sparing of the apical regions has been reported. Localized areas of dense calcification may occasionally be detected in this stage.

The first stage is typically observed during childhood, the second during adolescence, while the latter two stages generally appear later in life.

Thoracic Ultrasonography

Lung ultrasound can visualize pleural thickening and irregularities associated with PAM, as well as microliths appearing as hyperechoic foci without acoustic shadowing. However, in a patient diagnosed with PAM, thoracic ultrasonography produced findings that were unexpectedly inconsistent with HRCT results.[31] Given that HRCT is considered the gold standard in the diagnosis of PAM, the role and diagnostic contribution of thoracic ultrasound remain unclear.[32] The use of this imaging modality in PAM continues to be a subject of debate in medical literature.

Magnetic Resonance Imaging

While HRCT remains the primary imaging modality for the diagnosis of PAM, magnetic resonance imaging (MRI) has been considered as a complementary tool, particularly in research settings and in advanced cases. Hoshino et al. reported that numerous microliths, predominantly located in the lower lung zones, appeared with increased signal intensity on T1-weighted MRI sequences in one case.[33] Calcified microliths generally present as low-signal (hypointense) or signal voids on both T1- and T2-weighted MRI sequences; however, increased signal intensity on T1-weighted images has been observed in some cases.[33] Nevertheless, in a case series of five patients published by Hızal et al. The authors were unable to detect the increased signal intensity on MRI that Hoshino et al. had described, indicating that MRI might not provide additional diagnostic or follow-up value in PAM patients.[34]

Positron Emission Tomography (PET)

The role of 18F-FDG PET/CT in PAM has been proposed by several authors, suggesting that it may demonstrate variable patterns of pulmonary involvement as evidence of an underlying inflammatory process.[35] In a case reported by Ito et al., an increased FDG uptake was observed in lung regions spared from calcification, whereas no significant FDG uptake was detected in areas with dense calcifications.[36] This finding suggests that inflammation in these heavily calcified regions likely resolved long before, resulting in reduced metabolic activity. Therefore, FDG-PET has been reported to provide limited diagnostic or follow-up value in PAM.

In 2013, Shahoo et al. proposed the use of 18F-sodium fluoride PET/CT for the diagnosis of PAM. In this modality, areas of dense calcification that showed no uptake on FDG-PET demonstrated significant radiotracer accumulation, producing an imaging pattern described as the "hot furnace lung" appearance.[37] Due to sodium fluoride's high affinity for calcified tissues and the superior resolution of PET imaging, this technique allows for a clearer assessment of pulmonary calcifications and enables monitoring of disease progression in PAM. As a result, 18F-sodium fluoride PET/CT has emerged as a potentially more valuable imaging modality for both the diagnosis and follow-up of PAM compared to FDG-PET. However, because of its limited availability in many centers and concerns regarding cost-effectiveness, its use is generally reserved for selected cases, particularly in PAM patients with suspected extrapulmonary involvement requiring advanced diagnostic evaluation.

PATHOLOGY

Bronchoscopy/Bronchoalveolar Lavage

The identification of microliths in BAL fluid is considered sufficient for diagnosis when accompanied by compatible clinical findings and HRCT features.[28]

Microliths in sputum are not entirely specific to

PAM and may occasionally be observed in patients with COPD or lung cancer. However, histological examination demonstrating the characteristic lamellar structure of microliths can aid in differentiating them from other airway calculi. For instance, Curschmann's spirals, associated with asthma and chronic bronchitis, are composed of glycoproteins and are typically non-calcified. By contrast, the demonstration of the distinctive lamellar architecture of microliths in histological sections is a helpful distinguishing feature in the differential diagnosis of PAM.[6]

In addition, scanning electron microscopy (SEM) of BAL specimens can further support the diagnosis. SEM may reveal the spherical structure of microliths with a characteristic porous surface resembling cortical bone.[6]

Transbronchial Biopsy/Surgical Biopsy

In general, the radiographic features of PAM are so distinctive that the diagnosis can often be confidently established based on imaging alone. In cases where a definitive diagnosis cannot be established radiologically, it may be necessary to begin with the least invasive sampling method. Bronchoscopy allows for bronchoalveolar lavage (BAL) and lung biopsies via transbronchial forceps or cryobiopsy, depending on the expertise of the center.[28] Surgical lung biopsy via video-assisted thoracoscopic surgery (VATS) should be reserved for rare instances where noninvasive diagnostic methods fail to yield a definitive diagnosis. Histopathologically, PAM is characterized by numerous intra-alveolar microliths accompanied by interstitial fibrosis and thickening of the alveolar septa.[18] Histopathological examination reveals numerous intra-alveolar microliths occupying the alveolar spaces. These microliths exhibit a lamellar structure and display a purple-brown coloration, resembling psammoma bodies in morphology. A characteristic pericentral crescent-shaped halo is frequently observed surrounding the microliths.[3]

DIFFERENTIAL DIAGNOSIS

Clinicians should be aware that certain features of PAM, such as its nodular calcification pattern, may also be seen in other disorders. Conditions that can present relatively similar radiologic features include miliary tuberculosis, metastatic pulmonary calcification, sarcoidosis, pneumoconiosis, and dystrophic calcifications related to infectious or occupational etiologies. Particular caution is warranted in countries where tuberculosis remains endemic. Although miliary tuberculosis accounts for only 1-2% of all tuberculosis cases, it is still more common than PAM and often ranks higher on the differential diagnosis list when a miliary nodular pattern is observed on chest radiography.[38]

In addition to miliary tuberculosis, the differential diagnosis of PAM includes PAP, nodular pulmonary ossification, metastatic or dystrophic pulmonary calcification, post-varicella pneumonia, pneumoconiosis, and pulmonary amyloidosis.[18] In most cases, clinical history and laboratory investigations are sufficient to exclude these alternative diagnoses.

In the diseases included in the differential diagnosis, the patterns of calcification differ, and only rarely they progress to obscure the cardiac silhouette as can occasionally be seen in PAM. Unlike PAM, where calcifications are almost exclusively intra-alveolar, the metastatic and dystrophic calcifications seen in these mimickers are typically located in the interstitial or vascular compartments.[3]

Although miliary tuberculosis is included in the differential diagnosis of PAM, it should also be carefully considered as a potential coexisting condition. In the series of 1,022 cases by Castellana et al., five patients were reported to have a concurrent diagnosis of pulmonary tuberculosis.[7] Additionally, several case reports in the literature have documented tuberculosis as a comorbidity in patients diagnosed with PAM.[39-41] Therefore, clinicians should remain vigilant for the development of tuberculosis in patients with PAM. In cases of concurrent tuberculosis, treatment strategies must be carefully planned, and response to anti-tuberculous therapy should be closely monitored.

TREATMENT

PAM is a rare and slowly progressive disease for which no standardized effective treatment protocol has yet been established. Currently, there is no definitive or curative therapy available for PAM. Various pharmacological and supportive treatment options have been attempted; however, these approaches are generally aimed at alleviating symptoms or slowing disease progression. The literature consists mostly of individual case reports and some case series with small numbers of patients, and the reported treatment

responses remain heterogeneous. As a result, therapeutic decisions are typically individualized and based on clinical experience. Lung transplantation remains the only known effective treatment for advanced-stage PAM, although there is no standardized surgical protocol, and data on long-term outcomes are still lacking. The current management strategy focuses on symptomatic treatment, prevention of complications, management of comorbidities, and improvement of quality of life. This section will provide a detailed discussion of therapeutic approaches used in PAM and a review of the most recent findings in the literature.

Bisphosphonates bind to bone mineral surfaces and inhibit osteoclast differentiation, activity, and survival, thereby reducing osteoclast-mediated bone resorption. While agents like alendronate and risedronate are more potent inhibitors of osteoclast function, disodium etidronate exhibits comparatively lower anti-resorptive potency. However, in the context of PAM, disodium etidronate is theorized to offer a distinct advantage by interfering with the formation of hydroxyapatite crystals.[6]

Göçmen et al. reported the use of disodium etidronate therapy in a 3.5-year-old girl diagnosed with PAM. The treatment was administered at a dose of 15 mg/kg/day for approximately 36 months. Following therapy, partial clearing was observed in the basal regions of the lungs on chest radiographs, and an improvement in the patient's symptoms was reported. No serious adverse effects were noted during the course of treatment. This observation suggested that bisphosphonates may have a potential role in the treatment of PAM.[42] Mariotta et al. reported on a two-case series, describing the disease progression in one of their patients. In this progressive case, no radiological improvement was observed following a 6-month course of disodium etidronate therapy.[43] Similarly, Janković et al. (2002) administered a disodium etidronate-based treatment regimen to an 8.5 year old girl diagnosed with PAM over a period of 18 months but reported no significant clinical or radiological improvement.[44] In 2010, Özçelik et al. reported clinical and radiological improvement in two PAM patients who had been treated with disodium etidronate for 9 and 11 years, respectively.[45] In 2015, Çakır et al. described three siblings from the same family diagnosed with PAM an 11 year old boy and 4 year old twin sisters. The patients received daily disodium etidronate therapy at a dose of 200 mg for one year. At the end of the treatment period, radiological improvement was observed in two siblings, while no response was noted in the third. Although no adverse effects were reported during treatment, the uncertainty regarding therapeutic response continues to raise questions about the definitive role of bisphosphonates in the management of PAM.[46] Although bisphosphonate treatments have been reported at the case-based information in the literature, their role in PAM management remains unclear due to heterogeneous clinical responses, and their definitive efficacy is still debated. Additionally, because of potential adverse effects such as rickets, hyperphosphatemia, and bone fractures, patients receiving bisphosphonates should be closely monitored, with regular assessment of serum and urinary calcium phosphate levels.[47]

Azim et al. reported the outcomes of one-year alendronate sodium therapy in 12 patients diagnosed with PAM. The study noted significant improvement in clinical symptoms and pulmonary function tests following treatment. However, despite this clinical improvement, no significant changes were observed in chest radiographs.[48] In 2019, a case series from India involving three PAM patients treated with alendronate sodium was reported. After follow-up periods of 6 months, 1 year, and 2 months, clinical symptom improvement was observed in the patients, yet no significant radiological changes were detected.[49] Due to insufficient evidence, the role of alendronate sodium therapy in PAM remains unclear.

A 10-year-old girl with histopathological evidence of both PAM and lymphocytic interstitial pneumonia showed rapid improvement in lung function and exercise tolerance in response to glucocorticoid therapy.[27] In a patient diagnosed with PAM following varicella zoster infection, who also had diagnoses of antiphospholipid syndrome and discoid lupus erythematosus, inhaled budesonide treatment resulted in significant clinical improvement.[50] Corticosteroid treatment is generally considered ineffective in PAM, and any observed benefits are usually attributed to the treatment of a secondary interstitial inflammatory disease.[28]

All PAM patients who experience hypoxemia during rest, exercise, or sleep should receive supplemental oxygen therapy.[51] Additionally, smoking cessation is strongly recommended for all patients with PAM, as smoking may accelerate disease progression.[3] Pneumococcal and influenza vaccinations should be administered to all patients with PAM.[52]

Dietary phosphate restriction has been shown to reduce calcium accumulation and inflammation in PAM mouse models. However, there is no evidence yet whether the levels of phosphate restriction feasible for humans (approximately half of the average daily intake) are sufficient to reduce microlith burden as observed in experimental animal models. Clinical recommendations regarding phosphate intake in PAM patients can only be clarified after safety and efficacy studies in this area are completed.[6]

The whole-lung lavage is commonly used for PAP and, since microliths are localized only in the alveolar lumen, it is a reasonable treatment strategy for PAM. Unfortunately, there is no evidence supporting the effectiveness of this approach.[7,28]

Lung transplantation remains the only definitive treatment option; in advanced stages of the disease, bilateral lung transplantation is preferred. However, due to the lack of prognostic indices and clear guidelines, the optimal timing of transplantation remains uncertain and is generally considered when severe respiratory failure requiring supplemental oxygen or right heart failure develops. Therefore, referral of all patients before the onset of right ventricular dysfunction is recommended.[53] Bilateral lung transplantation is favored over unilateral, as transplanting only one lung may lead to persistent perfusion through the native lung, resulting in filling of the alveolar spaces and the formation of extensive intrapulmonary shunt areas.[7]

In 2024, Mardani et al. presented a study summarizing a successful bilateral lung transplantation and a literature review of 27 published cases in which lung transplantation was performed for PAM. The mean age at the time of transplantation across all cases was 47.26 years (SD=1.81), and 22 patients underwent bilateral transplantation. In terms of outcomes, no postoperative complications were reported in nine patients. Only one patient exhibited signs of infection, and among the postoperative cases who died after bilateral lung transplantation, widespread pleural involvement and prolonged ECMO duration (6 hours) were reported as contributing factors to uncontrollable hemodynamic instability and multiorgan failure.[54]

To date, there have been no documented cases of recurrence in the post-transplantation period.[51] The longest recorded survival after lung transplantation for PAM is 15 years.[55]

Post-transplantation complications are among the leading causes of mortality in patients who undergo lung transplantation. Infections rank as the second most common cause of death within the first 30 days postoperatively and become the leading cause within the first year. Other postoperative complications, such as anastomotic stenosis, acute rejection, and reperfusion edema, also contribute significantly to morbidity and mortality. Many of these complications can be recognized through characteristic imaging findings. For instance, infections may present with diffuse ground-glass opacities, localized atelectasis or consolidation, small intrapulmonary nodules, peribronchovascular interstitial thickening, and pleural effusion. Acute rejection is typically characterized by diffuse ground-glass opacities, consolidation, septal thickening, and pleural effusion. In cases of bronchial stenosis, CT imaging reveals narrowing of the bronchial lumen.[56]

PROGNOSIS

Although disease progression in PAM is typically slow, and most patients are either asymptomatic or present with only mild symptoms at the time of diagnosis, the prognosis is generally considered poor. Most patients eventually develop exertional dyspnea, followed by signs of hypoxemia at rest and progression to respiratory failure. Additionally, many patients experience secondary cardiac involvement, often as a complication of pulmonary hypertension, ultimately leading to cor pulmonale.[28]

On average, patients tend to survive 10-20 years after diagnosis. However, long-term survivors have been reported, with the longest continuous follow-up in a PAM patient lasting 58 years.[7]

CASE ANALYSIS

After a follow-up gap of approximately seven years, the patient presented again for re-evaluation. He reported a one-year history of dry cough, more prominent in the mornings and triggered by exertion, along with progressive exertional dyspnea. He denied cough triggers such as cold air, odors, dust, or smoke. On physical examination, his general condition was good and vital signs were stable. Oxygen saturation was 95% on room air, and pulse rate was 84 bpm. Respiratory system examination was unremarkable.

Pulmonary function tests revealed a mild restrictive ventilatory pattern. The diffusion capacity (DLco)

was reduced to 51% of predicted, consistent with impaired gas exchange secondary to parenchymal involvement. When compared to the chest radiograph taken in 2016, the previously lower-zone-limited micronodular opacities had progressed to involve all lung fields bilaterally (Figure 5). Following the progression observed on the chest radiograph, a repeat thoracic CT scan was deemed appropriate. On the thoracic CT, bilateral micronodules persisted; however, contrary to expectations, a marked regression was noted in the calcified density areas previously located in the basal regions, not the subpleural emphysema in upper lobes (Figure 6).

The patient was once again advised to quit smoking and to continue inhaled therapy. A low-phosphate diet was recommended. Family history was reassessed, and no similar disease was identified among the relatives. Routine follow-up was recommended.

CONCLUSION

Achieving significant progress in the treatment of PAM requires a better understanding of its underlying pathophysiology. Designing robust experimental and clinical studies is essential in this regard. Although PAM is a rare disease, which may seem to limit the ability of individual centers to conduct large-scale studies, international collaboration can enable the formation of broader patient cohorts. While the genetic



Figure 5. Posteroanterior chest radiograph of the patient from 2025. Bilateral widespread areas of nodular opacity are observed. Compared to the initial diagnostic imaging, a noticeable progression in the density of the opacities is evident.

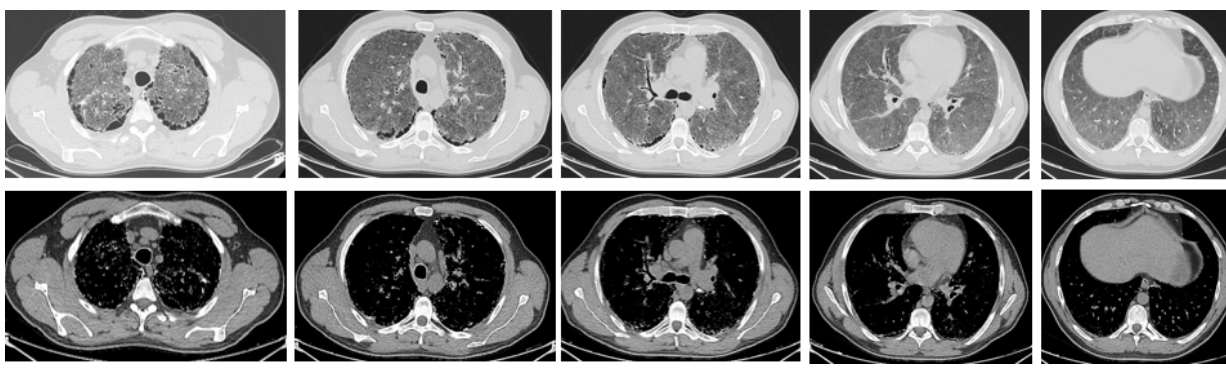


Figure 6. In the 2025 thoracic CT, bilateral widespread ground-glass nodular areas are observed. However, there is a regression in the calcified opacities located in the posterior segments of the lower lobes compared to the initial diagnostic imaging.

basis of the disease is increasingly being clarified, no genetic therapy is currently available. Once the genetic background is fully elucidated, it will facilitate timely interventions in terms of early diagnosis, predicting prognosis, treatment options, and family screening.

The establishment of international registries and patient databases will not only ensure consistency in patient follow-up but also ease the design of multicenter studies. Additionally, developing a disease severity scoring system that incorporates clinical and radiological parameters would greatly support patient stratification and research planning.

From a therapeutic perspective, recent insights into PAM pathogenesis suggest several promising approaches for clinical trials, including EDTA lavage, low-phosphate diets, and enhancement of osteoclast function. Pulmonary rehabilitation and supportive therapies should also be further investigated as adjunct treatments for PAM patients.

In terms of patient follow-up, expanding telemedicine and remote healthcare services offers significant advantages. These approaches facilitate regular monitoring of oxygen saturation, lung function, and other clinical parameters by allowing patients to connect with specialized centers without the burden of travel. Early detection of disease progression through home monitoring may help prevent complications and improve patient outcomes.

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CHAPTER 05

ACUTE SILICOSIS/SILICOPROTEINOSIS

AKUT SİLİKOZ/SİLİKOPROTEİNOZ

Prof. Dr. Metin Akgün

ACUTE SILICOSIS/SILICOPROTEINOSIS

AKUT SİLİKOZ/SİLİKOPROTEİNOZ

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ABSTRACT

Acute silicosis is a rare and rapidly progressive lung disease that develops after intense, short-term exposure to respirable crystalline silica. Acute silicoproteinosis, a severe subtype, is defined by diffuse intra alveolar accumulation of lipoproteinaceous material and clinically mimics pulmonary alveolar proteinosis (PAP); recent outbreaks in denim sandblasting and engineered stone fabrication underscore its current relevance and its predilection for young workers who may progress to respiratory failure within months. Pathogenesis centers on silica induced injury to alveolar macrophages, with impaired surfactant clearance, activation of the NLRP3 inflammasome and neutrophilic alveolitis, and early profibrotic pathway activation.

Clinically, patients develop rapidly worsening exertional dyspnea that may advance to rest dyspnea, together with dry cough, weight loss, fatigue, and hypoxemia; pulmonary function testing usually shows restriction with reduced diffusing capacity. Diagnosis integrates exposure history with high resolution chest CT showing a characteristic crazy paving pattern and bronchoalveolar lavage yielding opaque, milky fluid rich in PAS positive surfactant material; HRCT may also show air-space consolidations and centrilobular nodules, while hilar or mediastinal lymphadenopathy with eggshell calcification favors silica related disease. Microbiologic evaluation, including testing for tuberculosis, is warranted because silica exposure increases susceptibility to infection.

Management begins with immediate and permanent removal from further silica exposure, followed by supportive care-oxygen supplementation, pulmonary rehabilitation, and vigilant infection prevention and treatment. Whole lung lavage can improve oxygenation and symptoms in selected patients with heavy alveolar filling, while corticosteroids are used empirically with inconsistent, often transient benefit; in progressive or end stage disease, lung transplantation may be the only life saving option. Even after exposure cessation, retained silica can perpetuate inflammation and fibrogenesis, and whole lung lavage generally does not halt disease progression. Thus, overall prognosis remains poor in the absence of curative therapy. Investigational approaches-GM CSF supplementation to restore macrophage function, antifibrotic agents to slow scarring, targeted anti inflammatory therapies, statins, and mesenchymal stem cell-based interventions-are promising but not yet standard. Prevention through stringent exposure control and proactive medical surveillance remains the most effective strategy.

Keywords: *Acute silicosis; Silicoproteinosis; Pulmonary alveolar proteinosis; Lung disease; Silica exposure; Whole lung lavage; Occupational diseases*

ÖZET

Akut silikozis, solunabilir kristalin silikaya kısa süreli ve yoğun maruziyet sonrasında gelişen, hızlı seyirli ve nadir görülen bir akciğer hastalığıdır. Bunun ağır bir alt tipi olan akut silikoproteinozis, alveollerde lipoproteinöz materyalin yaygın birikimiyle karakterize olup klinik olarak pulmoner alveoler proteinozise benzer. Son yıllarda özellikle kot kumlama ve kuvars esaslı yapay taş üretimi gibi iş kollarında görülen olgular, bu tablonun genç işçilerde aylar içinde ölümcül solunum yetmezliğine ilerleyebildiğini göstermektedir.

Hastalığın patogenezinde alveoler makrofajların silikaya bağlı hasarı ve işlev kaybı, sürfaktanın temizlenemeyerek alveol boşluklarında birikmesine yol açar. Bu süreç NLRP3 inflamazomunun etkinleşmesine, nötrofil ağırlıklı inflamatuar yanıtın ortaya çıkmasına ve erken dönemde fibrotik süreçlerin

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başlamasına neden olur. Ayrıca GM-CSF sinyal bozukluğu, makrofaj olgunlaşması ve sürfaktan geri dönüşümünü daha da bozar. Klinik olarak efor dispnesi hızla artar ve kısa sürede istirahat dispnesine ilerler; kuru öksürük, kilo kaybı, halsizlik ve hipoksemi sık görülen bulgulardır.

Tanı, ayrıntılı mesleki öykü ile birlikte yüksek çözünürlüklü toraks BT'de "crazy-paving" olarak bilinen tipik görüntünün saptanmasına ve bronkoalveoler lavaj sıvısında PAS-pozitif proteinöz materyalin gösterilmesine dayanır. HRCT'de alveoler konsolidasyonlar ve sentrilobüler nodüller görülebilir; mediastinal lenf nodlarında "yumurta kabuğu" tarzı kalsifikasyon silika maruziyetini destekler. Pulmoner fonksiyon testlerinde restriktif patern ve karbonmonoksit difüzyon kapasitesinde belirgin azalma izlenir. Ayırıcı tanıda idiyopatik PAP, ARDS ve enfeksiyonlar dışlanmalıdır.

Tedavinin temelini maruziyetin derhal ve kalıcı olarak kesilmesi oluşturur. Destek tedavi kapsamında oksijen desteği, pulmoner rehabilitasyon ve enfeksiyonların önlenmesi esastır. Belirgin alveoler tutulumu olan olgularda tüm akciğer lavajı geçici klinik düzelme sağlayabilir. Kortikosteroidler ampirik olarak kullanılmakla birlikte etkinliği sınırlıdır. İlerlemiş hastalıkta akciğer nakli yaşam kurtarıcı tek seçenek olabilir. Ancak mevcut tedavilere rağmen kür sağlayan bir yöntem yoktur ve prognoz genellikle kötüdür.

Gelecekte GM-CSF takviyesi, antifibrotik ilaçlar, inflamasyonu baskılayan tedaviler ve mezenkimal kök hücre uygulamaları gibi yaklaşımlar umut vaat etmektedir. Bununla birlikte, bu ciddi meslek hastalığını önlemenin en etkili yolu, işyerinde toz kontrolünün sağlanması ve risk altındaki işçilerin düzenli sağlık izlemi ile erken tanı konulmasıdır.

Anahtar Kelimeler: *Akut silikozis; Silikoproteinozis; Alveoler proteinozis; Akciğer hastalığı; Silika maruziyeti; Total akciğer lavajı; Meslek hastalıkları*

INTRODUCTION

Silicosis is a chronic occupational lung disease caused by inhalation of respirable crystalline silica dust, traditionally categorized into three clinical forms based on exposure intensity and duration: chronic, accelerated, and acute silicosis.[1] Among these forms, acute silicosis is a rare, severe, and rapidly progressive entity arising after brief, intense exposure to high concentrations of silica dust, typically manifesting clinically within weeks to a few years after initial exposure.[2] Unlike the chronic form characterized by slow progression with silicotic nodules, acute silicosis rapidly advances, frequently resulting in severe respiratory impairment, respiratory failure, and death.[3]

Silicoproteinosis is a form of acute silicosis, first clearly described in a cohort of heavily exposed sandblasters.[4] It involves diffuse alveolar accumulation of surfactant-rich, lipoproteinaceous material within alveolar spaces, closely resembling pulmonary alveolar proteinosis (PAP).[5] Subsequent reports, including clusters among tombstone sandblasters in the 1970s, established acute silicoproteinosis as a fulminant clinical entity often resulting in death within a few years of onset.[6] In silicoproteinosis, severe alveolar macrophage injury impairs surfactant clearance, causing persistent accumulation of protein-lipid material within airspaces.[5,7] Therefore, silicoproteinosis represents an acute silicotic alveolar proteinosis characterized by alveolar filling rather than the fibrotic nodules typical in chronic silicosis, indicating a severe disruption of pulmonary surfactant homeostasis due to intense silica exposure. Although uncommon, acute silicoproteinosis remains highly relevant in the modern era. In recent years, it has re-emerged as an important occupational health concern due to outbreaks in industries with extremely high silica dust exposure, such as engineered stone fabrication for countertops and denim sandblasting.[8-10]

EPIDEMIOLOGY

Silicosis remains a significant occupational lung disease, contributing substantially to global morbidity and mortality.[11] Recent analyses indicate that the global burden of silicosis, measured by incidence and mortality, remains high, especially in low- and middle-income countries.[12] From 1990 to 2021, although age-standardized incidence rates have modestly declined due to demographic shifts, the absolute annual numbers of new cases and silicosis-related deaths have increased.[11,12] High incidence rates persist in countries with significant mining and sandblasting industries, including China, South Africa, and Chile, but cases continue to be documented even in high-income nations, highlighting silicosis as an ongoing global public health issue.[11]

Acute silicosis, including the silicoproteinosis subtype, accounts for a smaller proportion of cases compared to chronic forms but is increasingly recognized due to short-term, intense silica exposures, particularly in engineered stone fabrication, mining, tunneling, and unregulated sandblasting operations.[13-15] Engineered stone, commonly containing over 90% crystalline silica, has become popular for kitchen and bathroom countertops, resulting in significant outbreaks

among fabricators who inadequately control silica dust.[13] Acute silicoproteinosis outbreaks have been documented in Israel, Spain, Australia, and multiple clusters in the United States, predominantly affecting young workers (20-40 years old) who develop severe disease after relatively short exposure durations, often less than 10 years.[14,15] The earliest major outbreaks linked to engineered stone occurred around 2010-2012 in Israel and Spain, prompting global awareness and screening initiatives.[14,15] In Queensland, Australia, systematic screening revealed silicosis prevalence rates ranging approximately from 12% to 21%, reflecting the substantial risk associated with this material and high exposure in certain workplaces.[16]

PATHOGENESIS

Acute silicoproteinosis results from overwhelming exposure to respirable crystalline silica, leading to alveolar macrophage dysfunction, surfactant accumulation, acute inflammation, and early fibrogenesis.

Alveolar Macrophage Injury and Surfactant Accumulation: Following inhalation, silica particles less than 5 μm in diameter are deposited in the distal alveoli and phagocytosed by resident alveolar macrophages.[17] High intracellular silica burden disrupts phagolysosomal membranes, leading to leakage of proteolytic enzymes, generation of reactive oxygen species, and induction of apoptosis and pyroptosis.[18] As macrophages undergo functional impairment and depletion, their capacity to catabolize and recycle surfactant diminishes. The resultant accumulation of phospholipids and surfactant proteins forms dense, lipoproteinaceous material within alveolar spaces.[18] Birefringent silica crystals are often observed within this material on polarized light microscopy.[2] The filling of alveoli with this proteinaceous substance severely impairs gas exchange.[17,18]

Disruption of GM-CSF Signaling: Granulocyte-macrophage colony-stimulating factor (GM-CSF) is essential for alveolar macrophage differentiation and surfactant metabolism.[18] Silica-induced injury creates a state of functional GM-CSF deficiency, mirroring the mechanism observed in autoimmune pulmonary alveolar proteinosis.[18,19] Surviving macrophages frequently exhibit reduced responsiveness to GM-CSF, further impairing surfactant clearance.[19] In rare cases, silica exposure may trigger an autoimmune response, leading to production of anti-GM-CSF autoantibodies and further exacerbating alveolar dysfunction.[18]

NLRP3 Inflammasome Activation and Acute Inflammation: Crystalline silica strongly activates the NLRP3 inflammasome in alveolar macrophages, resulting in caspase-1-mediated processing and release of proinflammatory cytokines, particularly interleukin-1β (IL-1β) and interleukin-18 (IL-18).[20] These cytokines recruit neutrophils to the alveolar space, contributing to neutrophilic alveolitis and enhancing tissue injury through the release of proteases and oxidative radicals.[20,21] Concurrent activation of toll-like receptor 4 and NF-κB signaling further amplifies inflammasome gene expression and cytokine production.[21]

Pyroptosis and Inflammatory Amplification: Pyroptosis, a proinflammatory form of programmed cell death mediated by gasdermin D, is triggered in silica-exposed macrophages. This process results in cellular lysis and the release of IL-1β and damage-associated molecular patterns, perpetuating a feedback loop of inflammation, surfactant accumulation, and cellular injury.[19]

Early-Onset Fibrosis: Although acute silicoproteinosis is defined by alveolar filling rather than fibrotic nodule formation, fibrogenic processes can begin early. Transforming growth factor β (TGF-β) and other profibrotic cytokines are upregulated in response to epithelial injury and chronic inflammation, leading to fibroblast activation and collagen deposition. These changes may contribute to progressive respiratory impairment, even after cessation of exposure.[21]

RANKL-Mediated Osteoclast-like Macrophage Transformation: Recent experimental studies have identified an additional pathway in which silica exposure induces the expression of receptor activator of nuclear factor κB ligand (RANKL) in lung tissue. This promotes transdifferentiation of alveolar macrophages into osteoclast-like cells that express tartrate-resistant acid phosphatase and degrade extracellular matrix components. Although demonstrated primarily in animal models, this mechanism suggests a novel contributor to lung remodeling and irreversible structural damage in acute silicosis. It also offers a potential therapeutic target, as RANKL inhibition may prevent silica-induced matrix degradation and preserve alveolar architecture.[22]

CLINICAL MANIFESTATION

Symptoms usually begin within weeks to several months following high exposure and progress rapidly. The clinical presentation is dominated by progressive dyspnea on exertion, which can quickly advance to dyspnea at rest. Patients frequently have a persistent dry cough, fatigue, and unintended weight loss.[3,23,24] In some cases, patients produce small amounts of whitish, frothy sputum, reflecting surfactant-rich proteinaceous material.[5] Constitutional symptoms such as low-grade fever, night sweats, and malaise may be present, reflecting underlying inflammation. Pleuritic chest pain has been reported in some instances. High fever is uncommon unless secondary infections (e.g., tuberculosis or bacterial pneumonia) are present.[3,5]

On physical examination, patients commonly demonstrate tachypnea and diffuse bilateral inspiratory crackles on auscultation, indicating widespread alveolar involvement. In advanced stages, signs of hypoxemia such as cyanosis and digital clubbing may be noted. Chronic hypoxia can lead to pulmonary hypertension and right-sided heart strain (cor pulmonale).[23,25]

A detailed occupational and environmental history is essential. Most patients are relatively young adults with recent work histories in high-exposure settings, including denim sandblasting, artificial stone fabrication, mining, or tunnel excavation. Exposures are frequently described as intense and poorly controlled, with little or no respiratory protection. In outbreak settings, such as the Turkish denim sandblasting epidemic, many patients presented similarly within short intervals after exposure. Awareness of such industrial practices, even if illegal or unregulated, is crucial. Eliciting a clear temporal relationship between symptom onset and recent silica-intensive occupations can facilitate timely suspicion, diagnosis, and intervention.[10]

DIFFERENTIAL DIAGNOSIS

Several conditions may mimic the clinical and radiographic presentation of acute silicoproteinosis. Differentiation is critical, as management strategies and prognoses vary widely.

Idiopathic Pulmonary Alveolar Proteinosis (Pap)

This rare autoimmune condition resembles silicoproteinosis radiographically and histologically (with a characteristic crazy-paving pattern and alveolar filling) but typically occurs without occupational silica exposure.[26] Autoimmune PAP commonly presents with elevated serum GM-CSF autoantibodies and generally follows a more indolent clinical course compared to silicoproteinosis. Testing for GM-CSF autoantibodies aids in distinguishing idiopathic PAP from secondary forms. In acute silicoproteinosis, GM-CSF antibody testing is usually negative, unless a rare overlap with autoimmune PAP occurs.[27]

Acute Respiratory Distress Syndrome (Ards)

ARDS may present acute-onset severe dyspnea and diffuse bilateral pulmonary infiltrates similar to acute silicoproteinosis. However, ARDS is usually associated with an identifiable precipitant (e.g., sepsis, aspiration, trauma) and rapidly develops over hours to days. On imaging, ARDS typically exhibits dependent consolidations and lacks the smooth, interlobular septal thickening characteristic of silicoproteinosis. Clinical history of acute insult and rapid progression helps differentiate ARDS from acute silicoproteinosis.[28]

Infectious Causes

Miliary tuberculosis should be considered, particularly given silica exposure's known association with increased susceptibility to tuberculosis.[29] Radiologically, miliary TB is characterized by diffuse micronodular infiltrates (1-3 mm nodules) throughout the lungs, rather than the alveolar-filling pattern seen in silicoproteinosis.[30] Pneumocystis jirovecii pneumonia (PCP), particularly in immunocompromised individuals, presents with subacute dyspnea, fever, and diffuse ground-glass opacities, lacking the typical alveolar-proteinosis filling seen in acute silicoproteinosis.[31] Other fungal infections and endemic mycoses (e.g., histoplasmosis) may rarely mimic acute silicoproteinosis, but generally exhibit systemic or extrapulmonary involvement.

Hypersensitivity Pneumonitis (Hp)

Caused by inhalation of organic antigens, HP can present with diffuse lung disease and imaging findings like silicoproteinosis. However, HP imaging typically demonstrates centrilobular ground-glass nodules and mosaic attenuation, rather than uniform alveolar filling.[32] Bronchoalveolar lavage (BAL) in HP usually re-

veals marked lymphocytosis, whereas acute silicoproteinosis BAL predominantly shows neutrophils and a characteristic milky appearance due to surfactant accumulation.[33] Exposure history and positive serum precipitins further support an HP diagnosis.

By integrating clinical course, occupational exposure history, imaging features, and laboratory data, clinicians can reliably differentiate acute silicoproteinosis from these overlapping entities.

DIAGNOSTIC EVALUATION

Imaging: High-resolution computed tomography (HRCT) of the chest is the cornerstone of diagnosing acute silicoproteinosis. A typical early finding on HRCT is extensive bilateral ground-glass opacity with superimposed interlobular and intralobular septal thickening, the classic "crazy-paving" pattern.[33] This appearance reflects diffuse alveolar filling and interstitial infiltration.[33,34] However, acute silicoproteinosis often demonstrates additional features not typically seen in idiopathic alveolar proteinosis. HRCT frequently reveals bilateral air-space consolidations (often posterior) along with numerous centrilobular nodules (2-5 mm).[34,35] These findings reflect silica dust deposition and inflammatory reaction in small airways. Calcification within areas of consolidation is unusual and strongly suggests silica-related disease.[34]

Studies indicate the crazy-paving pattern may be less common than in idiopathic PAP; instead, silicoproteinosis often has a nodular and confluent appearance.[35] Hilar or mediastinal lymph node enlargement with eggshell calcification strongly favors silica-induced disease over idiopathic PAP.[36] Conventional chest radiography is less sensitive, showing bilateral alveolar infiltrates or fine reticulonodular patterns, often lagging behind HRCT findings. An HRCT is advised whenever acute silicosis is considered.[37]

Pulmonary Function Tests (PFTs): PFTs typically demonstrate a restrictive ventilatory defect, with reduced forced vital capacity (FVC), total lung capacity (TLC), and significantly decreased diffusing capacity for carbon monoxide (DLco). In early disease, PFTs might be near normal, but severe impairment typically develops as the disease progresses.[38]

Bronchoalveolar Lavage (BAL): BAL fluid in silicoproteinosis is typically opaque, milky, or turbid due to surfactant accumulation. Cytological analysis shows abundant periodic acid-Schiff (PAS)-positive granular material and numerous foamy alveolar macrophages. The BAL cell differential often shows neutrophil predominance, reflecting acute alveolitis.[39,40] BAL fluid should be evaluated microbiologically, including tests for Mycobacterium tuberculosis, as silicosis significantly increases TB risk. The presence of birefringent silica particles on polarized microscopy strongly supports the diagnosis.

Histopathology and Lung Biopsy: A lung biopsy (via VATS or cryobiopsy) may be necessary if other findings are inconclusive. Histopathology shows alveoli filled with dense PAS-positive, granular eosinophilic material (surfactant and debris). Aggregates of dust-laden macrophages containing polarizable silica crystals confirm heavy silica exposure. Unlike chronic silicosis, acute forms may lack classical silicotic nodules, but early interstitial fibrosis and small developing silicotic nodules can still be observed.[23,41] Type II pneumocyte hyperplasia is often present as a regenerative response. Mineralogical analysis (electron microscopy) can quantify silica particles in lung biopsies, conclusively linking pathology to silica exposure, although this is usually limited to investigative or medico-legal contexts.[23]

MANAGEMENT OF ACUTE SILICOPROTEINOSIS

Standard Management

The cornerstone of managing acute silicoproteinosis is immediate and permanent cessation of silica exposure. Once the diagnosis is suspected or established, the patient must be removed from any further exposure to respirable crystalline silica.[8] Continued inhalation of silica, especially at high concentrations, would only perpetuate alveolar injury, inflammation, and surfactant accumulation, accelerating respiratory decline. Patients should be counseled to never return to jobs involving silica dust. Unfortunately, even after exposure ceases, the silica particles already deposited in the lungs can persist for years and continue to drive pathological processes, meaning that disease progression may continue despite exposure cessation.[2] Nonetheless, eliminating further exposure is critical and can at least prevent compounding the lung burden.

Supportive care is central to management. Oxygen therapy is often required to correct hypoxemia. Depending on the severity of impairment, this can range from supplemental oxygen via nasal cannula at rest and with exertion, to high-flow oxygen systems, and

in some cases noninvasive positive pressure support. If a patient develops acute respiratory failure (e.g., during an infection or disease flare), invasive mechanical ventilation and intensive care support may be necessary. Close monitoring for respiratory failure is warranted given the rapid progression potential. Pulmonary rehabilitation can be beneficial, including supervised exercise training, breathing techniques, and energy-conservation strategies, to help maintain functional status and alleviate dyspnea. Nutritional support is also important, as these patients often have weight loss and the work of breathing is increased.[1]

Preventive measures are aimed at reducing complications. Patients should receive vaccinations for seasonal influenza and pneumococcal pneumonia according to guidelines, to lower the risk of common respiratory infections that could precipitate acute decompensation. Given the impaired alveolar macrophage function and surfactant overload in silicoproteinosis, individuals are predisposed to pulmonary infections.[18,27,42] There is also an elevated risk of Nocardia infection in patients with PAP-like syndromes.[43] Prompt treatment of infections is critical; clinicians should have a low threshold to obtain cultures and start appropriate antibiotics if a superimposed infection is suspected. Routine antimicrobial prophylaxis is not established in this condition, but a high index of suspicion for opportunistic infections should be maintained. Some experts recommend Pneumocystis pneumonia prophylaxis if high-dose corticosteroids are used, but this must be individualized. General supportive measures such as cough assist techniques, mucolytics (if the patient has trouble clearing secretions), and avoidance of respiratory irritants (like tobacco smoke) are also advised. Psychosocial support and vocational rehabilitation are important, since patients can no longer work in their prior occupation and often face disability at a young age.

Whole Lung Lavage

The whole lung lavage (WLL) remains the most widely used specific intervention for patients with significant alveolar proteinosis due to silicoproteinosis.[44] Borrowed from idiopathic PAP management, WLL aims to mechanically remove the accumulated lipoproteinaceous material from the alveolar spaces. The procedure is typically performed under general anesthesia using a double-lumen endotracheal tube to allow one lung to be ventilated while the other is sequentially filled with warmed saline, gently agitated, and drained. Each lung is lavaged with tens of liters of saline until the return fluid becomes clearer. Numerous case reports and small series have demonstrated that WLL can improve oxygenation, reduce dyspnea, and partially clear radiographic infiltrates in acute silicoproteinosis.[44,45] Patients often report subjective improvement in breathing in the weeks following lavage, corresponding with better arterial oxygen levels. However, WLL generally does not halt disease progression; the benefit may be temporary, especially if significant ongoing inflammation or fibrosis is present. Many patients require repeated WLL procedures at intervals to manage recurring alveolar proteinosis. The response to WLL is variable and more limited in patients who already have substantial fibrosis or irreversible lung damage. In those with predominantly alveolar filling and less fibrosis, the improvements from lavage tend to be more pronounced. Despite these limitations, WLL remains an important temporizing and symptom-relieving measure when performed at experienced centers. Each affected lung is usually lavaged once (typically 1-2 weeks apart for each side) as an initial treatment; the procedure can be repeated as needed if symptoms and infiltrates recur. Risks of WLL include anesthesia complications, transient hypoxemia, fluid imbalance, and, rarely, acute lung injury, but overall, it is considered safe in experienced hands.

Corticosteroids and Immunomodulation

Corticosteroids have been empirically used in acute silicoproteinosis to suppress inflammation, although their efficacy is not well established. Given the robust inflammatory component in acute silicosis, a trial of systemic corticosteroid therapy is often considered, especially in patients with relatively early-stage disease or rapid clinical worsening. Some case reports have documented transient symptomatic or radiographic improvement with high-dose corticosteroids in acute silicosis/silicoproteinosis.[3,8] For example, some patients have shown improved lung function and imaging findings after receiving corticosteroids over a course of weeks to months. However, controlled data are lacking, and the long-term benefit of steroids remains unproven. Steroid therapy also carries risks. Chronic corticosteroids can further depress immune function, increasing susceptibility to infections such as TB or opportunistic pathogens. In practice, the use

of corticosteroids should be carefully individualized. If instituted, it is crucial to first exclude active infections to avoid exacerbating an unrecognized infection. In patients with rapid clinical decline, high inflammatory markers, or significant ground-glass infiltrates on CT, a cautious trial of steroids may be reasonable.[3,8] If there is no objective improvement in symptoms, oxygenation, or imaging, steroids are typically tapered off to limit side effects.

Other immunomodulatory treatments have been considered given the immune dysregulation in acute silicosis. For instance, intravenous immunoglobulin (IVIG) has occasionally been used in autoimmune PAP. Its role in silicoproteinosis is unclear, except perhaps in cases with documented GM-CSF autoantibodies. These approaches are not routine. The mainstay remains supportive care, WLL, and cautious use of steroids.

Lung Transplantation

For patients with progressive acute silicoproteinosis unresponsive to medical therapy, bilateral lung transplantation may be the only life-saving option. Outcomes are generally favorable and comparable to those seen in idiopathic pulmonary fibrosis.[46] Ideal candidates are typically young individuals in their 30s or 40s, without significant comorbidities, and with rapidly worsening respiratory failure. In recent engineered stone outbreaks, many such patients have required transplant evaluation due to end-stage disease.[14]

Transplantation carries risks such as rejection, infections from immunosuppression, and limited organ availability. However, when successful, it can restore lung function and prolong life. Recurrence of silicoproteinosis does not occur in the transplanted lungs if silica exposure is avoided. Remaining silica in unresected hilar nodes has not been shown to cause disease in the graft. Unlike autoimmune PAP, secondary PAP due to silica does not recur post-transplant. Postoperative care follows standard lung transplant protocols, focusing on rejection, infection prevention, and medication side effects.

PROGNOSIS

The overall prognosis of acute silicoproteinosis is poor. This disease often continues to progress despite removal from exposure and aggressive supportive care.[24] Studies from artificial stone-associated silicosis cohorts have reported mortality rates ranging from approximately 19% to over 30% within just a few years of diagnosis, with many patients either dying or requiring lung transplantation.[25,47] By comparison, chronic silicosis typically has a much longer survival span, making the acute form particularly pernicious.

Clinical deterioration in acute silicoproteinosis is driven by the persistent accumulation of proteinaceous material in the alveoli, ongoing inflammation, and irreversible fibrosis. Even with interventions like whole lung lavage, the underlying pathogenic process often continues unabated.[25] In many patients, progressive massive fibrosis, the coalescence of fibrotic nodules into large conglomerate masses, can rapidly develop, severely impairing lung function.[47] The development of pulmonary hypertension, resulting from chronic hypoxemia and destruction of the pulmonary capillary bed, further worsens prognosis.[48]

Early diagnosis and immediate cessation of exposure appear to offer the best chance at slowing disease progression. Patients diagnosed at the initial stages who promptly discontinue exposure may experience periods of clinical stability. Lung function may remain impaired, but if fibrosis is limited, disease progression might plateau for some time.[24] However, relapses are common, especially in patients with significant fibrosis or recurrent pulmonary infections. Respiratory infections can cause acute exacerbations, which are frequently fatal. Reports exist of patients initially improving after treatments such as lavage and steroids, only to deteriorate rapidly due to opportunistic infections like Nocardia or Aspergillus pneumonia, or complications such as spontaneous pneumothorax due to ruptured cystic changes.[3,20]

Historically, acute silicosis has carried a grave prognosis; older case series described median survival of approximately 4-5 years post-diagnosis, with many patients succumbing to respiratory failure.[25] Advances in modern care have allowed some patients to receive lung transplants, dramatically improving individual survival outcomes. However, considering all patients (including those who do not receive transplants), overall mortality remains high. Without definitive intervention, acute silicoproteinosis remains a frequently fatal condition.

Prognosis also varies with the degree of lung fibrosis at diagnosis. Patients whose disease is detect-

ed early, during the predominant alveolar proteinosis phase and prior to extensive fibrosis, generally have better outcomes compared to those with advanced fibrosis.[24] The availability of advanced therapies such as lung transplantation can transform an otherwise terminal prognosis into a chronic, manageable condition for some patients.[47] Nevertheless, given that many affected individuals are young, the disease's impact in terms of lost years of life and disability remains substantial.[49]

Long-term outcome data for recent engineered stone cohorts continue to emerge. In Australian and U.S. cohorts of engineered stone workers, significant numbers have undergone lung transplantation or are on waiting lists, with several deaths reported within a few years of diagnosis.[47] Continued surveillance of these cohorts will provide more precise estimates of median survival and long-term outcomes.

EMERGING AND FUTURE THERAPEUTIC OPTIONS

Given the limited efficacy of existing treatments for acute silicoproteinosis, substantial research interest has focused on novel strategies targeting the underlying pathophysiology. These include approaches aimed at enhancing surfactant clearance, modulating inflammation, attenuating fibrosis, and promoting lung repair or regeneration.[50] While none of these experimental therapies have yet become standard of care, they offer hope for improving outcomes in the future.

GM-CSF Augmentation

Because impaired GM-CSF signaling contributes to defective surfactant clearance by alveolar macrophages.[50] Replacement therapy with recombinant GM-CSF has been a successful strategy in autoimmune PAP.[51] Several studies have demonstrated that inhaled GM-CSF can improve oxygenation, lung function, and radiologic findings in patients with GM-CSF autoantibody-mediated PAP.[51,52] In acute silicoproteinosis (a secondary PAP), the role of GM-CSF augmentation is still being defined. Since the fundamental issue is not an absolute GM-CSF deficiency but rather macrophage incapacitation by silica, it is unclear how much benefit GM-CSF therapy would provide. However, in patients with coexisting anti-GM-CSF antibodies or partial macrophage responsiveness, GM-CSF supplementation could be helpful. Early clinical experiences are anecdotal: some case reports have described silicoproteinosis patients receiving subcutaneous or inhaled GM-CSF with improvement in surfactant clearance and oxygenation.[52] Nevertheless, robust data are lacking, and clinical trials specifically evaluating GM-CSF in secondary PAP due to silica exposure would be valuable.[52]

Statins

Statins, widely used as cholesterol-lowering agents, also have immunomodulatory effects that may be beneficial in PAP syndromes. In idiopathic PAP, alveolar macrophages accumulate intracellular cholesterol and lipids, impairing their ability to process surfactant. Statins promote cholesterol efflux from macrophages and may thereby restore their function.[53] In a pilot study, oral statin therapy resulted in clinical and radiologic improvement in a subset of autoimmune PAP patients who were refractory to standard treatment.[53] In silica-induced PAP, the rationale is similar: statins might help clear intracellular lipid from dust-exposed macrophages and reduce lung inflammation. While not yet supported by strong evidence in silicoproteinosis, the safety and availability of statins make them attractive as adjunctive therapy in this setting.[53]

Anti-inflammatory Therapies

Silica-induced activation of the NLRP3 inflammasome and release of interleukin-1β (IL-1β) and IL-18 are key drivers of lung inflammation in acute silicosis.[54] This has prompted interest in therapies targeting this pathway. Anakinra, an IL-1 receptor antagonist, has been used in other inflammatory diseases and might reduce the intense neutrophilic alveolitis in silicotic lungs. In mouse models of silicosis, IL-1 blockade (using anakinra) substantially decreased silica-induced lung inflammation and attenuated inflammatory cell accumulation.[55] While human data are very limited, there is some indication of benefit: a case report in a patient with progressive silicosis noted that 6 months of anakinra therapy improved oxygenation, diffusing capacity (DLco), and PET imaging findings.[55] Direct NLRP3 inflammasome inhibitors and caspase-1 blockers are also under investigation in preclinical models of silica-induced lung injury.[55] Tumor necrosis factor-alpha (TNF-α) is another mediator implicated in silicosis. Anti-TNF therapies (e.g., infliximab) have theoretical benefit in reducing granulomatous inflammation, but they carry a high risk of serious infections such

as tuberculosis, a pre-existing concern in silicosis patients.[29] Other agents with anti-inflammatory properties, such as colchicine, have been tried in the past to inhibit inflammasome activation, though older studies in silicosis were inconclusive and did not show clear benefit.[56]

RANKL Inhibition

Recent studies suggest that silica-exposed macrophages may differentiate into osteoclast-like cells that contribute to lung matrix destruction.[22] This osteoclastogenesis appears to be driven by RANKL (Receptor Activator of Nuclear Factor-κB Ligand) produced in the silicotic lung. Inhibiting this pathway, for instance with denosumab, a RANKL-blocking monoclonal antibody used in osteoporosis, may offer a new therapeutic angle. This concept remains entirely theoretical at this point, but it exemplifies how emerging mechanistic insights can identify novel repurposing opportunities.[22]

Antifibrotic Therapy

Antifibrotic agents like nintedanib and pirfenidone, approved for idiopathic pulmonary fibrosis, have been explored in silicosis. These drugs target pro-fibrotic pathways and have shown benefit in preclinical models of silica-induced lung disease.[57,58] For example, pirfenidone administration in silica-exposed mice reduced inflammatory cytokines (TNF-α, IL-1β, IL-6), diminished collagen deposition, and improved lung mechanics.[57] Nintedanib has similarly attenuated fibrosis and inflammation in animal models of silicosis.[58] Small observational studies in patients with chronic silicosis have reported slower declines in lung function with these medications. Notably, the INBUILD trial demonstrated a significant reduction in the rate of FVC decline in patients with progressive fibrosing interstitial lung diseases, including pneumoconiosis.[58] In acute silicoproteinosis, where fibrosis can evolve rapidly, early initiation of antifibrotic therapy might be considered to slow irreversible damage, although no trials have yet been conducted in this specific population.

Mesenchymal Stem Cell (MSC) Therapy

MSCs possess anti-inflammatory, immunomodulatory, and tissue-reparative properties. In models of silica-induced lung injury, intravenous or intratracheal infusion of MSCs has reduced inflammatory cytokine levels, decreased fibrosis, and improved survival of treated animals.[59] For example, transplantation of adipose-derived MSCs into silica-exposed rats attenuated pulmonary fibrosis through anti-inflammatory and anti-apoptotic effects.[59] MSCs may also enhance macrophage surfactant-processing function and promote repair of the alveolar epithelium, addressing key aspects of silicoproteinosis pathology. Although early-phase trials in other lung diseases suggest MSC therapy is safe, no clinical studies have yet been performed in patients with silicosis.[59]

Future Directions

As our understanding of the molecular and immunologic mechanisms of acute silicoproteinosis evolves, a multipronged therapeutic approach will likely be necessary to improve outcomes. This could include combinations of interventions, GM-CSF supplementation, antifibrotics, anti-inflammatory drugs, and regenerative or cell-based therapies. Experimental strategies such as gene editing or transplantation of ex vivo-modified macrophages derived from stem cells may someday enable restoration of alveolar homeostasis. Recent preclinical work in a hereditary PAP model has shown transplantation of gene-corrected alveolar macrophages can durably engraft in the lung and normalize surfactant clearance, a concept that could be transformative if applied to silicoproteinosis in the future.[60]

CONCLUSION

Silicoproteinosis is a form of acute silicosis, initially characterized in heavily exposed sandblasters and later linked to other silica-intensive occupations. It is defined by the diffuse intra-alveolar accumulation of surfactant-rich, lipoproteinaceous material, closely resembling pulmonary alveolar proteinosis (PAP). Establishing a clear temporal association between symptom onset and recent silica exposure can greatly aid in timely suspicion, diagnosis, and intervention, an essential step given the potentially preventable yet progressive nature of the disease.

High-resolution computed tomography (HRCT) of the chest plays a central role in diagnosis. A hallmark early finding is extensive bilateral ground-glass opacities with superimposed interlobular and intralobular septal thickening, forming the classic “crazy-paving” pattern.

Eliminating further exposure is critical, as it can

at least prevent additional pulmonary damage. Early diagnosis and immediate cessation of exposure provide the best opportunity to slow disease progression. Patients diagnosed in the early stages who promptly discontinue exposure may experience periods of clinical stability. Although lung function often remains impaired, if fibrosis is limited, the progression may plateau temporarily. However, relapses are frequent, particularly in those with significant fibrotic changes or recurrent pulmonary infections.

In the absence of definitive treatment, acute silicoproteinosis remains a potentially fatal disease. As with all occupational illnesses, prevention through appropriate protective measures is paramount. Further studies exploring its etiopathogenesis and improved diagnostic strategies are urgently needed.

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CHAPTER 06

BIRT-HOGG-DUBÉ SYNDROME

BIRT-HOGG-DUBÉ SENDROMU

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BIRT-HOGG-DUBÉ SYNDROME

BIRT-HOGG-DUBÉ SENDROMU

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ABSTRACT

Birt-Hogg-Dubé (BHD) syndrome is an uncommon autosomal dominant condition that predominantly affects the lungs, kidneys, and skin. The underlying genetic basis involves pathogenic or likely pathogenic mutations in the FLCN gene, which encodes folliculin, a tumor suppressor protein implicated in various intracellular signaling cascades. These mutations disrupt normal folliculin function, leading to a broad clinical phenotype that can vary significantly, even among individuals harboring identical genetic alterations.

Diagnosis is commonly suspected when characteristic findings such as pulmonary cysts, recurrent pneumothorax, cutaneous fibrofolliculomas, and renal neoplasms are identified, either in isolation or in combination. Pulmonary involvement, particularly the development of multiple, bilateral, thin-walled cysts predominantly located in the lower lung zones, is the most frequent clinical manifestation. These cysts are a major contributor to spontaneous pneumothorax, which often serves as a presenting symptom. Skin findings typically include benign dome-shaped papules located on the face or upper body, consistent with fibrofolliculomas or trichodiscomas. Although renal manifestations are less prevalent, they carry greater prognostic significance due to their association with disease-specific mortality. The renal tumor spectrum most commonly comprises chromophobe renal cell carcinoma, oncocytomas, and hybrid oncocytic/chromophobe tumors, although clear cell and papillary subtypes have also been observed.

In the majority of cases, molecular confirmation is achieved through identification of pathogenic germline variants in FLCN. In scenarios where no pathogenic alteration is detected, diagnosis may still be established based on clinical features and typical radiologic findings. The 2024 ERN GENTURIS guideline outlines a multidisciplinary approach to diagnosis and surveillance, integrating clinical, imaging, and molecular assessments.

Currently, there is no curative or disease-specific therapy available for BHD syndrome. Therefore, clinical management emphasizes early recognition, regular monitoring for renal malignancies, and preventive strategies to reduce pneumothorax risk. Given its multisystem nature, lifelong follow-up and a personalized care model are essential. BHD syndrome is thus considered a hereditary cancer predisposition disorder that necessitates coordinated multidisciplinary management.

Keywords: *Birt-Hogg-Dubé syndrome; Cystic lung disease; Pneumothorax; Renal cell carcinoma*

ÖZET

Birt-Hogg-Dubé (BHD) sendromu, nadir görülen ve otozomal dominant kalıtım gösteren bir hastalık olup; akciğer, böbrek ve deri tutulumu ile kendini gösterir. Hastalığın genetik altyapısında, FLCN geninde saptanan patojenik ya da olası patojenik varyantlar yer almaktadır. Bu varyantlar, folikülin adlı tümör baskılayıcı proteinin ekspresyonunu bozarak sinyal iletim yollarında düzensizliklere yol açar.

Klinik yelpaze son derece heterojen olup aynı mutasyonu taşıyan bireyler arasında bile belirgin fenotipik farklılıklar gözlenebilir. Tanı, tipik olarak pulmoner kistler, spontan pnömotoraks, kutanöz fibrofolikülomalar ve renal tümörlerin birlikte veya ayrı ayrı gözlenmesiyle klinik olarak ile tanıdan kuşkulanılır. Çoğu olguda, moleküler tanı ile kesinleştirilir. Pulmoner tutulum, BHD sendromunun en yaygın fenotipik özelliğidir. Hastaların yaklaşık %80'inde multipl, ince duvarlı, bilateral ve bazal yerleşimli pulmoner kistler izlenir. Bu kistik yapıların varlığı, spontan pnömotoraks gelişimi açısından majör

bir risk faktörüdür. Kutanöz bulgular sıklıkla baş-boyun bölgesinde sınırlı, benign karakterde, fibrofoliküloma veya trikodiskoma ile uyumlu papüler lezyonlar şeklinde izlenir. Renal tutulum, daha seyrek gözlenmesine rağmen, BHD sendromunda mortalite ile ilişkilidir. Renal tümör spektrumunda en sık olarak kromofob renal hücreli karsinom, onkositoma ve hibrit tip tümörler yer alır. Daha nadiren clear cell ve papiller alt tipler de bildirilmiştir. Bu tümörler çoğunlukla bilateral ve multifokal yerleşim gösterir.

Tanı, çoğu olguda FLCN geninde saptanan patojenik veya muhtemel patojenik germline mutasyonların genetik test ile doğrulanmasıyla kesinleşir. Ancak genetik test ile mutasyon gösterilemeyen olgularda dahi, karakteristik klinik bulgular tanıyı destekleyici olabilir. 2024'te yayımlanan ERN GENTURIS kılavuzu, BHD sendromuna yönelik tanı ve takip algoritmasını klinik, radyolojik ve moleküler düzeyde sistematik biçimde tanımlamaktadır.

Hastalığa yönelik spesifik veya küratif bir tedavi mevcut olmayıp, başlıca yaklaşım renal malignitelerin erken tanısı ve takibi ile pnömotoraks gelişiminin önlenmesi ve yönetilmesine dayanmaktadır. Sistemik tutulum potansiyeli, renal malignitelerle ilişkili mortalite riski ve yaşam boyu izlem gereksinimi nedeniyle BHD sendromu, multidisipliner yaklaşımla yönetilmesi gereken kalıtsal bir tümör predispozan sendromudur.

Anahtar Kelimeler: *Birt-Hogg-Dubé sendromu; Kistik akciğer hastalıkları; Pnömotoraks; Renal hücreli karsinom*

CASE PRESENTATION

A 46-year-old, lifelong non-smoker woman was referred to the pulmonary outpatient clinic for further evaluation of multiple pulmonary cystic lesions incidentally identified on thoracic computed tomography (CT) imaging performed at another facility. She reported mild exertional dyspnea, without chest pain, cough, hemoptysis, or systemic symptoms. There was no history of recent respiratory infections, trauma, or exposure to occupational or environmental risk factors. Her past medical history was notable for a left-sided primary spontaneous pneumothorax two years earlier, which had been managed with tube thoracostomy. No subsequent radiological or clinical follow-up had been conducted. She had no known chronic medical conditions, was not taking any regular medications, and denied any exposure to pulmonary toxins.

Upon clinical evaluation, the patient's vital parameters were stable, with peripheral oxygen saturation measured at 97% while breathing ambient air. Pulmonary auscultation revealed vesicular breath sounds without adventitious sounds. Dermatologic examination demonstrated multiple well-circumscribed, skin-colored papules measuring 1-5 mm in diameter, primarily located on the forehead and malar regions (Figure 1).

Multiple cystic lucencies were observed on the posteroanterior chest radiograph (Figure 2), predominantly in the left lower lung zone. A prior high-resolution computed tomography (HRCT) scan of the chest demonstrated numerous thin-walled cysts of varying

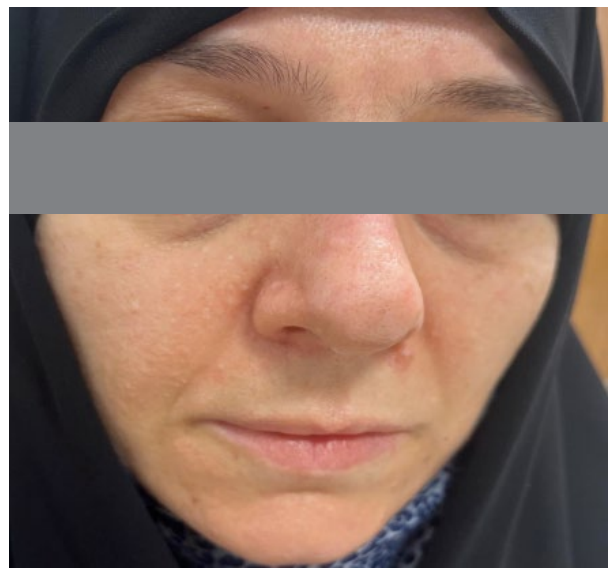


Figure 1. A 46-years-old female had numerous pale flesh-colored papules (fibrofolliculomas) are seen on the face.

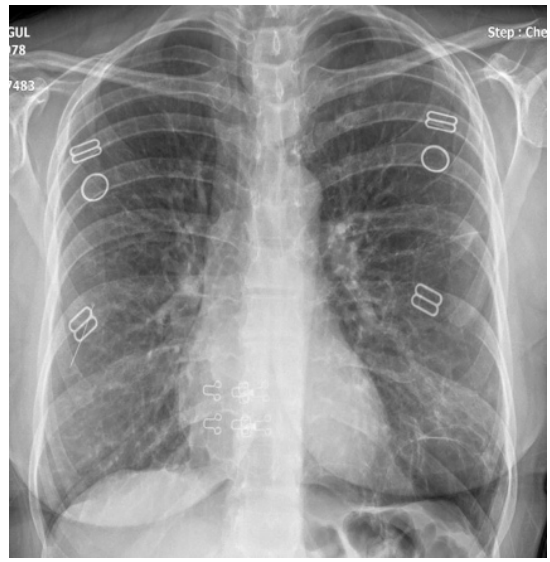


Figure 2. On the chest X-ray cystic opacities are seen especially left lower side.

sizes, distributed bilaterally with a predilection for the basal, subpleural, and paramediastinal regions. Several cysts exhibited lobulated contours and internal septations. There was no evidence of pneumothorax, parenchymal consolidation, or interstitial fibrosis (Figure 3). Further inquiry into her family history revealed that her father had undergone bilateral nephrectomy at the age of 59 due to renal tumors, and her paternal uncle had been hospitalized multiple times in his 40s for episodes described as spontaneous lung collapse. This pattern raised suspicion for a hereditary disorder involving pulmonary and renal manifestations.

INTRODUCTION

Birt-Hogg-Dubé syndrome (BHD) is an infrequent hereditary condition inherited in an autosomal dominant fashion, with clinical involvement typically seen in the pulmonary system, skin, and kidneys. The disorder is genetically linked to alterations in the FLCN gene, which encodes folliculin, a protein with tumor suppressor function. These molecular changes are recognized as the underlying genetic drivers of the disease.[1,2]

EPIDEMIOLOGY

The exact prevalence of BHD syndrome is unknown. However, epidemiological estimations indicate that it affects approximately 1 in 200,000 individuals.[3] Genomic studies in specific populations indicate a higher prevalence; for instance, a study conducted in the United States identified pathogenic FLCN variants, estimating their prevalence at approximately one in 3,234 individuals. In comparison, a study conducted in the United Kingdom reported that the prevalence ranged from 1 in 1,490 to 1 in 4,190.[4,5] The heterogeneity in clinical symptoms leads to disparities in prevalence estimations among various studies.

Before 2010, studies indicated a near-equal sex distribution; however, more recent researches from East Asia and the United States have revealed a female predominance, whereas studies from Italy, the Netherlands, and France have demonstrated a male predominance.[6-11] The age at diagnosis varies significantly with reported cases ranging from 2 to 92 years, with the mean global age at diagnosis estimated to be in the 40s.[12,13] Previous studies indicated a higher incidence of BHD syndrome in Europe and the United States in comparisons based on race and ethnicity; however, recent data suggest a more uniform global prevalence.[1,13]

PATHOGENESIS AND GENETICS

Genetic alterations in the FLCN gene represent the underlying cause of BHD syndrome. The gene spans 14 exons and is situated on chromosome 17p11.2.1 Fluorescence in situ hybridization studies have shown that FLCN mRNA is broadly expressed, particularly

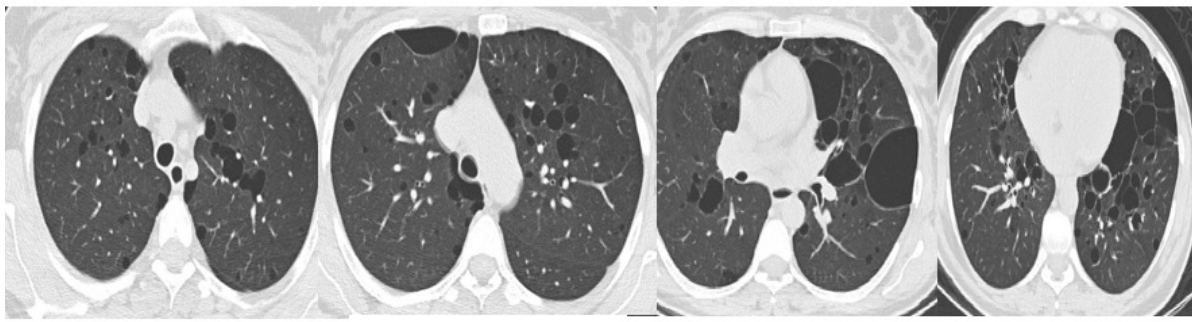


Figure 3. Thoracic CT scan shows bilaterally, multiple, vary in shape cystic lesion on axial images.

in the skin, lungs, kidneys, and several exocrine and neural tissues.[14] The primary role of FLCN in regulating cellular mechanisms related to cell growth, and the process in which these mechanisms become dysregulated in BHD syndrome, has not been fully elucidated. The principal function of FLCN in cellular regulation, particularly in pathways governing cell proliferation, remains incompletely defined. Folliculin is a tumor suppressor protein that exerts its effects through interaction with two major binding partners: folliculin-interacting protein 1 (FNIP1) and protein 2 (FNIP2).[15-17] These complexes modulate the activity of critical signaling kinases, including mechanistic target of rapamycin complex 1 (mTORC1) and AMP-activated protein kinase (AMPK) which are central to cell growth, metabolism, and tumor suppression.[18] Beyond its classical roles, the FLCN/FNIP axis is implicated in broader tumor-related and metabolic regulatory pathways, potentially linking BHD syndrome to other neoplastic conditions.

Although over 600 different FLCN variants have been identified worldwide, the most common mutation is a cytosine insertion or deletion (c.1285dupC/delC) within an eight-cytosine stretch in exon 11 of the FLCN gene.[1,19,20] A Japanese study found no detectable FLCN mutations in 16 out of 157 patients who were clinically suspected of having BHD syndrome based on personal and family history.[21] Additionally, two distinct case reports have shown patients diagnosed with BHD syndrome primarily on clinical criteria, despite no identifiable FLCN mutation. In one of these cases, reduced folliculin protein expression was observed in the absence of a detectable FLCN gene mutation.[22,23]

CLINICAL MANIFESTATIONS

BHD syndrome is characterized by three cardinal features: pulmonary cysts often leading to spontaneous pneumothorax, renal tumors, and various cutaneous lesions, with fibrofolliculomas being the most characteristic. Phenotypic variability has been observed even among families sharing the same FLCN mutation.[24] Some individuals with FLCN mutations might remain asymptomatic, while others may exhibit severe pulmonary, renal, and cutaneous symptoms. There are also reports of families with FLCN mutations presenting with isolated pulmonary involvement.[25,26] No clear genotype-phenotype correlation has been established between mutation type or location and cutaneous or renal manifestations. However, studies have found a strong link between FLCN mutations in exon 9 and an increased risk of spontaneous pneumothorax in patients harboring mutations in exons 9 and 12.[19] Studies involving diverse ethnic groups have shown that East Asian patients tend to present with more frequent pulmonary symptoms and pneumothorax. In contrast, they have fewer renal tumors and cutaneous lesions compared with Caucasian patients.[27,28] Additionally, a mean diagnostic delay of 9 to 13 years is reported.[6]

Pulmonary Manifestations

Pulmonary cysts develop in approximately 80% of individuals with BHD syndrome and may present with clinical manifestations ranging from no symptoms to spontaneous pneumothorax.[29] Cysts are most commonly detected in the fourth decade of life, although they can be observed from puberty to the eighth decade.[30] HRCT is the optimal imaging technique for assessing these cysts. The typical radiologic finding

consists of bilateral, thin-walled cysts surrounded by normal lung parenchyma.[31] Pulmonary cysts show significant variability in size, shape, and number. Typically, the diameter of pulmonary cysts is under 1 cm, but there have been documented instances of tiny cysts and those exceeding 2 cm.[32] Larger cysts often exhibit a lobulated and multiseptated morphology.[31] They are typically round, oval, or irregular in shape. The number of cysts may vary from a few to several hundred, predominantly located in the basal, subpleural, or paramediastinal sections of the lungs. Numerous cysts may also be found in the hilar or central areas, particularly near the main bronchi and pulmonary vessels.[21] Larger cysts are often located near bronchi and vessels, and may contain structures traversing their lumens. Smaller cysts typically affect bronchovascular bundles and interlobar fissures.[21] Longitudinal data on changes in cyst size over time remain inconclusive. Research conducted prior to 2020 often indicated that cyst sizes remain stable. A study released in 2023 suggested that large bilateral cysts may enlarge over time, and that both their number and morphology may change.[21,33]

The mechanism of cyst development in BHD syndrome is thought to be multifactorial. Researchers have demonstrated that the loss of folliculin in type II pneumocytes impairs intercellular adhesion, increases cell mortality, and potentially contributes to airway dilation.[34] Additionally, researchers have identified altered microRNA expression secondary to folliculin deficiency as another mechanism inducing cell death.[35] Due to gravitational effects, the basal regions of the lungs are more actively engaged in respiration. In these areas, cells with reduced adhesion due to folliculin deficiency may experience increased mechanical stress during breathing, promoting cyst formation.[36] Moreover, the absence of folliculin in mesenchymal cells has been demonstrated to influence myofibroblast development, resulting in reduced deposition of elastin and type III collagen in the alveolar septa.[37] Collectively, these findings suggest that structurally vulnerable lung regions are more susceptible to cyst formation under mechanical and cellular stress.

Patients with BHD syndrome have a 50-fold higher incidence of spontaneous pneumothorax compared to the general population.[38] Reported rates of pneumothorax vary among studies, ranging from 24% to 74%.[30] Research including 1,059 patients with BHD syndrome revealed a pneumothorax frequency of 50% and a recurrence rate of 66%. No significant difference in pneumothorax laterality was found, and the median age at first pneumothorax was 34 years.[13] Earlier onset of the first pneumothorax is associated with a higher risk of recurrence.[39] The presence of pulmonary cysts, as well as quantity, dimensions, overall volume, and familial history of pneumothorax, have been identified as risk factors for pneumothorax in BHD syndrome.[29] Conversely, Gunji et al. found no association between cyst quantity and pneumothorax.[40] In contrast, Lee et al. reported an inverse correlation between cyst size and pneumothorax incidence.[28]

Two studies assessing the clinical manifestations and pulmonary function tests of patients with BHD syndrome revealed that most individuals were asymptomatic, with dyspnea and cough reported as the most common respiratory symptoms. In both studies, more than 85% of patients showed normal results for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), and the FEV1/FVC ratio. In one study, residual volume (RV) was abnormal in up to 40% of patients, whereas in the other, only 3% showed abnormalities. Diffusing capacity of the lung for carbon monoxide (DLco) was within normal limits in approximately 70% of patients. Longitudinal follow-up revealed no significant changes over time in FEV1, FVC, FEV1/FVC, TLC, RV, or DLco.[41,42]

One study found that cigarette smoking independently downregulates folliculin expression. It also demonstrated that individuals with chronic obstructive pulmonary disease (COPD) have lower folliculin levels than healthy controls.[43] These findings imply that patients with BHD syndrome may be at increased risk for developing COPD, beyond that associated with smoking alone.

Although no strong association has been established between BHD syndrome and lung cancer, isolated cases have reported the presence of lung adenocarcinoma, atypical adenomatous hyperplasia and micronodular pneumocyte hyperplasia in affected individuals.[44]

Histological examination of cysts excised post-pneumothorax often reveals nonspecific features attributed to mechanical stress, inflammation, and tissue remodeling. These features may resemble bullae, emphysema, or other cystic lung diseases.[45] However, the histopathological features of non-ruptured cysts in

BHD syndrome show distinct differences from those seen in other cystic lung diseases These cysts are lined by typical type II pneumocytes and lack inflammation or fibrosis. Their walls are thin and often merge with interlobular septa, bronchovascular bundles, or the stroma of the visceral pleura. Additionally, thin intraluminal structures resembling alveolar septa may divide the cyst cavity into multiple compartments.[45-47] At present, no specific immunohistochemical marker is available to definitively differentiate BHD syndrome-related cysts from other types.

Cutaneous Manifestations

Cutaneous manifestations of syndrome are observed in approximately 50% of patients.[13] Prevalence is approximately 20% in Asian populations and may be as high as 80% in European and American populations.[13,28] The reasons for this variation-whether due to genetic predisposition, environmental influences, or differences in diagnostic practices-remain unclear. For example, pulmonologists reported a prevalence of 20%, while dermatologists observed a rate as high as 83%.[48] Cutaneous lesions in BHD syndrome are benign and typically pose no clinical concern aside from aesthetic appearance. Since many patients do not undergo dermatological evaluation, the true prevalence is likely underestimated.[49] The probability of developing cutaneous symptoms in familial cases is estimated to range from 80% to 90%.[24] These lesions are predominantly observed during the fourth and fifth decades of life.[50,51] As patients age, the size of lesions tends to increase. Additionally, male patients often present with larger and more numerous lesions than females.[52]

Among the cutaneous findings in BHD syndrome, fibrofolliculomas and trichodiscomas are the most frequently observed.[53] Acrochordons are the third most common type of cutaneous lesion associated with BHD syndrome.[54] Fibrofolliculomas are asymptomatic, firm, dome-shaped papules that are white or skin-colored. They are benign hamartomas arising from the hair follicle apparatus.[52,55] They commonly occur on the face, head, neck, and upper extremities.[52,55] Lesions typically range from 1 to 10 mm in size and may present as isolated papules or coalescent plaques.[55,56] Trichodiscomas are also benign hamartomas derived from the hair follicle apparatus.[57] Clinically, trichodiscomas are indistinguishable from fibrofolliculomas and primarily located in the head and neck regions.[52] Although the exact pathophysiology is unclear, they are believed to arise from hair mantle stem cells through hamartomatous proliferation.[58] Histopathology establishes the differentiation between fibrofolliculomas and trichodiscomas. Acrochordons are soft, pedunculated, skin-colored lesions commonly found on the eyelids, neck, and axillae and they are benign and not specific to BHD syndrome.[59] In addition to the three primary lesions, case reports have described associations between BHD syndrome and several other cutaneous findings, including the cystic variant of fibrofolliculoma, periocular fibromas, connective tissue nevi, multiple angiomatous nodules (angiolipomas), periungual fibromas, angiofibromas, and intraoral papules.[55,60-65] Despite all these lesions being benign, an elevated risk of melanoma has been documented in association with BHD syndrome.[66] Nevertheless, the evidence from these investigations is insufficient to reach definitive conclusions.

Since the biopsy of cutaneous lesions resulted with fibrofolliculomas and trichodiscomas strengthen the diagnosis of BHD syndrome in a patient with pneumothorax history, familial pneumothorax and/or BHD syndrome history and cystic lung disease, patients should be evaluated in systematic way in the inspection of skin.

Renal Manifestations

Renal tumors are the only malignancies with a clearly established association with BHD syndrome. The likelihood of kidney cancer development in Patients with BHD syndrome is approximately 6.9 times greater than in the general population.[38] Research indicates that the incidence of renal cell carcinoma (RCC) in patients with BHD syndrome varies from 20% to 40%.[13,50,56] Although renal tumors have the lowest incidence among manifestations of BHD syndrome, they are responsible for the highest mortality, estimated at around 30%.[24,67] The incidence of kidney malignancies increases with age, peaking between 45 and 55 years.[13,21,68] Renal tumors are less commonly observed in East Asian patients than in Caucasian patients.[27,28]

BHD syndrome has been associated with several kidney tumor histologies, predominantly chromophobe tumors and hybrid chromophobe/oncocytic tumors.[13] Although chromophobe renal cell carcinoma and oncocytoma are the most common histological subtypes in BHD syndrome, clear cell, papillary, and mixed-type carcinomas have also been reported in

over 50% of patients with renal involvement. These tumors frequently exhibit bilateral and multifocal distributionn.[2]

The gross pathology of RCC differs based on the tumor type and size. Chromophobe tumors and hybrid chromophobe-oncocytic tumors are the most common subtypes. These lesions are macroscopically indistinguishable and require histological evaluation for definitive diagnosis. Both tumor types are generally well-defined and may be lacking a complete fibrous capsule; when preserved in formalin, they often exhibit a more yellowish color.[69] Conversely, clear cell and papillary subtypes typically show more aggressive characteristics and are commonly linked to poor prognoses.[18,70]

Although renal angiomyolipomas (AMLs) are classically considered hallmark lesions of tuberous sclerosis complex (TSC) and are frequently encountered in patients with lymphangioleiomyomatosis (LAM), emerging evidence suggests that AMLs may also occur, albeit rarely, in individuals with BHD syndrome. Several case reports have described the presence of renal AMLs in genetically confirmed BHD syndrome, raising the possibility of a phenotypic overlap between BHD syndrome and TSC.[71-73] Therefore, in patients presenting with renal AML, particularly when accompanied by pulmonary cysts, spontaneous pneumothorax, or characteristic cutaneous lesions, BHD syndrome should be considered in the differential diagnosis. The diagnosis of renal LAM does not exclude BHD syndrome; recognizing this possibility facilitates the inclusion of BHD syndrome in the diagnostic evaluation.

Other Related Disorders

The involvement of FLCN gene mutations in mTORC1, AMPK, and in key tumor suppressor and metabolic signaling networks suggests a potential association between BHD syndrome and malignancy. Nonetheless, apart from kidney tumors, no definitive association with non-renal malignancies has been established. Secondary malignancies related to FLCN mutations may represent incidental clinical findings rather than causal associations. Although earlier small-scale studies suggested an elevated risk of colorectal cancer in BHD syndrome, a subsequent study involving 223 individuals found no significant increase in the incidence of colorectal cancer or polyps.[38,74] Interestingly, a UK-based study reported an increased risk of colorectal cancer specifically in BHD patients carrying the FLCN c.1285dupC mutation. Tong et al. reported 40 distinct cancer types associated with BHD syndrome.[52]

DIAGNOSIS

The first formal clinical guideline for the diagnosis and management of BHD syndrome was issued by the European Reference Network (ERN) in 2024 (Table 1).[75] Prior to this, most studies relied on the diagnostic criteria proposed by Menko et al. in 2009.[2]

The current guideline recommends establishing the diagnosis of BHD syndrome either through clinical criteria or, more commonly, via genetic confirmation of a pathogenic FLCN mutation. A definitive diagnosis of BHD syndrome can be made if genetic testing confirms a pathogenic or likely pathogenic FLCN mutation. Not all individuals with clinical features of BHD syndrome have detectable pathogenic or likely pathogenic FLCN mutations. However, a clinical diagnosis may still be appropriate in such cases.[75]

In the differential diagnosis of BHD syndrome, lymphangioleiomyomatosis, emphysema, pulmonary Langerhans cell histiocytosis and tuberosclerosis should be considered in terms of multiple cystic lesions in the lungs. And also, cutaneous neoplasms, fibrous papules of the nose, sebaceous hyperplasia, tuberosclerosis complex that mimics clinically fibrofolliculomas of BHD syndrome.

CLINICAL EVALUATION

BHD syndrome can occur in both sexes and across all age groups, not limited to young individuals.[12,13] According to the ERN, BHD syndrome should be suspected in patients presenting with any of the following clinical features, reflecting its involvement of the skin, lungs, and kidneys:[75]

1. Recurrent primary spontaneous pneumothorax in individuals without previously known lung disease
2. Multiple bilateral pulmonary cysts, especially localized in the lower lobes, without a clear etiological explanation
3. Bilateral or multifocal renal tumors, including renal cell carcinoma or oncocytoma
4. Renal cell carcinoma diagnosed before the age of 50, or in the presence of a positive family history

Table 1. ERN GENTURIS BHD syndrome diagnostic criteria.[75]

Major Criteria	Minor Criteria
At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset	Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
Pathogenic FLCN germline mutation	Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology
	A first-degree relative with BHD syndrome

** One major or two minor criteria.*

5. Multiple cutaneous papular lesions showing clinical features compatible with fibrofolliculomas or trichodiscomas
6. Co-occurrence of any of the above-mentioned skin, pulmonary, or renal findings, whether in the same individual or among first-degree relatives, regardless of a known family history of BHD syndrome

It is important to recognize that the full spectrum of clinical manifestations in BHD syndrome may not be present concurrently. Upon suspicion or identification of involvement in one organ system, clinicians should consider evaluating the other systems and conducting genetic testing. In all patients with multiple facial papules suspected to be fibrofolliculomas, a skin biopsy should be performed, HRCT of the lungs and contrast-enhanced CT or MRI of the kidneys are recommended for comprehensive evaluation.[75]

GENETIC TESTING-COUNSELING

Assessment of the FLCN gene can be conducted via single-gene analysis or as a component of broader genetic testing methods such as multigene panels, whole-exome sequencing, or genome-wide analysis. In clinical practice, multigene panels are most frequently employed. For individuals diagnosed with BHD syndrome, the identification rate of pathogenic variants (PVs) in the FLCN gene has been reported to range from 88% to 96%.[76] However, many missense alterations detected in this gene are still of uncertain clinical relevance and are commonly categorized as variants of uncertain significance (VUS).[75] It is therefore advised that such VUS be evaluated through detailed family segregation analyses and interpreted within the appropriate clinical context. Genetic testing for FLCN should be considered when any of the following clinical findings are present:[75]

1. Recurrent or familial cases of primary spontaneous pneumothorax
2. Bilateral pulmonary cysts predominantly located in the lower lung zones, without an identifiable cause
3. Multifocal or bilateral renal tumors, such as renal cell carcinomas or oncocytomas
4. Renal cell carcinoma presenting before the age of 45 or with a positive family history
5. Multiple skin-colored papules with clinical features of fibrofolliculomas or trichodiscomas, with histopathological confirmation of at least one lesion
6. A combination of dermatologic (e.g., fibrofolliculomas), pulmonary (e.g., lung cysts), and renal (e.g., renal tumors) manifestations in a single patient or among first-degree relatives

Genetic screening is advised for adult individuals who are closely related to those carrying a confirmed or likely pathogenic mutation in the FLCN gene. Routine testing is typically avoided in people under the age of 18. It is important to note that a negative result does not definitively exclude the possibility of BHD syndrome.

MANAGEMENT, FOLLOW-UP AND PROGNOSIS

Currently, no specific or curative treatment is available for BHD syndrome. Clinical management emphasizes early identification of the disease, prompt recognition

and intervention for renal tumors, and strategies aimed at minimizing the risk of pneumothorax.[75]

Following a diagnosis of BHD syndrome, patients should undergo dermatologic evaluation and be referred to a specialist if indicated. However, routine dermatologic follow-up is not required, as the cutaneous manifestations of BHD syndrome do not carry a risk of malignant transformation.[75] Treatment is generally not necessary but may be considered for cosmetic reasons. Available treatment options include shave excision, electrodessication (with or without curettage), and laser ablation using carbon dioxide (CO_2) or erbium:YAG lasers; however, recurrence is common.[77-79] Topical rapamycin, an inhibitor of the mTOR pathway, has been evaluated but has not demonstrated efficacy.[80]

There is currently no effective or established treatment for BHD syndrome-associated cystic lung disease. All patients diagnosed with BHD syndrome should undergo HRCT for lung assessment. However, routine imaging is generally not recommended in asymptomatic individuals under 20 years of age.[75] Management is limited to the prevention and treatment of pneumothorax. Although a direct causal link between smoking and pulmonary cysts or pneumothorax in BHD syndrome has not been firmly established, smoking cessation and avoidance of secondhand and thirdhand smoke are strongly recommended. Patients should receive pneumococcal and annual influenza vaccinations. During surgery, positive-pressure ventilation should be avoided due to the risk of cyst rupture. The size and number of pulmonary cysts may correlate with pneumothorax risk.[81] However, follow-up imaging is not routinely recommended and should only be performed when clinically indicated.[75,81] Routine pulmonary function testing is not required unless new respiratory symptoms arise.[75] Due to the high recurrence rate of pneumothorax, patients should be informed of their risk and educated about early warning signs such as dyspnea and chest pain. Prompt medical evaluation is recommended if these symptoms occur. Pleurodesis is advised following the initial occurrence of pneumothorax.[82] Data on the risk of cyst rupture due to barometric pressure changes during air travel or diving in patients with BHD syndrome remain limited. The estimated risk of pneumothorax during air travel is approximately 0.63%, while the risk during diving is approximately 0.33%.[83] Individuals with BHD syndrome considering careers involving air travel (e.g., pilots) or frequent diving should consult specialists regarding individual risk assessment and preventative approaches.[75]

All individuals with a confirmed diagnosis of BHD syndrome should undergo contrast-enhanced CT or magnetic resonance imaging (MRI) to evaluate renal involvement. Initiation of screening is generally recommended at 20 years of age, irrespective of the presence or absence of known renal lesions. For those with identified renal masses, an active surveillance strategy is typically adopted until tumors reach a diameter of approximately 3 cm, at which time nephron-sparing surgical intervention is generally considered.[75] This conservative management strategy is favored due to the lifelong risk of developing multiple renal tumors in individuals with BHD syndrome. Moreover, prior surgeries may complicate future resections and impair radiologic interpretation.[18,54,84] Evidence supports the effectiveness of percutaneous thermal ablation for treating renal malignancies and current guidelines consider it an acceptable alternative to surgical intervention.[75,85-87] To date, no studies have evaluated kidney transplantation outcomes in patients with BHD syndrome. The primary concern regarding transplantation in BHD syndrome is the potential for cancer recurrence or de novo tumor development under immunosuppression.[88] A published case from Japan highlighted successful long-term disease stabilization using everolimus in a patient with metastatic RCC.[89] Metastatic disease is generally managed similarly to other forms of metastatic RCC, although no prospective studies specifically addressing this population are currently available. In BHD syndrome, ongoing research aims to clarify optimal renal cancer screening protocols, investigate the molecular basis of pulmonary cyst formation, and delineate the natural course of the disease, with the ultimate goal of guiding targeted therapeutic development.[90]

The prognosis of BHD syndrome depends on renal tumors because renal cancer represents the leading cause of mortality in patients with BHD syndrome. Because BHD syndrome is a rare condition, comprehensive data on overall survival remain limited. Nonetheless, early diagnosis and routine surveillance are crucial to improving long-term survival outcomes in individuals affected by this condition.

CASE ANALYSIS

This case highlights the necessity of a comprehensive diagnostic approach in young individuals presenting

with recurrent spontaneous pneumothorax. While the preliminary clinical picture appeared to be an isolated thoracic event, the detection of subtle dermatological lesions and a subsequently revealed family history of kidney malignancies and pneumothorax raised suspicion of an underlying genetic condition.

The diagnostic process during hospitalization was guided by clinical reasoning and supported by imaging and histopathological evidence. HRCT of the chest revealed numerous thin-walled pulmonary cysts, predominantly located in the basal and subpleural regions. Dermatologic evaluation identified multiple facial papules, and histopathological analysis confirmed a fibrofolliculoma. These findings, along with a significant family history, raised suspicion for BDH syndrome. Genetic testing subsequently identified a pathogenic FLCN c.1285dupC mutation. The diagnosis was made based on the presence of multiple lung cysts, characteristic skin lesions, a pathogenic FLCN mutation wand a family history of recurrent pneumothoraces and renal tumors. No pathological findings were detected on abdominal imaging, and regular follow-up is planned.

In addition to organ-specific management, a preventive care strategy was implemented. The patient received genetic counseling and was advised to avoid established risk factors for pneumothorax, including smoking, scuba diving, and sudden barometric pressure fluctuations. Cascade testing was recommended for first-degree relatives; however, genetic testing in asymptomatic minors was deferred.

CONCLUSION

Birt-Hogg-Dubé syndrome is a rare hereditary disorder characterized by a broad clinical spectrum involving the pulmonary, dermatological, and renal systems. It warrants a high index of suspicion, particularly in patients presenting with recurrent spontaneous pneumothorax, bilateral pulmonary cysts, typical cutaneous manifestations, and a family history of renal neoplasms. Failure to establish an early diagnosis may delay the detection and management of potentially life-threatening renal malignancies, not only in the affected individual but also in genetically predisposed relatives. In this regard, molecular analysis of the FLCN gene constitutes a cornerstone of diagnostic confirmation and informs both patient care and familial genetic counseling. Early recognition facilitates timely surveillance for renal tumors, reduces the risk of pneumothorax recurrence, and helps avoid unnecessary invasive interventions. The optimal management of Birt-Hogg-Dubé syndrome necessitates a coordinated, multidisciplinary approach involving pulmonologists, dermatologists, urologists, and clinical geneticists. Enhancing clinical awareness is key to mitigating diagnostic delays and improving patient outcomes. Despite its rarity, the syndrome presents with distinct clinical and radiological features that enable early recognition when carefully assessed. Prompt diagnosis and long-term surveillance not only improve survival and quality of life but also reduce the burden of overtreatment.

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CHAPTER 07

LYMPHANGIOLEIOMYOMATOSIS

LENFANJİYOLEYOMİYOMATOZİS

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LYMPHANGIOLEIOMYOMATOSIS

LENFANJİYOLEYOMİYOMATOZİS

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a female-predominant, low-grade systemic neoplasm characterized by the proliferation of abnormal smooth muscle-like cells resulting in progressive cystic lung disease. Other key manifestations of LAM include recurrent spontaneous pneumothoraces, lymphatic complications such as lymphadenopathy and chylous effusions, and renal AML. LAM occurs almost exclusively in women and appears to be estrogen-responsive, with symptoms worsening during pregnancy and with the use of estrogen-containing drugs. LAM occurs in two forms: sporadically (S-LAM) or in association with tuberous sclerosis complex (TSC-LAM).

LAM occurs from biallelic loss of function mutations in either TSC1 on chromosome 9q34 or TSC2 on chromosome 16p13, with TSC2 mutations being more common. LAM is classified as a perivascular epithelioid cell tumor (PEComa). LAM cells migrate or metastasize to distant sites despite appearing morphologically benign. The origin of LAM cells has been a mystery for decades, although recent evidence seems to suggest the uterus as the likely source of origin. One proposed mechanism for the migration of LAM cells is the fragmentation or "shedding" of LCCs into the lymphatic system and extra-lymphatic spaces. Once in the lymphatic system, LCCs attach to lymphatic channels through interactions with the lymphatic endothelial cell layer. LAM cells can then proliferate and form new LAM cell clusters.

The average age of diagnosis of LAM is around 35 years, although there is wide variability. The most common presenting manifestations leading to an initial diagnosis of LAM are related to the pulmonary involvement of LAM. Approximately one third of patients with LAM present with spontaneous pneumothorax. Another one third of patients present with other pulmonary symptoms such as shortness of breath, wheezing, cough, or hemoptysis. The most common reported symptoms in women with LAM include dyspnea on exertion and chronic fatigue. Increasing use of thoracic CT scans (e.g., coronary calcium scoring scans) has also resulted in incidental discovery of cystic lung disease and early discovery of LAM in several instances and is becoming more common. Renal AMLs can be seen in about one-third of women with sporadic LAM where they mostly tend to be single lesions and unilateral.

The natural course of LAM is a slow progressive decline in lung function. Approximately 25% of patients require supplemental oxygen after 10 years. After symptom onset, the estimated transplant-free survival is 90% at 10 years and 64% at 20 years. In patients with TSC, LAM is the second most common cause of death and the leading cause of death in adult women with TSC.

Definitive diagnosis of LAM must have three components: 1) supportive clinical history; 2) characteristic CT findings of lung cysts; and 3) one of the following: TSC, renal angiomyolipomas, serum VEGF-D ≥ 800pg/mL, chylous pleural effusion or chylous ascites, lymphangioleiomyomas, presence of LAM cells in effusions or lymph nodes, or histopathological confirmation by biopsy of the lung or biopsy of abdominopelvic tumors. All attempts must be made to establish a definitive diagnosis of LAM prior to initiation of treatment with mTOR inhibitors.

General principles of management in LAM include pharmacological therapy to address the underlying molecular mechanisms driving the pathogenesis of LAM, management of LAM-associated complications, and supportive care such as: 1. Trial of bronchodilators with continued use in patients with evidence of clinical benefit; 2. Vaccination against common respiratory pathogens such as pneumococcus,

influenza, RSV, and SARS-CoV-2; 3. Regular exercise and consideration of pulmonary rehabilitation to address dyspnea and muscular deconditioning; 4. Supplemental oxygen therapy as indicated based on resting or exertional desaturation; 5. Screening for osteoporosis, especially in postmenopausal patients and patients with limited physical activity due to LAM; 6. Assessing for and proactively addressing mental health concerns such as anxiety and depression; and 7. Counseling to stay physically active, maintain healthy nutrition and avoidance of pulmonary toxins such as cigarette smoke.

The last two decades have seen tremendous progress in LAM including, but not limited to, improved understanding of the molecular pathogenesis, discovery of a blood-based diagnostic biomarker, advent of a safe and effective suppressive therapy, publication of clinical practice guidelines, and the establishment and expansion of a worldwide network of clinics that not only provides high quality clinical care but also facilitates collaborative research in LAM as well as multiple other rare lung diseases. With close collaboration among the LAM patients, scientists and clinicians, LAM is well poised to continue to be an exemplar of how to make meaningful progress in a rare disease in the future as the LAM community continues its journey towards improved understanding of the molecular perturbations that drive LAM and use that knowledge to develop novel, remission inducing therapies for LAM.

Keywords: *Rare interstitial lung disease; Lymphangioleiomyomatosis; LAM; Pneumothorax; Angiomyolipoma; Sirolimus*

ÖZET

Lenfanjiyoleyomiyomatozis (LAM), daha çok kadınlarda görülen, anormal düz kas benzeri hücrelerin proliferasyonu ile karakterize, ilerleyici kistik akciğer hastalığına yol açan düşük dereceli sistemik bir neoplazmdır. LAM'ın önemli klinik özellikleri arasında, tekrarlayan spontan pnömotorakslar, lenfatik komplikasyonlar (lenfadenopati, şilöz efüzyonlar) ve renal anjiyomiyolipom (AML) yer alır. Semptomlar gebelik sırasında ve östrojen içeren ilaçların kullanımında kötüleşir. Sporadik (S-LAM) ve tüberoskleroz kompleksi ile ilişkili (TSC-LAM) olmak üzere iki formda ortaya çıkar.

LAM, TSC1 (9q34) veya TSC2 (16p13) genlerindeki işlev kaybı mutasyonlarından kaynaklanır; TSC2 mutasyonları daha yaygındır. LAM, perivasküler epiteloid hücre tümörü (PEComa) olarak sınıflandırılır. Morfolojik olarak benign görünmesine rağmen LAM hücreleri uzak bölgelere göç eder veya metastaz yapar. LAM hücrelerinin kökeni uzun süre belirsiz kalmış olsa da, son veriler uterusun olası kaynak olduğunu düşündürmektedir. Olası patogenetik mekanizmalardan biri, LAM hücre kümelerinin parçalanarak veya "dökülerek" lenfatik sisteme ve lenfatik dışı boşluklara geçmesidir. Lenfatik sisteme girdiklerinde, lenfatik endotel hücre tabakası ile etkileşimler aracılığıyla kanallara tutunur, çoğalır ve yeni hücre kümeleri oluşturur.

LAM tanısı konma yaşı ortalama 35 yaş civarıdır, ancak bu değişkenlik gösterir. Tanıya yönelten en yaygın klinik belirtiler, genellikle akciğer tutulumuna bağlıdır. LAM hastalarının yaklaşık üçte birinde ilk başvuru nedeni spontan pnömotorakstır; hastaların diğer üçte biri ise nefes darlığı, hırıltı, öksürük veya hemoptizi gibi solunumsal semptomlarla doktora başvurur. Kadınlarda en sık bildirilen semptomlar, efor dispnesi ve kronik yorgunluktur. Toraks bilgisayarlı tomografisi (BT) çekilmesindeki artış (ör. koroner kalsiyum taramaları) da kistik akciğer hastalığının ve dolayısıyla LAM'ın rastlantısal olarak saptanmasına yol açmakta ve erken tanı olasılığını artırmaktadır. Sporadik LAM'lı kadınların yaklaşık üçte birinde renal AML saptanır; bunlar genellikle tek odaklı ve tek taraflıdır.

LAM'ın doğal seyri, akciğer fonksiyonlarında yavaş ama ilerleyici bir düşüştür. Hastaların yaklaşık %25'i, semptom başlangıcından 10 yıl sonra ek oksijen desteğine ihtiyaç duyar. Semptom başlangıcından sonra akciğer nakli endikasyonuna dek sağkalım oranı 10 yılda %90, 20 yılda %64'tür. TSC hastalarında LAM, en sık ikinci ölüm nedeni olup, yetişkin TSC tanılı kadınlarda en sık ölüm nedenidir.

LAM'ın kesin tanısı üç bileşeni içermelidir: 1. Destekleyici klinik öykü, 2. Akciğer kistlerinin karakteristik BT bulguları, 3. Aşağıdakilerden en az biri: TSC varlığı, renal anjiyomiyolipomlar, serum VEGF-D ≥ 800 pg/mL, şilöz plevral efüzyon veya şilöz asit, lenfanjiyoyomiyomlar, efüzyonlarda veya lenf düğümlerinde LAM hücrelerinin varlığı ya da akciğer veya abdominopelvik tümör biyopsisiyle histopatolojik doğrulama. Kesin tanı konması, özellikle mTOR inhibitörleri ile tedaviye başlamak için zorunludur.

LAM hastalarına yaklaşımda temel ilkeler; hastalığın patogenezini yönlendiren moleküler mekanizmaları hedefleyen farmakolojik tedavi, LAM'a bağlı komplikasyonların yönetimi ve destekleyici bakımı içerir. Bunlar arasında: 1. Klinik yarar sağlanan hastalarda bronkodilatör denemesi ve devamı, 2. Pnömokok, influenza, RSV ve SARS-CoV-2 gibi yaygın solunum patojenlerine karşı aşılama, 3. Nefes darlığı ve kas kondisyon kaybını gidermek için düzenli egzersiz ve pulmoner rehabilitasyon, 4. İstirahat veya efor sırasında desatürasyon varlığında ek oksijen desteği, 5. Özellikle postmenopozal hastalarda ve fiziksel aktivitesi sınırlı olanlarda osteoporoz taraması, 6. Anksiyete ve depresyon gibi ruh sağlığı sorunlarının proaktif değerlendirilmesi ve yönetimi, 7. Fiziksel olarak aktif kalma, sağlıklı beslenme ve sigara dumanı gibi pulmoner toksinlerden kaçınma konusunda danışmanlık yer alır.

Son yirmi yılda LAM konusunda moleküler patogenezin daha iyi anlaşılması, kan tahlilinde saptanabilen bir biyobelirtecin keşfi, güvenli ve etkili baskılayıcı tedavilerin geliştirilmesi, klinik uygulama kılavuzlarının yayımlanması ve yalnızca yüksek kaliteli klinik bakım sunmakla kalmayıp aynı zamanda LAM ve diğer nadir akciğer hastalıklarında iş birliğine dayalı araştırmaları kolaylaştıran küresel klinik ağların kurulup genişletilmesi gibi büyük ilerlemeler kaydedilmiştir.

LAM hastaları, bilim insanları ve klinisyenler arasındaki yakın iş birliği sayesinde LAM, nadir bir hastalıkta anlamlı ilerleme kaydetmenin örneklerinden biri olmaya devam etmektedir. LAM topluluğu, hastalığı yönlendiren moleküler bozulmaların daha iyi anlaşılması ve bu bilgilerin yeni, remisyon sağlayıcı tedavilerin geliştirilmesine dönüştürülmesi yönünde ilerlerken, gelecekte de bu alanda bir model olma potansiyelini sürdürmektedir.

Anahtar Kelimeler: *Nadir interstisyel akciğer hastalıkları; Lenfanjiyoleyomiyomatozis; LAM; Pnömotoraks; Anjiomiyolipom; Sirolimus*

CASE PRESENTATION

A 27-year-old woman with no significant past medical history presented to the emergency room with chief complaints of dyspnea on exertion and left sided pleuritic chest pain. Her physical examination was significant for sinus tachycardia and reduced air entry on the left side. Laboratory studies including serum chemistry and complete blood count were unremarkable. Chest X-ray showed large left hydropneumothorax (Figure 1a). A chest tube was placed, and she was admitted to the hospital for further evaluation. CT chest obtained during the hospitalization showed diffuse thin-walled cysts in bilateral lungs and marked enlargement of the thoracic duct (Figure 1b). She then underwent video-assisted thoracic surgery (VATS) with mechanical pleurodesis along with a diagnostic wedge biopsy. The biopsy showed numerous small thin-walled cysts lined with spindle-shaped cell proliferations with eosinophilic cytoplasm. Immunohistochemical stains were positive for desmin, actin, HMB45, estrogen receptor and progesterone receptor. Based on the biopsy results, the patient was diagnosed with lymphangioleiomyomatosis (LAM).

Subsequent work up included detailed assessment to evaluate for underlying Tuberous Sclerosis Complex (TSC) and abdominal imaging to look for renal angiomyolipomas (AMLs), both of which were negative. Abdominal imaging revealed multiple enlarged retroperitoneal lymph nodes. Serum vascular endothelial growth factor-D (VEGF-D) level was obtained and was elevated at 5010pg/mL, consistent with her diagnosis of LAM. Following the resolution of her pneumothorax, she established care in the clinic with a plan to serially monitor lung function.

INTRODUCTION

LAM is a female-predominant, low-grade systemic neoplasm characterized by the proliferation of abnormal smooth muscle-like cells resulting in progressive cystic lung disease. Other key manifestations of LAM include recurrent spontaneous pneumothoraces, lymphatic complications such as lymphadenopathy and chylous effusions, and renal AML.[1,2] LAM occurs almost exclusively in women and appears to be estrogen-responsive, with symptoms worsening during pregnancy and with the use of estrogen-containing drugs.[3-5] LAM occurs in two forms: sporadically (S-LAM) or in association with tuberous sclerosis complex (TSC-LAM). Tuberous sclerosis complex (TSC) is an autosomal dominant genetic syndrome characterized by neuropsychiatric disorders, skin manifestations and widespread benign tumor proliferation.[6] Mutations in the TSC genes are the key driver for the pathogenesis of LAM and lead to hyperactivation of the mechanistic target of rapamycin (mTOR) kinase pathway that results in unchecked growth and proliferation of the LAM cells.[7] Improved understanding of the molecular pathogenesis of LAM led to the

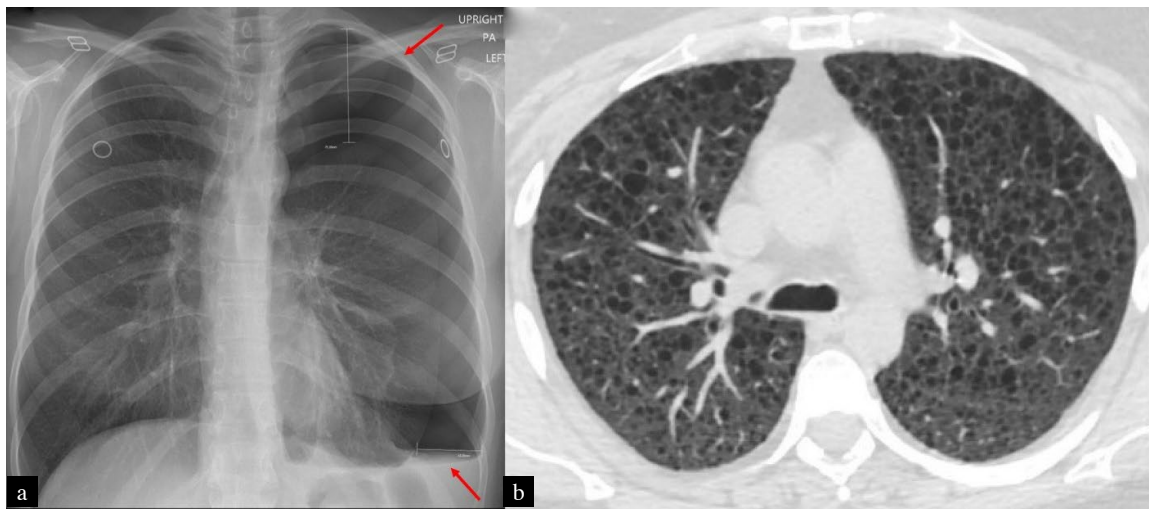


Figure 1. Presenting manifestation of LAM in the highlighted case: **a)** Presenting chest X-ray demonstrating large left pneumothorax (arrow), **b)** Axial view of CT chest showing multiple, small bilateral, thin-walled cysts characteristic of LAM.

conduct of pivotal trials that have helped establish the oral mTOR inhibitor, sirolimus, as an FDA-approved treatment for LAM. The use of sirolimus has been shown to stabilize lung function decline, improve the quality of life, shrink AMLs, mitigate chylous effusions, and reduce the risk of spontaneous pneumothoraces, and is the mainstay of treatment for LAM.[8-12]

EPIDEMIOLOGY

The prevalence of LAM was previously thought to range between 4-8 cases per million women.[13] However, more recent studies have reported that the prevalence of LAM is closer to approximately 20 cases per million women.[14,15] Extrapolating these numbers to the world's population, there should be approximately 80,000-100,000 women with LAM. Given the widespread delays in diagnosis and under-reporting, these estimates almost certainly represent minimum prevalence rather than true prevalence. The prevalence of TSC is estimated to be 1 in 5000.[16] Approximately one-third of women with TSC have LAM and the prevalence of LAM in women with TSC appears to increase with increasing age with one study reporting about 80% of women with TSC to have LAM by the age of 40 years.[17] Despite this observation, most LAM patients in registries and pulmonary clinics tend to have sporadic LAM rather than TSC-LAM.[18] While the exact reasons for this paradox are not clear, it is likely to be driven by other healthcare needs in TSC assuming a higher priority than LAM. The published natural history studies in LAM consist primarily of Caucasian and Asian women. However, there is no known differential racial or ethnic propensity to develop LAM; rather this might be related to socioeconomic factors and reflect differences in access to healthcare.

MOLECULAR PATHOGENESIS

LAM occurs from biallelic loss of function mutations in either TSC1 on chromosome 9q34 or TSC2 on chromosome 16p13, with TSC2 mutations being more common. TSC-LAM results from one germline mutation and one somatic mutation, while sporadic LAM results from two somatic mutations.[19,20] TSC1 and TSC2 act as tumor suppressor genes and encode the proteins hamartin and tuberin, respectively. Hamartin and tuberin form a protein complex that inhibits Ras homolog enriched in brain (Rheb), a GTP-binding protein that activates mTORC1 kinase. When either hamartin or tuberin are not functional, they are not able to form the protein complex, thus freeing Rheb to upregulate mTORC1, leading to phosphorylation of downstream targets ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), thereby increasing synthesis of proteins that promote cell cycle progression and lymphangiogenesis.[7,21]

LAM is classified as a perivascular epithelioid cell tumor (PEComa). LAM cells migrate or metastasize to distant sites despite appearing morphologically benign. The origin of LAM cells has been a mystery for decades, although recent evidence seems to suggest the uterus as the likely source of origin.[22] One proposed mechanism for the migration of LAM cells is the fragmentation or "shedding" of LCCs into the lymphatic system and extra-lymphatic spaces. Once in the lymphatic system, LCCs attach to lymphatic channels through interactions with the lymphatic endothelial cell layer. LAM cells can then proliferate and form new LAM cell clusters.[23,24]

Female sexual hormones, especially estrogen, have been implicated in the pathogenesis of LAM in preclinical models as well as by clinical observations such as the female predominance of LAM, worsening of disease activity with exogenous estrogen use and during pregnancy, and the presence of cyclical symptom variability coinciding with the hormonal fluxes of the menstrual cycle in a subset of women with LAM.[3-5,25-27,28] Other key pathogenic aspects of LAM include the LAM cells ability to evade detection by the immune system via multiple mechanisms such as expression of immune checkpoint inhibitors and their ligands and alteration in natural killer cell function, and their ability to recruit other immune cells and fibroblasts, that in turn lead to progressive destruction of the pulmonary parenchyma by the secretion of matrix degrading enzymes.[29-35]

CLINICAL MANIFESTATIONS

The average age of diagnosis of LAM is around 35 years, although there is wide variability.[2] The most common presenting manifestations leading to an initial diagnosis of LAM are related to the pulmonary involvement of LAM. Approximately one third of patients with LAM present with spontaneous pneumothorax. Another one third of patients present with oth-

er pulmonary symptoms such as shortness of breath, wheezing, cough, or hemoptysis. The most common reported symptoms in women with LAM include dyspnea on exertion and chronic fatigue. Increasing use of thoracic CT scans (e.g., coronary calcium scoring scans) has also resulted in incidental discovery of cystic lung disease and early discovery of LAM in several instances and is becoming more common. Renal AMLs can be seen in about one-third of women with sporadic LAM where they mostly tend to be single lesions and unilateral.[18,36] In contrast, renal AMLs are seen in about 80-90% of women with TSC-LAM where they often tend to be bilateral and have multiple lesions.[36] Lymphatic complications such as pelvic and retroperitoneal lymphadenopathy, abdominal lymphangioleiomyomas, and chylous effusions such as chylothorax, can be seen in about 20% of women with sporadic LAM.[37] For reasons that are not entirely clear, the lymphatic manifestations of LAM are much less commonly seen (<5%) in TSC-LAM.[36]

The natural course of LAM is a slow progressive decline in lung function. Approximately 25% of patients require supplemental oxygen after 10 years.[38] After symptom onset, the estimated transplant-free survival is 90% at 10 years and 64% at 20 years.[39] In patients with TSC, LAM is the second most common cause of death and the leading cause of death in adult women with TSC.[40]

DIAGNOSIS

History and Physical Examination

Detailed history and physical examination focused on ascertaining the presence of underlying TSC and excluding elements present in other cystic lung diseases is the key first step in the diagnostic evaluation of patients with suspected LAM.[41] The presence of characteristic cystic lung disease in a woman with TSC is generally sufficient to establish a clinical diagnosis of TSC-LAM without the need for histopathological confirmation.[42]

Laboratory Findings

Elevated serum VEGF-D level ≥800pg/ml in women with cystic lung disease is highly specific to help establish a confirmed diagnosis of LAM and exclude other common cystic lung diseases.[43,44] However, it is worth noting that the sensitivity of VEGF-D as a diagnostic biomarker is approximately 60% and as such the presence of a normal VEGF-D value does not exclude the possibility of LAM. The current American Thoracic Society (ATS)/Japanese Respiratory Society (JRS) LAM Clinical Practice Guidelines recommend checking VEGF-D levels prior to pursuing invasive diagnostic testing with women with suspected LAM.[8]

Radiology

Computed tomography (CT) of the chest is essential for the diagnosis of LAM. Characteristic findings are multiple round thin-walled intraparenchymal cysts that are present diffusely in bilateral lung fields (Figure 1). An expert radiologist can accurately identify LAM based on CT findings alone with high sensitivity and specificity.[45] However, given the need for long-term, and even lifelong, treatment, the LAM Guidelines recommend not using CT findings alone to establish a confirmed diagnosis of LAM.[46] The diagnostic criteria for LAM are summarized in Table 1.

Other potential CT chest findings in patients with LAM include chylous pleural effusions (~10-15%), mediastinal lymphadenopathy (~10%), and, rarely, ground glass changes in the pulmonary parenchyma reflecting chylous congestion. In patients with TSC-LAM, multiple pulmonary nodules, representing clusters of dividing type II pneumocytes, referred to as multifocal micronodular pneumocyte hyperplasia (MMPH), may also be seen. MMPH is generally a benign condition that does not tend to progress over time.[47]

Patients with known or suspected LAM should also have abdominal and pelvic CT imaging obtained in the initial evaluation to screen for the presence of renal and hepatic angiomyolipomas (AMLs). Renal AMLs are found in the majority (80-90%) of patients with TSC where they are often multiple and bilateral and in about one-third of patients with S-LAM where they are often limited to a single lesion in one kidney.[18,36] Hepatic AMLs may be found in up to one-third of patients with TSC-LAM but are generally not seen in patients with S-LAM.[36]

Pulmonary Function Tests

At initial diagnosis of LAM, approximately 60% of patients have airflow obstruction on spirometry, 30% of patients have normal spirometry, and 10% of patients have a restrictive defect.[18] Approximately 20-25% of patients have a significant response to bronchodilators. Diffusing capacity of the lungs for carbon

Table 1. Diagnostic criteria for LAM.

Definitive diagnosis of LAM requires all three of the following:
1. Compatible clinical history
2. HRCT chest with characteristic findings of LAM
3. At least one additional feature: • Diagnosis of TSC • Presence of renal AML* • Elevated serum VEGF-D ≥ 800pg/mL • Chylous effusion • Lymphangioleiomyomas* • LAM cells or LAM cell clusters on cytology of effusions or lymph nodes • Histologic confirmation by lung biopsy

** AMLs or lymphangioleiomyomas can generally be diagnosed radiologically and do not require invasive diagnostic procedures*
***AML=** angiomyolipoma, **LAM=** lymphangioleiomyomatosis, **TSC=** Tuberous Sclerosis Complex, **VEGF-D=** vascular endothelial growth factor-D*

monoxide (DLco) can be reduced in most patients, including those with normal spirometry. Patients with TSC-LAM are more likely to present with normal spirometry and DLco than patients with S-LAM. Pulmonary function tests (PFT) including spirometry with bronchodilator, lung volumes, and diffusing capacity should be obtained on initial evaluation. Serial PFTs is the mainstay to monitor for disease progression in untreated patients and to assess response to treatment in patients on sirolimus.

Role of Invasive Testing

Surgical lung biopsy is considered the gold standard for the diagnosis of LAM but is not always necessary to make a definitive diagnosis. When patients have characteristic cysts on CT chest without other features of LAM (clinical, laboratory), lung biopsy is recommended to confirm the diagnosis. Transbronchial lung biopsy (TBBx) has a diagnostic yield of over 50% and may obviate the need for surgical lung biopsy, which carries a higher risk of procedural complications.[48] If biopsy is needed to confirm the diagnosis of LAM, patients should have TBBx prior to surgical lung biopsy.[46] If TBBx is non-diagnostic, surgical lung biopsy should be considered. Transbronchial cryobiopsy has shown promise in the diagnosis of LAM and might be a reasonable approach in centers that are well versed in this technique.[49] Bronchoalveolar lavage has not been shown to have utility due to its low sensitivity and is not recommended in the diagnostic evaluation of LAM.

Pathology

LAM cells typically have two distinct morphological subtypes: proliferating small spindle shaped cells and cuboidal epithelioid cells. LAM cells exhibit overlapping features of myogenic (expressing α-actin) and melanocytic (expressing gp100 recognized by HMB-45 antibody) differentiation.[50] In addition, these cells also express estrogen and progesterone receptors. This immunohistochemical profile is observed in tumors known as perivascular epithelioid tumors (PEComas), and as such LAM also belongs in that category.[51] As LAM cells invade the lung parenchyma, they disrupt the normal architecture of lung tissue, leading to the destruction of vessels, obliteration of distal airways, and loss of elastic fibers in the alveolar walls. This process results in the formation of thin-walled cysts outlined by LAM cells, often accompanied by the proliferation of type II pneumocytes.[52] LAM lesions often abundant lymphatic channels, forming an anastomosing meshwork of slit-like spaces lined by LYVE1, podoplanin, and VEGFR3-positive lymphatic endothelial cells.[53] LAM cells or LAM cell clusters (spherical aggregates of LAM cells lined by a single layer of endothelial cells) can also be identified through cytological examination of chylous effusions.[46]

DIAGNOSTIC CRITERIA

Diagnostic criteria for LAM have been developed by the American Thoracic Society and the Japanese Respiratory Society (Table 1)46. Definitive diagnosis

of LAM must have three components: 1) supportive clinical history; 2) characteristic CT findings of lung cysts; and 3) one of the following: TSC, renal angiomyolipomas, serum VEGF-D ≥ 800pg/mL, chylous pleural effusion or chylous ascites, lymphangioleiomyomas, presence of LAM cells in effusions or lymph nodes, or histopathological confirmation by biopsy of the lung or biopsy of abdominopelvic tumors. All attempts must be made to establish a definitive diagnosis of LAM prior to initiation of treatment with mTOR inhibitors.

TREATMENT

General principles of management in LAM include pharmacological therapy to address the underlying molecular mechanisms driving the pathogenesis of LAM, management of LAM-associated complications, and supportive care such as:

1. Trial of bronchodilators with continued use in patients with evidence of clinical benefit;
2. Vaccination against common respiratory pathogens such as pneumococcus, influenza, RSV, and SARS-CoV-2;
3. Regular exercise and consideration of pulmonary rehabilitation to address dyspnea and muscular deconditioning;
4. Supplemental oxygen therapy as indicated based on resting or exertional desaturation;
5. Screening for osteoporosis, especially in postmenopausal patients and patients with limited physical activity due to LAM;
6. Assessing for and proactively addressing mental health concerns such as anxiety and depression;
7. Counseling to stay physically active, maintain healthy nutrition and avoidance of pulmonary toxins such as cigarette smoke.

Sirolimus

The first line treatment for LAM is the oral mTOR complex 1 inhibitor, sirolimus. Sirolimus forms a complex with FK binding protein 12 (FKBP-12) that inhibits activation of mTOR. The efficacy of sirolimus in the treatment of LAM has been evaluated in multiple clinical trials but the pivotal trial of sirolimus that led to its eventual approval by the United States Food and Drug Administration (FDA) was the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial.[9] The MILES trial was a double-blind, placebo-controlled, randomized trial that enrolled 89 women with LAM who had at least moderate impairment of lung function as defined by forced expiratory volume in 1 second (FEV_1) <70%. Patients were treated with sirolimus or placebo for 12 months followed by a 12-month period of observation off treatment. The primary outcome was the rate of change in FEV_1 (FEV_1 slope) in the first 12 months. Lung function in the sirolimus group stabilized during the initial 12-month period while subjects in the placebo group experienced a decline in FEV_1. After discontinuation of sirolimus, subjects experienced a decline in FEV_1 at a similar rate to the placebo group. In addition, sirolimus treatment was associated with a reduction in serum VEGF-D levels as well as an improvement in health-related quality of life. Based on the MILES trial results, sirolimus was approved by the US FDA for the treatment of LAM in 2015. Since then, sirolimus as a treatment for LAM has been approved by regulatory agencies in over 40 countries across the world. In addition to stabilizing lung function decline, treatment with sirolimus has also been shown to shrink AMLs, decrease the risk for future spontaneous pneumothoraces, reduce the size of lymphangioleiomyomas, resolve chylous effusions, and improve the overall lifespan of women with LAM.[10-12,54,55]

Pharmacological therapy with sirolimus should be considered for women with LAM in any of the following circumstances: 1) reduced FEV_1 <70% predicted, 2) other physiological measures suggesting substantial disease burden such as abnormal DLco, air trapping, and/or resting of exertional oxygen desaturation, 3) rapidly declining lung function (FEV_1 slope ≥90ml/year), 4) renal AML(s) that are greater than 3cm in size or growing, 5) problematic/symptomatic chylous effusions or large symptomatic lymphangioleiomyomas.[8] Treatment with sirolimus has recently been shown to reduce the risk of future pneumothoraces and high pneumothorax burden despite pleurodesis might also be another indication to treat.[12] The safety and efficacy of early administration of low-dose (1 mg/day) sirolimus to prevent the progression of LAM in patients with preserved lung function is currently being investigated in a randomized, placebo-controlled trial (Multicenter Interventional LAM Early Disease [MILED] trial; NCT03150914).

In general, sirolimus is very well tolerated. The most common side effects of sirolimus treatment

include stomatitis, diarrhea, acne, lower extremity edema, and hyperlipidemia.[56] The adverse effects from sirolimus tend to be more common in the first few months following treatment and decrease over time.[57] Furthermore, most adverse effects of sirolimus are dose dependent and in most patients using a lower dose can help mitigate the side effects while still preserving treatment efficacy.[54,58] Sirolimus is a potent inhibitor of wound healing and should be withheld a week before surgery and until the wounds are fully healed after surgery (typically 1-2 weeks).[56,59]

Everolimus

Everolimus is another mTOR inhibitor that has shown efficacy in the stabilization of lung function in patients with LAM. In a phase II multicenter open-label study, treatment with everolimus led to improvement in FEV_1, stability of FVC, improvement in 6-minute walk distance, and decreased VEGF-D levels.[60] Everolimus is FDA approved for the treatment of multiple TSC manifestations such as AMLs, subependymal giant cell astrocytomas, and epilepsy. Although not FDA approved for the treatment of LAM, everolimus is a reasonable alternative in patients who are not able to tolerate sirolimus therapy.

PNEUMOTHORAX

Spontaneous pneumothorax is a common complication of LAM and more than two-thirds of the patients with LAM experience at least one spontaneous pneumothorax in their lifetime with a very high risk (~70%) of recurrence.[61] The risk of recurrence can be reduced in half (to about 30%) with pleurodesis. As such, pleurodesis is recommended following the first episode of spontaneous pneumothorax in women with LAM rather than waiting for a recurrent event.[46] VATS-guided mechanical pleurodesis is the preferred mode of initial pleurodesis with the use of talc reserved for patients who experience recurrent events despite mechanical pleurodesis. It is worth noting that prior pleurodesis is not a contraindication for future lung transplantation.[46]

ANGIOMYOLIPOMAS

The primary goal of management in AMLs is to reduce the risk of hemorrhage and preserve renal function and the management strategies are similar to those in the context of TSC.[62] Options for management include surveillance, medical therapy with mTOR inhibitors, embolization, and nephron-sparing surgery. AMLs less than 3 cm carry a very low risk of bleeding and can generally be serially monitored. Symptomatic lesions, AMLs that are rapidly increasing in size, those larger than 8 cm and those with notable aneurysms are at high risk of rupture.[63,64] mTOR inhibitors are the first line treatment option for AMLs >3cm, especially if there are other concomitant LAM treatment indications.[65] Endovascular arterial embolization is preferred treatment for spontaneous rupture of AMLs and may also be a reasonable alternative for single lesions with significant aneurysmal burden who otherwise do not need mTOR inhibitor treatment for LAM.[65,66]

LYMPHATIC MANIFESTATIONS

For chylothorax and chylous ascites, treatment should be guided by the size of the effusion and symptom burden. For moderate-large, persistent, or symptomatic effusions, mTOR inhibitors are the first line option.[8] It is worth noting that it might take a few months (even 6-12 months) for mTOR inhibitors to take full effect; but they are effective in most patients.[11] Invasive procedures, such as dynamic, intranodal contrast enhanced MRI and catheter directed embolization of leaking vessels via the thoracic duct are the preferred mode of management in patients with refractory effusions despite treatment with mTOR inhibitors.[67] Cystic lymphangioleiomyomas should generally not be drained or resected due to high chance of inducing a chronic leak.[65]

LUNG TRANSPLANTATION

Between 1995 and 2018, LAM accounted for 0.9% of adult lung transplants.[68] Although no strict criteria for the timing of lung transplantation in LAM exist, common indications for referral to a lung transplant center include New York Heart Association (NYHA) functional class III or IV, severely reduced lung function defined by FEV_1 <30% predicted, hypoxemia requiring supplemental oxygen at rest, pulmonary hypertension, and refractory pneumothorax.[2] Many patients with LAM have undergone pleurodesis prior to lung transplant referral. Although history of pleurodesis increases peri-operative bleeding risk, it does not impact mortality or overall length of hospital stay, and as such, prior pleurodesis is not a contraindication for future lung transplantation.[46,61] The survival after lung transplant is 94% at 1 year, 73% at 5 years, and

56% at 10 years, which is better than other chronic pulmonary diseases.[68]

PREGNANCY AND CONTRACEPTION

Pregnancy is known to be associated with accelerated progression of LAM and increased risk of pneumothoraces, chylous effusions, and rupture of AMLs.[3,4] Women, particularly those with moderate-severe disease, should be counseled about the potential for these risks associated with pregnancy. Sirolimus is typically avoided during pregnancy, however, some published reports, including a recently published report of 12 pregnancies from 9 women with LAM who took sirolimus during pregnancy, have suggested that the use of sirolimus might be safe and might help mitigate the pregnancy-related risk of lung function decline and other LAM complications such as pneumothoraces.[4,69,70-80] Improved understanding of the potential role of mTOR inhibitors to mitigate disease progression during pregnancy is a major unmet need in LAM. Due to the risk of disease progression with exposure to exogenous estrogen, estrogen-based contraceptives should be avoided in women with LAM.[5,81]

NATURAL HISTORY AND PROGNOSIS

LAM is a gradually progressive disease with 5, and 10-year transplant-free survival rates approaching 94%, and 85%, respectively, and a median survival exceeding 20 years following diagnosis.[39] The rate of FEV_1 decline has been reported to range between 47-134 ml/year in various studies, with an average rate of FEV_1 decline of ~90 ml/year in the NHLBI LAM Registry.[39,82-86] Lung function declines faster in premenopausal women compared with postmenopausal women.[39,57] Other variables that have been associated with faster disease progression include elevated VEGF-D levels, radiological cyst burden, and bronchodilator responsiveness on spirometry.[39,57,87-89] Other poor prognostic markers of LAM include impaired DLco, worse histology score, presentation with dyspnea, and the need for supplemental oxygen.[39,90-94] More recently, using data derived from two large LAM natural history cohorts, a LAM prediction model has been developed that can help provide individualized prognostic predictions regarding the risk of FEV1 decline in untreated patients and help clinicians and patients make timely decisions regarding starting treatment with sirolimus.[95] The model can be accessed freely at: https://medmonitoring.shinyapps.io/LAMPApp/.

CASE ANALYSIS

Two months later, the patient presented to the emergency department with worsening dyspnea on exertion. Vital signs were significant for tachycardia, tachypnea, and oxygen saturation of 94% on ambient air. Physical examination revealed decreased breath sounds over the right lung. Chest X-ray showed a large right pleural effusion (Figure 2a). Thoracentesis was performed with removal of 4 liters of milky white fluid from the right pleural cavity. Pleural fluid analysis showed triglyceride level of 3,262 mg/dL consistent with chylothorax. Sirolimus was initiated during the hospital admission, and the patient was discharged. She had re-accumulation of pleural fluid and underwent two more thoracenteses in the two weeks following discharge. However, the effusion resolved after being on sirolimus for three weeks. She remains on treatment with sirolimus with stable lung function tests and has not had any recurrence of her pneumothorax or chylothorax (Figure 2b).

CONCLUSION

The last two decades have seen tremendous progress in LAM including, but not limited to, improved understanding of the molecular pathogenesis, discovery of a blood-based diagnostic biomarker, advent of a safe and effective suppressive therapy, publication of clinical practice guidelines, and the establishment and expansion of a worldwide network of clinics that not only provides high quality clinical care but also facilitates collaborative research in LAM as well as multiple other rare lung diseases. With close collaboration among the LAM patients, scientists and clinicians, LAM is well poised to continue to be an exemplar of how to make meaningful progress in a rare disease in the future as the LAM community continues its journey towards improved understanding of the molecular perturbations that drive LAM and use that knowledge to develop novel, remission inducing therapies for LAM.



Figure 2. Lymphatic complications of LAM as experienced by our patient: **a)** Chest X-ray done a few months following diagnosis to investigate new onset dyspnea on exertion revealing large right-sided pleural effusion (arrow) which was determined to be a chylothorax following diagnostic and therapeutic thoracentesis, and **b)** Recent chest X-ray demonstrating complete resolution of chylothorax following treatment with sirolimus.

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CHAPTER 08

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

PULMONER LANGERHANS HÜCRE HİSTİYOSİTOZU

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PULMONARY LANGERHANS CELL HISTIOCYTOSIS

PULMONER LANGERHANS HÜCRE HİSTİYOSİTOZU

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ABSTRACT

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare interstitial lung disease characterized by the proliferation and infiltration of CD1a+ and Langerin+ dendritic cells, typically affecting young adult smokers. Although it can occur as part of a systemic Langerhans cell histiocytosis (LCH), PLCH most often presents as an isolated pulmonary manifestation. Pathogenesis is strongly associated with cigarette smoking, which induces cytokine release, dendritic cell activation, and abnormal accumulation in distal bronchioles, leading to bronchiolocentric granulomatous inflammation and subsequent cystic lung remodeling.

Clinically, patients may present with non-specific respiratory symptoms such as dry cough, dyspnea, and chest pain; however, many cases are incidentally detected on radiological imaging. Recurrent pneumothorax is a hallmark feature and may be the initial presentation in some patients. High-resolution computed tomography (HRCT) plays a crucial role in diagnosis. Radiological findings typically include bilateral, upper-lobe-predominant nodules and irregular cysts, frequently with relative sparing of costophrenic angles. Pulmonary function tests (PFTs) may show either obstructive, restrictive, or mixed patterns, and diffusing capacity for carbon monoxide (DLco) is often reduced.

Histopathological confirmation is required in uncertain cases, with transbronchial or surgical lung biopsies demonstrating characteristic Birbeck granule–containing Langerhans cells. Recent studies have identified somatic mutations, including BRAF V600E and MAP2K1, suggesting a neoplastic component and offering potential targets for therapy.

Smoking cessation is the cornerstone of management and may lead to disease stabilization or regression. In progressive or symptomatic disease, corticosteroids or chemotherapy may be considered, although evidence is limited. Targeted therapies against BRAF mutations have shown promise in refractory cases. Lung transplantation remains a consideration for end-stage disease.

In conclusion, PLCH is a unique smoking-related interstitial lung disease with heterogeneous clinical behavior. Early diagnosis, smoking cessation, and tailored management are essential to improve outcomes and reduce complications such as pulmonary hypertension and respiratory failure.

Keywords: *Pulmonary Langerhans cell histiocytosis; Histiocytosis X; Recurrent pneumothorax; Smoking; Pulmonary cysts; BRAF mutation; Cystic lung diseases*

ÖZET

Pulmoner Langerhans Hücreli Histiyositoz (PLCH), çoğunlukla genç erişkin sigara içicilerinde görülen nadir bir interstisyel akciğer hastalığıdır. Hastalık, CD1a+ ve Langerin+ dendritik hücrelerin proliferasyonu ve akciğer dokusunda birikimi ile karakterizedir. PLCH, sistemik Langerhans hücreli histiyositozun bir parçası olarak ortaya çıkabileceği gibi, çoğunlukla sadece akciğer tutulumu şeklinde izlenir. Hastalığın patogenezi sigara dumanı maruziyeti ile yakından ilişkilidir. Sigara dumanı sitokin salınımını artırır, dendritik hücre aktivasyonunu tetikler ve distal bronşiollerde anormal hücre birikimine yol açar. Bu süreç bronşiol merkezli granülomatöz inflamasyon ve ardından kistik akciğer yapısının ortaya çıkmasına neden olur.

Klinik olarak hastalar çoğunlukla kuru öksürük, nefes darlığı ve göğüs ağrısı gibi özgül olmayan yakınmalarla başvurur. Bazı olgular ise rastlantısal olarak görüntüleme sırasında saptanır. Tekrarlayan pnömotoraks hastalığın karakteristik bulgusu olup bazı hastalarda ilk belirtidir. Görüntüleme bulguları

tipik olarak bilateral, üst zonlarda yoğunlaşan nodüller ve düzensiz kistler şeklindedir; kostofrenik açıların göreceli olarak korunması sıktır. Yüksek çözünürlüklü bilgisayarlı tomografi (YÇBT), tanıda kritik öneme sahiptir. Solunum fonksiyon testlerinde (SFT) obstrüktif, restriktif veya karışık paternler görülebilir ve karbon monoksit difüzyon kapasitesi (DLco) sıklıkla azalmıştır.

Tanının kesinleştirilmesi gereken durumlarda transbronşiyal veya cerrahi akciğer biyopsisi yapılır. Histopatolojide karakteristik olarak Birbeck granülleri içeren Langerhans hücreleri gözlenir. Son yıllarda BRAF V600E ve MAP2K1 gibi somatik mutasyonların tanımlanması, hastalığın neoplastik özellik taşıdığını ve hedefe yönelik tedavi seçeneklerinin geliştiğini göstermektedir.

Tedavide sigara bırakma temel yaklaşımdır ve hastalığın stabilizasyonu veya gerilemesi sağlanabilir. İlerlemiş veya semptomatik olgularda kortikosteroidler veya kemoterapi seçenekleri değerlendirilebilir ancak kanıtlar sınırlıdır. BRAF mutasyonu pozitif dirençli olgularda hedefe yönelik tedaviler umut vadetmektedir. Son dönem hastalıkta akciğer nakli gerekebilir.

Sonuç olarak, PLCH heterojen klinik seyirli, sigara ile ilişkili özgün bir interstisyel akciğer hastalığıdır. Erken tanı, sigaranın bırakılması ve hastaya özel tedavi stratejileri komplikasyonların azaltılması ve yaşam kalitesinin artırılması açısından büyük önem taşır.

Anahtar Kelimeler: *Pulmoner Langerhans hücreli histiyositozis; Histiyositozis X; Yineleyen pnömotoraks; Sigara içimi; Akciğer kistleri; BRAF mutation; Kistik akciğer hastalıkları*

CASE PRESENTATION

A previously healthy 27-year-old man with no known history of pulmonary disease applied at a pulmonology clinic due to the sudden onset of severe pleuritic chest pain. Initial assessment revealed a spontaneous right-sided pneumothorax (Figure 1). On admission, his vital signs were as follows: oxygen saturation 98% (with supplemental oxygen), heart rate 88 bpm, and blood pressure 120/70 mmHg.

Chest radiography and thoracic CT revealed not only pneumothorax but also widespread parenchymal abnormalities in both lungs, including irregularly bordered nodules with cavitation and cystic changes, predominantly in the upper lobes. The lingula and medial segments of the middle lobe were relatively spared, and the lesions extended to the costophrenic angles (Figure 2). Based on these findings, the patient underwent video-assisted thoracoscopic surgery (VATS) with wedge resection of the right upper lobe, mainly due to prolonged air leakage. Histopathological analysis confirmed PLCH, revealing stellate-shaped fibrotic scars, eosinophilic infiltration, and clusters of CD1a and S100 positive Langerhans cells.

Following diagnosis, the patient was strongly advised to cease smoking, and he successfully quit

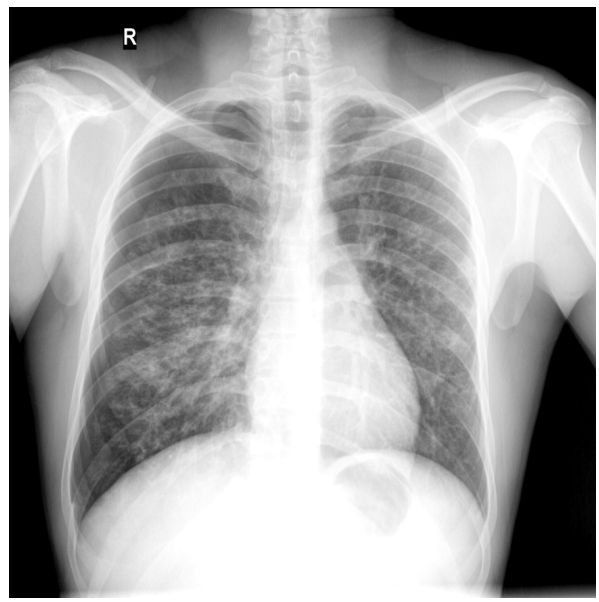


Figure 1. Posteroanterior chest radiograph of the patient from 2014, at first admission. There are reticulonodular opacities predominantly in the upper and middle lung zones bilaterally, with preservation of the costophrenic angles, and a pneumothorax line is observed in the right lung.

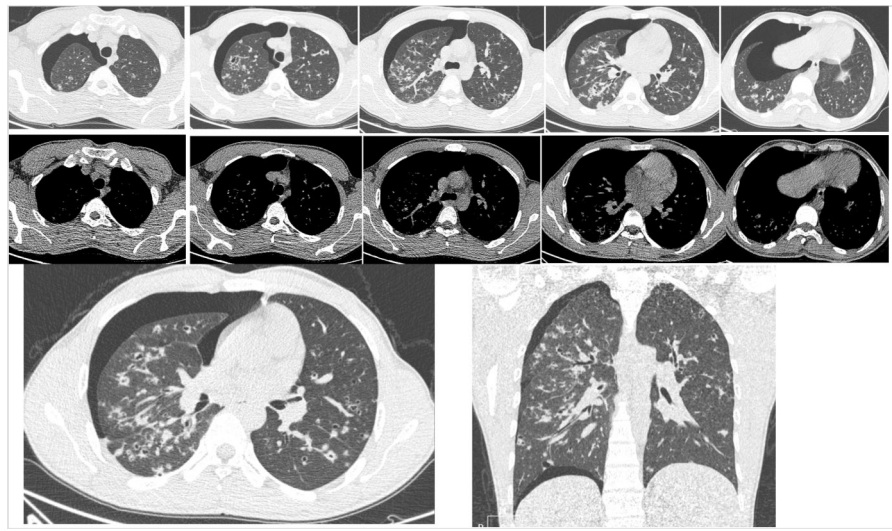


Figure 2. Thorax CT (2014) reveals irregularly bordered nodules with cavitation and cystic changes, predominantly in the upper lobes. The lingula and medial segments of the middle lobe were relatively spared, and the lesions extended to the costophrenic angles.

permanently (with a prior history of 10 pack-years). Treatment with inhaled ipratropium bromide was initiated, resulting in significant symptomatic improvement.

His occupational history revealed prior work in construction for two years, followed by twelve years of employment in a copper processing facility with ongoing exposure to copper dust. Given the risk of exacerbating lung damage, he was advised to avoid exposure to dust and chemicals, and his workplace physician was formally notified.

INTRODUCTION

LCH is a rare disease characterized by the tissue infiltration of CD1a+ myeloid cells that share many features with Langerhans cells, presenting a wide clinical spectrum ranging from a self-limited process localized to a single organ to severe, life-threatening multisystem involvement.[1] The term PLCH refers to a lung condition that may be confined to the lungs in adults or may occur as part of a broader systemic disease.[2] PLCH is most commonly identified in young adults, with over 90% of patients being active smokers or having a history of smoking at diagnosis.[1] LCH is generally diagnosed between the ages of 20 and 40 and affects males and females almost equally.[3,4]

Some patients are asymptomatic, and the diagnosis is frequently discovered incidentally through radiological imaging. Typical respiratory complaints include a persistent dry cough and shortness of breath, while wheezing or coughing up blood are less common. Additionally, systemic signs such as fatigue, chest discomfort, fever, and weight loss may occur.[1] The clinical course of PLCH is unpredictable and varies widely, with the disease either resolving spontaneously, particularly in young smokers, or progressing to multi-organ failure and death, leaving uncertainty as to whether it represents a neoplastic disorder or a reactive proliferation of Langerhans cells.[2,5]

Approximately 90% of patients show reduced carbon monoxide diffusion capacity (DLco). In pulmonary function tests (PFTs), both restrictive and obstructive patterns may occur. Chest radiographs typically reveal a micronodular, reticular, or cystic pattern involving both lungs while sparing the bases. High-resolution computed tomography (HRCT) scans classically demonstrate a combination of nodules and cysts predominantly in the upper and middle lobes, with relative sparing of the lung bases.[1] The cysts vary in size and shape, ranging from round to irregular forms and may be associated with nodules and thick-walled cavities. In patients with characteristic HRCT findings and a history of smoking, clinical diagnosis can often be established.[6]

A characteristic finding in bronchoalveolar lavage (BAL) fluid is the presence of more than 5% CD1a+

cells, which shows high specificity compared to sensitivity.[4] In selected cases, lung biopsy may be necessary. Histopathologically, LCH is characterized by cellular peribronchiolar nodules containing Langerhans cells and inflammatory cells with progression to fibrotic nodules.[2]

Based on the number of affected organs, the Histiocyte Society categorizes LCH into single organ or multisystem disease. Single-organ involvement usually affects sites such as bone, skin, or lungs and tends to have a more favorable prognosis, often allowing for spontaneous remission. In contrast, multisystem disease involves multiple sites including bone, skin, the hypothalamic-pituitary axis, lymph nodes, lung lesions, and less commonly the central nervous system. This form is linked to a worse prognosis, particularly when high-risk organs like the liver, spleen, or hematopoietic system are affected.[7] Chronic cases of LCH may also develop complications such as pulmonary hypertension and interstitial fibrosis.[8]

Smoking cessation is the most crucial aspect of managing PLCH. Tobacco use is a major factor in disease development, and cessation has a beneficial impact on its progression. The natural course of PHLC is unpredictable; around half of the patients experience improvement, 30-40% maintain stable disease, while 10-20% may progress to chronic respiratory failure with repeated episodes of pneumothorax.[4]

EPIDEMIOLOGY

PLCH is an uncommon interstitial lung disease that primarily affects smokers. It has previously been known by other names such as pulmonary eosinophilic granuloma, pulmonary Langerhans cell granulomatosis, and pulmonary histiocytosis X.[9] The overall incidence of LCH is estimated at 4-9 cases per million annually in children and 1-2 cases per million annually in adults.[10] PLCH mostly occurs in young adults aged between 20 and 40 years, with no clear preference for either sex. Reports indicate a rising incidence, particularly among Asian populations. While a few familial occurrences point to potential genetic factors, the majority of isolated PLCH cases arise sporadically.[8]

PATHOGENESIS

The exact pathogenesis of PLCH remains unclear, but it is mainly considered to result from a combination of inflammatory reactions triggered by cigarette smoke and neoplastic mechanisms. Strong evidence exists linking cigarette smoking as a causative factor for PLCH in adults. More than 90% of adult patients diagnosed with PLCH are either active smokers or have experienced substantial exposure to secondhand smoke.[8]

Tobacco smoke promotes the build-up of inflammatory cells within the lungs. Among these cells are Langerhans cells which release a variety of cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor-beta (TGF-β), and chemokine ligand 20 (CCL20). Moreover, bronchial epithelial cells and fibroblasts also produce GM-CSF, which acts as a strong growth factor for Langerhans cells.[11] Cigarette smoking is thought to stimulate the release of TNF-α, GM-CSF, TGF-β, and CCL20 from dendritic cells, Langerhans cells, and neighboring lung cells. This results in the ongoing activation of dendritic cells, Langerhans cells, and their precursors. Such continuous stimulation promotes the local growth and accumulation of Langerhans cells in the peribronchial areas. Furthermore, the excessive recruitment of circulating monocytes (likely directly induced by cigarette smoke exposure) is considered a major mechanism contributing to the expansion of dendritic and Langerhans cell populations surrounding the small airways.[8]

In pediatric cases of PLCH, the link to cigarette smoking is less well established. Nonetheless, there is evidence suggesting that adolescents who begin smoking may be at increased risk of developing PLCH as young adults, particularly if they have a history of childhood LCH outside the lungs.[12]

Discontinuation of smoking has been associated with either partial or complete resolution of pulmonary abnormalities. PLCH typically features marked peribronchial inflammation, indicating that inhaled substances like tobacco smoke may damage the small airways. Tobacco use leads to an increased presence of macrophages within the lungs; the recruitment and clustering of these cells around small airways, in the interstitial spaces, and within distal alveolar regions is characteristic of several smoking-induced lung disorders, PLCH among them. A particularly intriguing and unresolved issue is why only a small subset of smokers go on to develop PLCH, suggesting that intrinsic genetic or immune-related factors (or other environmental exposures) might act as a secondary trigger. In

those affected, smoking may provoke an exaggerated inflammatory reaction, activating multiple pulmonary cell types, including epithelial and immune cells. This process perpetuates a destructive cycle of chronic inflammation, tissue damage, and structural lung remodeling. It is still unclear whether this is driven by a failure in natural anti-inflammatory pathways or by concurrent external factors such as viral infections. Clarifying these mechanisms remains a critical focus of current research efforts.[8]

Although there is a consensus on the role of smoking in the development of PLCH, the exact effects of smoking on the function, activation, and tissue accumulation of Langerhans cells have not been fully elucidated. Nevertheless, current data indicate that various immune and molecular pathways induced by cigarette smoke exposure play a role in the pathogenesis of PLCH. In this process, co-stimulatory molecules such as CD40, CD80, and CD86; chemokine receptors like CCR7; matrix metalloproteinases including MMP-2 and MMP-9; proinflammatory cytokines such as IL-17 and CXCL8; and immunoregulatory molecules like CD40L have been reported to be involved in the pathogenesis.[13-17]

In recent years, genetic mutations associated with clonal proliferation have also been identified in the pathogenesis of PLCH in some cases. The presence of BRAF V600E and MAP2K1 mutations has been demonstrated in patients with LCH, and these mutations have been reported to play a role in disease pathogenesis.[18,19] The BRAFV600E mutation leads to persistent activation of the mitogen-activated protein kinase (MAPK) signaling cascade. While this mutation is frequently found in several types of cancer (especially melanoma), it is not exclusively associated with malignancy, as it can also occur in certain benign conditions.[20] In experimental models, mice harboring the BRAFV600E mutation developed lung lesions resembling those seen in PLCH when exposed to cigarette smoke, whereas such lesions did not arise in mice kept in normal air conditions. These findings support the concept that PLCH is a myeloid neoplasm with an accompanying inflammatory process, and that tobacco smoke likely serves as a key environmental trigger in the formation of the characteristic lung lesions.[21]

Although the complex mechanisms in the pathogenesis of PLCH are becoming increasingly clear, the disease lies at the intersection of cigarette smoke-induced inflammation and clonal proliferation caused by genetic mutations. Therefore, PLCH should be considered a multifaceted disease in which both chronic inflammation and myeloid neoplastic processes play a role. This understanding highlights the importance of early smoking cessation as well as the potential use of targeted molecular therapies.

CLINICAL MANIFESTATIONS

PLCH exhibits a variable clinical presentation ranging from minimal symptoms to progressive respiratory failure. Patients are frequently asymptomatic, with the diagnosis often made incidentally based on radiographic abnormalities, while those who are symptomatic commonly present with a persistent dry cough and shortness of breath, and less commonly with wheezing or hemoptysis; systemic manifestations such as fatigue, chest pain, fever, and unintended weight loss may also occur.[1,2,5]

Patients with PLCH have a shorter life expectancy compared to the general population, and deaths are generally associated with pulmonary complications and respiratory failure. Continued smoking in affected individuals has been linked to a worse prognosis.[22] Similarly, in a retrospective analysis by Vassallo et al., the severity of respiratory function impairment at diagnosis was found to be associated with poor prognosis.

Pneumothorax occurs in approximately 15% of patients.[22] It may sometimes be the initial presenting feature of the disease. Pneumothorax can be bilateral, may recur during the disease course, and its management is not standardized. Recurrences tend to be ipsilateral.[11] Mendez et al. reported that among 102 patients with PLCH followed in their clinic over a 23-year period between 1976 and 1998, 16 patients (16%) developed pneumothorax. The mean age at diagnosis was 29.4 years, and all patients were smokers. Additionally, 63% of these patients experienced multiple pneumothorax recurrences. The recurrence rate of pneumothorax was as high as 58% ipsilaterally when managed with observation or chest tube without pleurodesis, whereas there was no recurrence after surgical treatment combined with pleurodesis.[23] This finding suggests that pleurodesis may be effective in reducing the risk of recurrence in the management of pneumothorax associated with PLCH.

Radzikowska et al., in their study evaluating data from 90 PLCH patients followed between 2000 and 2015, reported that pneumothorax was the initial pre-

senting symptom in 29 patients (32%). Cases presenting initially with pneumothorax were found to be younger, predominantly male, and exhibited more pronounced respiratory function impairment. Furthermore, thoracic CT findings in these patients played a decisive role in reaching the diagnosis of PLCH.[24] In a retrospective study by Guen et al. evaluating pneumothorax development in 43 PLCH patients, findings obtained during a median follow-up period of 49.1 months showed that approximately half of the patients experienced recurrent pneumothorax within 2 years after the first episode, with 75% of these recurrences being ipsilateral. It was determined that thoracic surgery did not reduce the risk of pneumothorax recurrence. Additionally, univariate analyses identified the presence of air trapping on pulmonary function tests as an independent risk factor for pneumothorax recurrence.[25] These findings indicate that pneumothorax is a common and recurrent complication in PLCH patients. Close monitoring is especially emphasized for patients with evidence of air trapping.

Apart from the classic pulmonary involvement, rare different pulmonary presentations of PLCH have also been reported in the literature with case examples. Peng et al. diagnosed PLCH by biopsy performed during bronchoscopy in a 26-year-old patient without a history of smoking, who presented with exercise-induced wheezing and hemoptysis. For the first time in PLCH, widespread lesion distribution in the trachea and bilateral main bronchi with varying degrees of airway narrowing was reported.[26] This finding has been described as a new imaging feature of PLCH, characterized by diffuse thickening of the tracheobronchial walls. This case suggests that diffuse tracheobronchial involvement without parenchymal disease may represent a rare form of PLCH.

Cammarata et al. performed a CT-guided transthoracic fine-needle aspiration biopsy on a solitary pulmonary nodule measuring 19 mm detected in a heavy smoker male patient in his 60s due to suspicion of malignancy. Histopathological examination revealed histiocytic infiltration positive for CD1a and Langerhans cell antibodies, confirming the diagnosis of pulmonary LCH. The patient was followed without treatment and advised to quit smoking. Although he did not completely quit, the patient reduced smoking, and during one-year follow-up, the nodule size decreased to 14 mm.[27] A solitary pulmonary nodule without cavitation is a rare and atypical clinical presentation in PLCH.

Pulmonary hypertension is a serious and common complication that occurs in advanced cases (affecting 40% of all patients) and its severity correlates linearly not with interstitial involvement but with vascular involvement, which should be evaluated in every case.4

PULMONARY FUNCTION TESTS

Lung function abnormalities in PLCH are variable and depend on both the predominant anatomical lesions and the duration of the disease. Pulmonary function at rest is normal in approximately 10-15% of patients. The most common functional abnormality, present in 70-90% of patients, is a decreased diffusion capacity for carbon monoxide (DLCO). Many patients exhibit an obstructive pattern of impairment. Changes in the flow-volume curve are observed in about 50% of patients, with a reduced FEV1/FVC ratio detected in 20-30% of newly diagnosed PLCH patients and a much higher proportion in those with advanced diseases. Additionally, the high prevalence of smoking among these patients may contribute to the abnormalities observed in pulmonary function tests.[28]

In a study by Miao et al., pulmonary function test data of 74 PLCH patients were evaluated. Pulmonary function was normal in 16.2% of patients, while 83.8% exhibited ventilatory and/or diffusion impairments. Analysis of ventilatory patterns revealed restrictive defects in 25.7%, obstructive defects in 16.2%, and mixed ventilatory defects in 2.7% of patients. The most frequent abnormality was a decreased diffusion capacity, observed in 81.1% of cases. They also demonstrated that an estimated FEV1 ≤ 55% was associated with poorer survival.[29]

RADIOLOGICAL FINDINGS

Chest X-ray

The abnormalities seen on chest radiographs vary according to the stage of the disease. The earliest change is a bilateral reticular or reticulonodular pattern involving the middle and upper lung zones.[30] Associated cysts generally indicate advanced disease. PLCH typically affects the middle and upper lung zones, with preservation of the costophrenic angles.[31] Lymphadenopathy and pleural effusions are rare.[30] In advanced disease, nodular lesions are sparse or absent, and cysts become the predominant radiographic abnormality, sometimes mimicking an emphysematous appearance.[28]

High-Resolution Computed Tomography

HRCT is now crucial for detecting and characterizing lung parenchymal changes in PLCH. It can identify abnormalities in the lung tissue even in rare cases where chest X-rays appear as normal. HRCT provides more detailed information about parenchymal lesions, such as the cavitation of nodules, which are not easily visible on standard radiographs. In PLCH, HRCT typically shows a combination of nodules that may be well-defined or poorly defined, along with cysts that vary in shape, size, and wall thickness.[7]

The predominant HRCT pattern of PLCH changes depending on the disease stage, showing nodular, nodular-cystic, cystic, or fibrotic appearances. In the early phase (within six months), a nodular pattern is most commonly observed. These nodules are typically distributed in a centrilobular manner, which corresponds to the bronchiolocentric origin of PLCH lesions. As the disease advances, cystic lesions become more prominent. While most cysts measure less than 1 cm, their size can vary, and they may appear as isolated or merged structures, occasionally resembling centrilobular emphysema. Long-term follow-up with repeated CT scans has shown that radiologic findings progress from nodules to cavitated nodules, then to cysts with thick walls, and eventually to cysts with thin walls.[28]

Radiological findings in PLCH often include stellate-shaped nodules primarily located in the upper and middle lung lobes, exhibiting a centrilobular, peribronchial, or peribronchiolar distribution. The lower regions of the lungs are typically spared.[28] In advanced stages of PLCH, small stellate scars are frequently seen encircled by areas of emphysema. Follow-up CT scans over time can demonstrate the progression of PLCH, showing changes from lung nodules to a mixture of irregularly shaped cysts and nodules that resemble bullous emphysema.[32]

While PLCH is typically diagnosed based on characteristic CT findings such as pulmonary cysts, non-cystic nodular lesions have also been rarely reported. Therefore, multiple pulmonary nodules that spontaneously appear and regress may also represent a form of PLCH. Supporting this notion, Manabe et al. reported a pathologically confirmed case of such spontaneously regressing non-cavitating nodular lesions, suggesting they may be a manifestation of PLCH.[33]

Uncommon variants of PLCH are exceedingly rare and pose considerable difficulties in diagnosis. A range of unusual radiologic findings have been described, such as solitary nodules, highly uneven radiographic abnormalities, cystic lesions containing air-fluid levels, localized "alveolar" consolidations, pleural effusions, and enlargement of mediastinal lymph nodes. Ground-glass opacities observed on high-resolution CT scans may indicate changes similar to respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), which is commonly seen in the lungs of smokers.[28]

Pleural effusion is extremely rare, and mediastinal lymphadenopathy is unusual. Pulmonary artery enlargement has been reported in some patients. Ultimately, although HRCT findings may often be sufficient for diagnosis in patients with typical clinical features, further evaluation with bronchoscopy, BAL, and/or biopsy may be required to confirm the diagnosis in suspicious or atypical cases.

BRONCHOSCOPY/BRONCHOALVEOLAR LAVAGE

During bronchoscopy, the bronchial tree usually looks normal or exhibits only nonspecific inflammation associated with smoking. Biopsy samples taken from the bronchial mucosa are generally not diagnostic for PLCH but can be valuable in ruling out other conditions, particularly in patients who present with unusual or atypical findings.[28]

In BAL fluid, total cell counts are usually elevated, with values often exceeding 1×10^6 cells·mL^{-1}, and there is a marked predominance of alveolar macrophages. This finding reflects exposure to cigarette smoke and is strongly correlated with the level of daily cigarette consumption. In the small minority of nonsmoking patients, alveolar cell counts may be normal. The proportion of alveolar lymphocytes is normal or decreased, and the CD4/CD8 ratio is typically reduced, as also seen in smokers.[28] In PLCH, the aim of BAL is primarily to exclude infection, and the detection of more than 5% CD1a-positive and CD207-positive Langerhans-like cells in BAL samples is considered a significant finding that supports the diagnosis of PLCH.[34,35] However, in clinical practice, BAL rarely provides a definitive diagnosis. While thoracic CT findings can guide diagnosis in typical cases, BAL is more useful in the differential diagnosis of patients without characteristic radiological features.

BIOPSY

Transbronchial lung biopsy (TBLB) is the primary

diagnostic tool used to obtain tissue samples from patients with suspected PLCH. The diagnostic yield of TBLB varies between 17% and 50%. However, compared to other cystic lung diseases such as lymphangioleiomyomatosis (LAM), the diagnostic rates of TBLB in PLCH tend to be lower. This can be attributed to several factors, including the patchy distribution of the disease, a reduced number of active nodules in advanced stages, the small size of biopsy specimens, difficulty in accessing distal bronchiolar lesions via bronchoscopy, and the potential crushing of Langerhans cells during the procedure, which may obscure the typical pathological findings. For these reasons, surgical lung biopsy remains the gold standard due to its high diagnostic capacity. Transbronchial lung cryobiopsy (TBLC) has garnered attention in the diagnosis of interstitial lung diseases because it is less invasive than surgical lung biopsy and provides larger tissue samples compared to TBLB. Although TBLC may be associated with complications such as bleeding or pneumothorax, it allows for the acquisition of larger samples without crush artifacts and offers a less invasive alternative to open lung biopsy.[36]

Biopsy samples should ideally be taken from areas with abundant nodules as seen on HRCT. Lung biopsy findings typically show a characteristic cluster of Langerhans-like cells on histology, which stain positive for CD1a, CD207, and S100 proteins.[34]

TREATMENT

Many patients with PLCH experience spontaneous recovery or remain clinically stable without any treatment, which makes it difficult to evaluate the effectiveness of various therapies. Furthermore, the low prevalence of PLCH presents a significant challenge in recruiting an adequate number of patients for controlled therapeutic studies.[28]

Management of PLCH is typically determined by the severity and progression of the disease. In cases where the disease is localized, especially among younger individuals, PLCH frequently resolves on its own. Beyond quitting smoking, medical treatment is often not needed. For patients with more severe or worsening disease, therapies such as corticosteroids and/or chemotherapy agents (including cladribine, vinblastine, methotrexate, cyclophosphamide, and etoposide) may be employed.3 Nonetheless, since the disease can reactivate in the lungs or other organs, ongoing monitoring through regular follow-up is essential.[11] Additionally, smoking cessation lowers the risk of smoking-related complications commonly seen in PLCH patients, such as primary lung cancer, cardiovascular disease, and progressive decline in lung function caused by chronic obstructive pulmonary disease.[28]

Systemic corticosteroid therapy has long been considered a treatment option, with reports suggesting improvements in symptoms, imaging findings, and pulmonary function. However, the optimal dosage and duration of corticosteroid use remain unclear due to a lack of robust clinical studies. Moreover, there is a possibility that the perceived benefits may actually be related to smoking cessation rather than the steroids themselves. Relapse rates following treatment are also notably high (around 80%) and extended use of systemic corticosteroids carries a significant risk of serious side effects. As a result, this form of treatment is no longer routinely advised. In contrast, inhaled corticosteroids might be beneficial for patients who exhibit reversible airway obstruction.[11]

In adults, (particularly in patients with isolated PLCH) the disease exhibits various clinical courses, and many therapeutic agents are tolerated differently. Chemotherapeutic and immunomodulatory agents are mainly recommended in multisystemic LCH and progressive cases; however, their efficacy in isolated PLCH remains controversial. Agents such as cladribine or cytarabine, vinblastine plus prednisone, azathioprine, and cyclophosphamide have been used for this purpose. Although most experience with these agents comes from pediatric cases, their use has also been reported in progressive PLCH cases with multisystem involvement.[11,37]

A retrospective analysis of 35 adult LCH patients, including 17 with lung involvement, who received treatment with vinblastine and corticosteroids showed a response rate of 70%. However, during a 5-year follow-up, the relapse rate reached 40%.[38] No patient receiving vinblastine treatment showed any improvement in ventilatory function. According to Cantu et al., vinblastine was found to be less effective compared to cladribine or cytarabine in adult patients with multifocal bone involvement, of whom 28% had pulmonary lesions.[39] The impact of these treatments on lung function measures was not addressed. More recently, Néel et al. documented an overall response rate of 91% in 22 adult patients with extrapulmonary onset LCH treated with cladribine. However, disease

progression was observed in 30% of the patients over a 5-year follow-up period.[40]

In contrast to studies involving pediatric patients, adults are more likely to develop irreversible neurotoxicity following prolonged vinblastine treatment and secondary malignancies following long-term therapy with etoposide or cladribine.[41]

In recent years, BRAF and MAPK pathway mutations have been reported to play a significant role in the pathogenesis of LCH. As a result, targeted therapies directed against these mutations have emerged. BRAF inhibitors (vemurafenib, dabrafenib) and MEK (MAPK kinase) inhibitors (such as trametinib) have shown promising outcomes in cases with refractory or disseminated disease.[42,43]

In patients with obstructive symptoms, bronchodilator therapy may be beneficial. Long-term oxygen therapy is indicated in those with hypoxemia. In cases with exercise intolerance, pulmonary rehabilitation should be considered. Seasonal influenza, pneumococcal, and COVID-19 vaccinations are recommended for all patients unless contraindicated.

In patients with advanced, irreversible respiratory failure or severe pulmonary hypertension, lung transplantation should be considered. However, cessation of smoking is an absolute prerequisite for listing. Although rare, recurrence of PLCH after lung transplantation has been reported.[44]

EXTRAPULMONARY INVOLVEMENT

The Histiocyte Society has proposed a classification scheme dividing histiocytic disorders into three main groups: dendritic cell histiocytosis, macrophage cell histiocytosis, malignant histiocytosis. LCH belongs to the dendritic cell histiocytosis group and is also classified according to the extent of organ involvement. The acute disseminated multisystem form of LCH (formerly known as Letterer-Siwe disease) is typically seen in children under 3 years of age and often has a fatal course. Multifocal LCH (formerly known as Hand-Schüller-Christian disease) is more common in infancy and childhood and generally has a better prognosis. Single-system LCH is frequently observed in young adults and usually presents with involvement of the lungs, brain, or bones.

Isolated PLCH in adults almost always develops in association with current or past tobacco smoking. Pulmonary involvement can also be seen in cases with multisystem disease, but it is usually not the primary affected organ. However, when predominant lung involvement is present, it is considered a poor prognostic factor.[30,45] Although pulmonary involvement in LCH can be a component of multisystem disease, pulmonary LCH (PLCH) in adults most often presents as a single-system disease.[46]

In the study conducted by Wang et al., the ribs were identified as the most frequently affected sites of extrapulmonary involvement, observed in two-thirds (66.7%) of cases, while additional sites included the pituitary gland, skin, and thyroid. The authors also proposed that adult PLCH could be divided into two distinct groups, noting that patients with isolated pulmonary involvement, typically under the age of 40, had a significantly more favorable prognosis compared to those with extrapulmonary disease, who were generally older than 40.[47]

Bone represents the most frequently affected site in LCH, with lesions that may present as solitary or multiple within the same bone, most commonly involving the skull, mandible, pelvis, ribs, clavicle, and vertebrae. Clinically, these bone lesions can be asymptomatic or may lead to localized pain, sometimes accompanied by swelling of the surrounding soft tissues.[48]

In a multicenter prospective cohort study conducted by Schönfeld and colleagues including 77 PLCH patients, clinically apparent bone involvement was detected at diagnosis in 8 patients (10%).[49] In a more recent single-center series of 40 adult PLCH patients, symptomatic bone involvement was present at diagnosis in 2 patients (5%), and radiographic LCH-related bone lesions were observed in 7 patients (18%).[50] Tazi et al. have investigated bone involvement in patients diagnosed with PLCH in a prospective multicenter study. They found that skeletal radiographs were generally normal in asymptomatic cases, and bone scintigraphy did not provide additional benefit beyond plain radiography.[46]

PLCH may be associated with various endocrinopathies, most commonly central diabetes insipidus.[51] Central diabetes insipidus usually develops due to inflammatory processes or neoplastic infiltration of non-neuronal tissue rather than primary neuronal tissue tumors. The clinical presentation is dominated by polyuria and polydipsia. Thickening and involvement of the pituitary gland can be detected by MRI and PET-CT, aiding in diagnosis.[52] Cases of central diabe-

tes insipidus occurring before or after the diagnosis of PLCH have been reported.[51-54]

In LCH patients, cutaneous manifestations such as eczema or seborrheic dermatitis may occur, with the scalp being the most commonly affected area. Skin-involved LCH lesions can be limited to the skin alone and may resolve spontaneously or with minimal chemotherapy.[55] Rarely, skin lesions can represent the most clinically apparent manifestation of a potentially life-threatening multisystem disease. Cutaneous involvement of LCH can be treated successfully with spontaneous remission or short-term chemotherapy.[56] Cases of skin involvement have also been reported in patients being followed with a diagnosis of PLCH.[46]

One of the significant concerns in patients with PLCH is the association with malignancies. The risk of developing both hematologic and solid tumors has been previously reported in patients with LCH, including those with PLCH. However, the type and frequency of these malignancies vary depending on the extent of LCH involvement, the studied population, and the treatments applied (chemotherapy or radiotherapy).[5,44] In the series reported by Benattia et al., 7 out of 27 malignancies (30%) were of hematologic origin, and none of these hematologic malignancies developed after the diagnosis of PLCH. The mechanisms leading to the development of hematologic malignancies in patients with LCH, including PLCH, have not yet been clearly elucidated.[57]

PROGNOSIS

A prospective cohort study evaluating long-term outcomes in adult patients with PLCH reported an estimated 10-year survival rate of 93%. In this study, serious complications such as chronic restrictive lung disease and pulmonary hypertension were observed in only a minority of patients during the early stages of the disease.[3] Among patients presenting with isolated pulmonary involvement at diagnosis, extrapulmonary organ involvement rarely developed during follow-up. Furthermore, an increased risk of malignancy (particularly lung carcinoma) has been highlighted in patients with PLCH.[22] Since the risk of malignancy is increased, with a particularly notable predisposition to lung carcinoma, in patients with PLCH, regular cancer screening is recommended.

Smoking cessation is the most critical intervention that positively impacts disease progression, with early cessation shown to slow the course of the disease. In any case of suspected PLCH, physicians should address smoking habits with the patient and offer appropriate support for smoking cessation.

CASE ANALYSIS

Through follow-up, the patient reported intermittent exertional dyspnea, and a productive cough associated with perspiration, but denied hemoptysis, wheezing, systemic symptoms, or recurrence of pneumothorax. On his most recent examination, breath sounds were mildly diminished bilaterally with no additional pathological findings. Pulmonary function tests indicated a mild restrictive pattern with stable diffusion capacity (DLco: 71%). The latest chest radiogram has improved in comparison to the time of diagnosis, with less reticulations (Figure 3). High-resolution CT imaging showed marked regression of the previously observed nodular and cystic lesions (Figure 4).

After ten years, the patient remains clinically and radiologically stable under combination inhaler therapy (budesonide-formoterol), with no evidence of functional decline or radiological progression. Regular follow-up is ongoing at six-month intervals.

CONCLUSION

PLCH is a unique smoking-related interstitial lung disease with heterogeneous clinical behavior. Early diagnosis, smoking cessation, and tailored management are essential to improve outcomes and reduce complications such as pulmonary hypertension and respiratory failure. Smoking cessation is an essential step in PLCH management.

In recent years, genetic mutations affecting the MAPK pathway, such as BRAF V600E and MAP2K1, have been identified in the pathogenesis of PLCH. These discoveries have led to the development of targeted therapeutic approaches. BRAF inhibitors and MEK inhibitors have emerged as promising treatment options, particularly in refractory or advanced-stage disease.

In the future, a better understanding of the molecular and immune pathogenesis of PLCH is expected to facilitate the development of personalized treatment strategies and more effective prevention of disease progression. Furthermore, the development of biomarkers for early diagnosis and the wider adoption of multidisciplinary care models may contribute significantly to improving patients' quality of life.

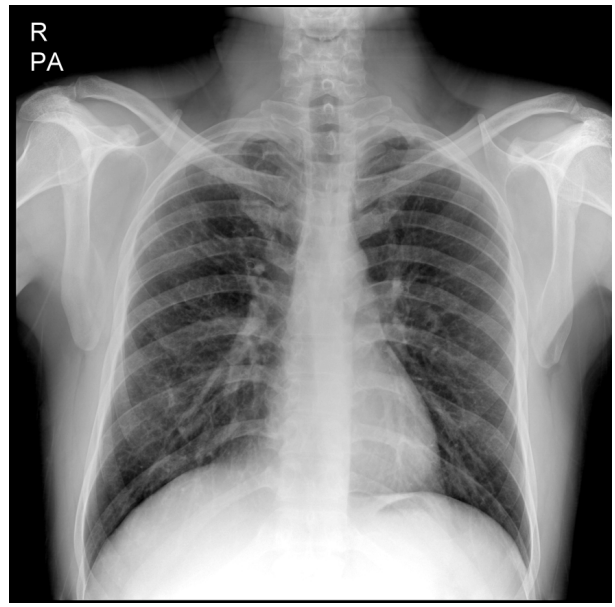


Figure 3. Posteroanterior chest radiograph of the patient, revealing mild reticulation in both lungs.

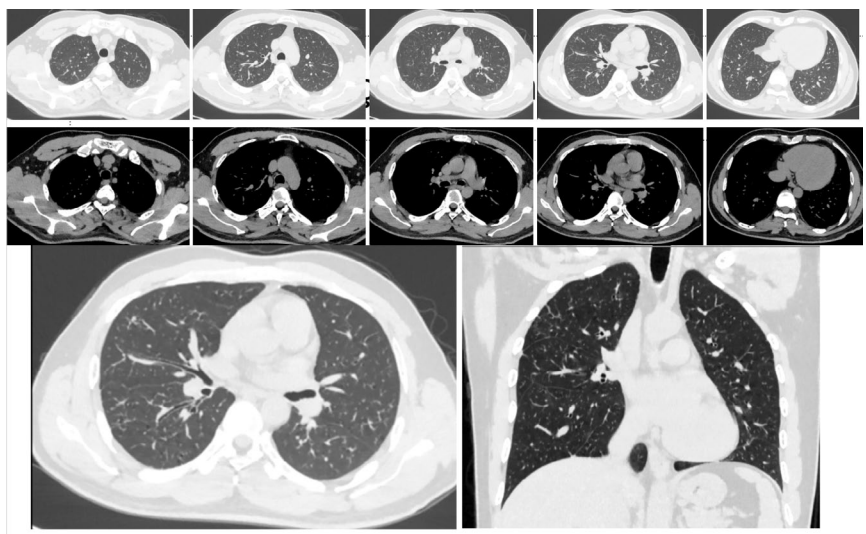


Figure 4. Thorax CT reveals near-complete resolution of nodules and cystic lesions after 10 years in the patient who completely quit smoking.

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CHAPTER 09

HERMANSKY-PUDLAK SYNDROME

HERMANSKY-PUDLAK SENDROMU

Assist. Prof. Dr. Merve Erçelik

HERMANSKY-PUDLAK SYNDROME

HERMANSKY-PUDLAK SENDROMU

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ABSTRACT

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive, multisystemic disorder characterized primarily by oculocutaneous albinism, bleeding tendencies, and variable involvement of other organs including lungs, colon, and immune system. Globally, HPS has an estimated prevalence between 1 in 500,000 and 1 in 1,000,000, although it is notably higher (1 in 1,800) in northwestern Puerto Rico, particularly for the HPS-1 subtype. Research in Germany has indicated that up to 35% of individuals with albinism may have a milder form of HPS, highlighting the potential benefit of broader screening efforts. HPS arises from mutations in 11 distinct genes responsible for proteins involved in lysosome-related organelle (LRO) biogenesis, resulting in disrupted protein trafficking and impaired organelle function. Each of the 11 HPS subtypes corresponds to specific genetic mutations but shares overlapping clinical manifestations. Among these, HPS-1 is recognized as the most severe subtype. Universal clinical features across all subtypes include tyrosinase-positive oculocutaneous albinism and varying degrees of platelet dysfunction leading to bleeding complications. Certain subtypes, notably HPS-1, HPS-2, and HPS-4, may additionally present severe complications such as pulmonary fibrosis, granulomatous colitis, immunodeficiency, or neurodegenerative changes. Pulmonary fibrosis, particularly prominent in the HPS-1 subtype, is the leading cause of mortality in these patients.

The onset of pulmonary fibrosis typically occurs in middle adulthood (30–40 years) in HPS-1 and HPS-4, while presenting earlier in childhood or young adulthood in HPS-2. Diagnosis of pulmonary fibrosis in HPS typically relies on high-resolution computed tomography (HRCT). Early-stage disease commonly manifests as basal, subpleural lung changes, progressing to bilateral reticular patterns, septal thickening, and, in advanced stages, loss of lung volume, honeycombing, and traction bronchiectasis. The radiological appearance of HPS-related fibrosis differs notably from idiopathic pulmonary fibrosis, particularly due to characteristic ground-glass opacities. The clinical diagnosis of HPS is based on identifying skin and hair hypopigmentation, distinctive ocular findings, and electron microscopy demonstrating absent platelet dense bodies. Genetic sequencing can confirm the diagnosis and identify the specific subtype. Despite trials of antifibrotic treatments, lung transplantation remains the sole definitive therapy for pulmonary fibrosis in HPS. Management strategies for other manifestations of the disease depend on the specific organ involved, and routine annual evaluations are generally advised. Emerging therapies, including gene therapy and gene editing, hold promise for future treatment.

Keywords: *Hermansky-Pudlak syndrome; Albinism; Pulmonary fibrosis; Interstitial lung diseases; Rare interstitial lung diseases*

ÖZET

Hermansky-Pudlak sendromu (HPS), okülokutanöz albinizm, kanama diyatezi ve bazı hastalarda pulmoner fibrozis, granülomatöz kolit ve/veya immün yetmezlik ile karakterize multisistemik, otozomal resesif bir hastalıktır. HPS'nin küresel yaygınlığının 500.000'de 1 ile 1.000.000'de 1 arasında olduğu tahmin edilmektedir. Porto Riko'nun kuzeybatı bölgesinde yaşayanların 1.800'de 1'inde HPS-1 alt tipi mevcuttur. Alman albino popülasyonunun %35'inin hafif HPS'ye sahip olma adayı olduğu gösterilmesi, daha geniş taramalar ile hastalığa sahip popülasyonun daha net ortaya konulabileceğini göstermektedir. HPS, lizozomla ilişkili organellerin (LRO'lar) biyogenezinde rol oynayan proteinleri kodlayan 11 farklı gendeki varyantlar tarafından oluşur. Mutasyonlar protein trafiği ve organel işlevi gibi hücresel süreçlerde kusurlara yol açar. Her biri belirli bir gendeki mutasyona bağlı olan, ancak

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hepsi benzer klinik özelliklerle sonuçlanan 11 HPS alt tipi vardır. En şiddetli alt tip HPS-1'dir. HPS'li tüm hastalarda, alt tipe bakılmaksızın, tirozinaz pozitif okülokutanöz albinizm (OCA) ve hafiften şiddetliye değişen trombosit disfonksiyonuna bağlı kanama bozukluğu mevcuttur. Alt tiplerde değişen mutasyonlara göre pulmoner fibrozis, granülomatöz kolit, bağışıklık yetersizliği ve nörodejenerasyon görülebilir. Pulmoner fibrozis, HPS'nin en ciddi komplikasyonlardan biridir. Bu komplikasyon, HPS hastalarında önde gelen ölüm nedenidir. HPS-1, HPS-2 ve HPS-4 alt tiplerinde gözlenir. HPS-1'li hastaların hepsinde HPS pulmoner fibrosis (HPS-PF) gelişir. HPS-1 ve HPS-4 orta yaş grubunda (30-40 yaş), HPS-2 ise çocukluk ve genç erişkinlik döneminde ortaya çıkar. HPS tanısı, yüksek çözünürlüklü bilgisayarlı tomografi (HRCT) ile konur. Erken hastalıkta, baskın olarak akciğerin alt kısımlarında subplevral bölgeleri ve şiddetli hastalıkta akciğer parankimini diffüz şekilde içeren bilateral retikülasyonlar ve septal kalınlaşmalar görülebilir. Karakteristik anormallikler arasında IPF'den farklı olarak, buzlu cam opasiteleri, interstisyel alanlarda retikülasyonlar ve ileri hastalıkta akciğer hacminin kaybı, balpeteği görünümü ve traksiyon bronşektazisi bulunur. HPS'nin indeks vakalardaki klinik tanısı, cilt ve saçta hipopigmentasyon, karakteristik göz bulguları ve elektron mikroskobunda trombosit delta granüllerinin (yoğun cisimler) yokluğunun gösterilmesiyle mümkün olur. Genetik dizileme yöntemi kullanılabilir. HPS için antifibrotik tedaviler denense de akciğer nakli, HPS-PF'li hastalar için mevcut tek tedavi yöntemi olmaya devam etmektedir. Tutulan organa göre tedavi modaliteleri değişiklik göstermektedir. Genellikle yıllık takipler önerilmektedir. Gen terapisi ve gen düzenleme HPS için potansiyel tedavilerdir.

Anahtar Kelimeler: *Hermansky-Pudlak sendromu; Albinizm; Pulmoner fibrozis; İnterstisyel akciğer hastalıkları; Nadir interstisyel akciğer hastalıkları*

CASE PRESENTATION

A 44-year-old male patient presents to the outpatient clinic with dyspnea. His mMRC score is 3-4. He has hemoptysis, a cough, and sputum production. He has no orthopnea, paroxysmal nocturnal dyspnea, or chest pain. He is an active smoker with a cigarette smoking history of 45 pack-years. He works in accounting. The patient, who has albinism, was told 15 years ago at another center that he had bubbles in his lungs. Three years after his first visit, the patient began to experience dyspnea, which increased in the fifth year, with an mMRC score of 3-4 at that time. Seven years after his first visit, the patient was suspected of having Histiocytosis X. The chest computer tomography (CT) scan was reported as cystic lung disease leading to interstitial lung disease. Bronchoalveolar lavage fluid was obtained; abundant macrophages, few polymorphonuclear leukocytes, and rare eosinophils were observed. It was interpreted as benign cytology. Surgical biopsy was recommended to the patient, but he did not accept it. Long-term oxygen therapy was given due to respiratory failure, but he does not use it regularly.

Physical examination revealed albinism, clubbing, and nystagmus. Bilateral subscapular rales were present. On the chest X-ray, there is an increase in nodular opacity along the midclavicular line in the right lung middle zone, as well as bilateral, widespread interstitial opacities (Figure 1). Thoracic CT images show multiple bilateral cystic lesions of varying shapes on axial sections (Figure 2). Pulmonary function tests showed FEV1 67%, FVC 64%, FEV1/FVC 85%, and DLco 19%. Arterial blood gas analysis showed a partial oxygen pressure of 35 mmHg, a partial carbon dioxide pressure of 27.1 mmHg, and an oxygen saturation of 67.6%. Echocardiography revealed normal left heart dimensions and enlarged right heart chambers. No valve defect was observed. The basal wall of the right ventricle was severely hypokinetic, while the middle and apical walls were akinetic. The pulmonary artery systolic pressure was 95 mmHg.

Hermansky-Pudlak syndrome, and combined fibrosis and emphysema was considered in the patient. A hematology consultation was requested regarding bleeding issues. The patient was referred to for lung transplantation.

INTRODUCTION

Hermansky-Pudlak syndrome (HPS) is a multisystemic disorder with autosomal recessive inheritance characterized by oculocutaneous albinism (OCA), bleeding tendencies, and additional complications that may include pulmonary fibrosis, granulomatous colitis, and immunodeficiency in some patients.[1] HPS arises from variants in 11 distinct genes encoding proteins involved in the biogenesis of lysosome-related organelles (LROs), resulting in defects in cellular processes such as protein trafficking and organelle function. HPS is classified into various subtypes, each corresponding to specific genetic mutations, yet exhibiting overlapping clinical manifestations.[2] Among these, HPS-1 represents the most common and typically severe form, whereas HPS-2 and HPS-4 also demonstrate pronounced severity. Neurological manifestations are uniquely notable in the HPS-10 subtype. Patients with HPS-3 and HPS-5 through HPS-9 variants generally present milder clinical features.[3]

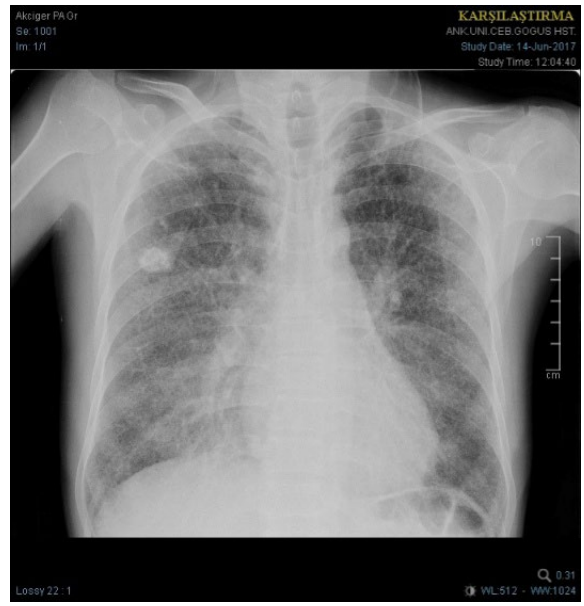


Figure 1. On the chest X-ray. Nodular opacity increases in the midclavicular line in the right lung middle zone, bilateral widespread interstitial opacity increases.

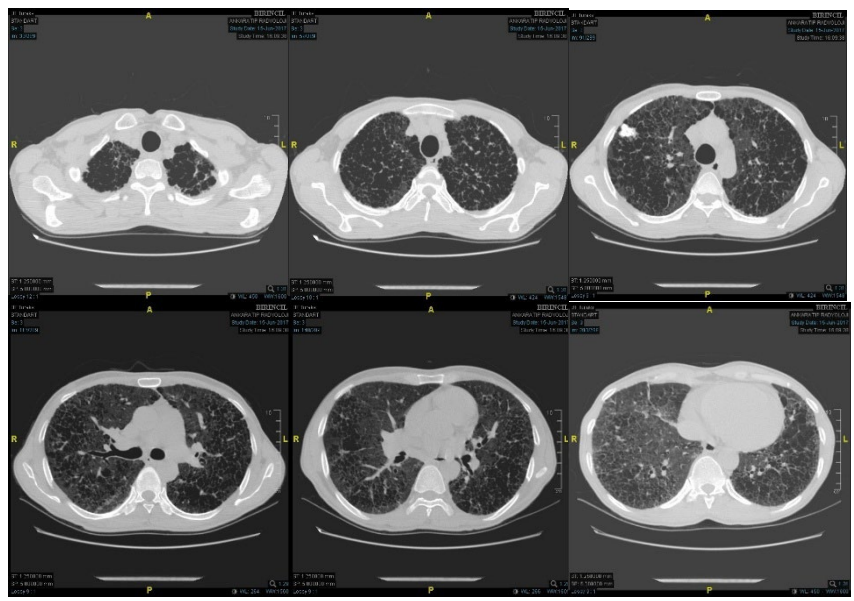


Figure 2. Thorax CT scan images show bilaterally, multiple, vary in shape cystic lesion on axial images.

EPIDEMIOLOGY

Globally, the prevalence of HPS is estimated to be between 1 in 500,000 and 1 in 1,000,000, although exact frequency remain uncertain.[2] HPS cases have been identified across diverse ethnic groups worldwide, including Western Europe, the Indian subcontinent, Japan, China, the Middle East, and among Hispanic populations outside Puerto Rico.[4] The highest reported prevalence is found in Puerto Rico, particularly the northwestern region, where approximately 1 in 1,800 individuals has the HPS-1 subtype, and 1 in 21 individuals carry the founder mutation, a 16-base pair duplication within exon 15 of the HPS1 gene.[5] The

HPS-1 subtype is also predominant among non-Puerto Rican populations, comprising approximately 25% of cases.[6] In central Puerto Rico, HPS-3 affects around 1 in 4,000 individuals.[7] Additionally, studies suggest that about 35% of individuals with albinism in Germany could have a mild form of HPS, underscoring the importance of comprehensive screening for better disease characterization.[8] This study is highlighting the potential benefit of broader screening efforts.

GENETICS AND PATHOGENESIS

HPS is caused by mutations in 11 different genes responsible for encoding proteins crucial for lysosome-related organelle (LRO) biogenesis.[4] The proteins produced from these genes interact within specialized multiprotein complexes known as HPS protein-associated complexes (HPACs), including Adapter Protein-3 (AP-3) and three distinct Lysosome-Related Organelle Complexes (BLOC-1, BLOC-2, and BLOC-3).[9-11] These HPACs mediate LRO biogenesis by regulating the intracellular transport within the endo-lysosomal pathway. LROs are distinct intracellular compartments with lysosome-like characteristics, contributing to critical cellular activities such as storage, secretion, and immune response. Examples of well-defined LROs include melanosomes, platelet granules, endothelial cell-specific Weibel-Palade bodies, lytic granules found in natural killer (NK) cells and cytotoxic T lymphocytes, as well as basophilic and azurophilic granules present in leukocytes.[12-14]

The diverse clinical symptoms observed in HPS, including hypopigmentation, platelet dysfunction, immune system impairment, and pulmonary fibrosis, directly result from abnormalities in LRO formation and function.[10] Pulmonary fibrosis, a major complication of HPS, predominantly involves dysfunctions of the AP-3 and BLOC-3 complexes. Mutations in HPS genes trigger pulmonary fibrosis via several pathways, including disruption of alveolar type II epithelial cells (AT2), inappropriate immune responses, metabolic abnormalities, abnormal fibroblast proliferation in lung tissue, defective autophagy, and accelerated cellular senescence.[15]

CLINICAL MANIFESTATIONS

All patients with HPS, regardless of subtype, have tyrosinase-positive OCA and bleeding disorders ranging from mild to severe due to platelet dysfunction. OCA is characterized by hypopigmentation of hair and skin.[16] Depending on the mutations in the subtypes, pulmonary fibrosis, granulomatous colitis, immune deficiency, and neurodegeneration may be observed.[17]

Oculocutaneous Albinism

Albinism refers to a diverse set of uncommon genetic conditions marked by disruptions in melanin production, leading to either partial or complete absence of pigment, reduced visual sharpness, sensitivity to light (photophobia), and involuntary eye movements (nystagmus), and it is generally classified into two broad groups.[18] Oculocutaneous albinism (OCA) is characterized by diminished pigmentation in the eyes, skin, and hair, often accompanied by misrouting of optic nerves, underdevelopment of the fovea, nystagmus, and vision loss. OCA can be further subdivided into syndromic and non-syndromic types. Among the syndromic forms, HPS and Chediak-Higashi syndrome are the most prevalent ones.

The degree of pigment loss in HPS patients varies by subtype. Those with BLOC-2 complex mutations (such as HPS3, HPS5, or HPS6) generally show milder hypopigmentation than individuals with BLOC-3 mutations (e.g., HPS1, HPS4). Individuals with lighter skin pigmentation are more vulnerable to ultraviolet-induced conditions, including sunburn, solar keratosis, accelerated skin aging, and various skin cancers. In OCA, the risk of UV-triggered skin malignancies is elevated due to limited melanin-based protection and oxidative stress caused by eumelanin and pheomelanin derivatives.

The severity of visual complications, such as foveal hypoplasia and decreased acuity, is closely linked to the extent of hypopigmentation.[19] Clinical symptoms frequently observed include lazy eye (amblyopia), light sensitivity, uncontrolled eye movements, strabismus, and other forms of visual impairment. These ophthalmic issues are typically more pronounced in patients carrying BLOC-2 mutations (HPS3, HPS5, or HPS6), owing to BLOC-2's specific functions in retinal development and maintenance as noted earlier.[20]

Bleeding Diathesis and Platelet Dysfunction

Platelet δ granules store critical factors such as serotonin, calcium, and Adenosine diphosphatedan (ADP), which are released during platelet activation to support aggregation. In individuals with HPS, the

absence of significant reduction of these granules disrupts the release of these factors, leading to impaired platelet activation and bleeding symptoms despite normal platelet counts.[20] It often appears in infancy and persists throughout life. Bleeding can occur with minor trauma to the skin, tooth extraction, or dental cleaning, and in many women with HPS, it may occur with menstrual bleeding. Frequent and recurrent epistaxis are common.[16] Due to bleeding diathesis complications, anticoagulants and antiplatelet agents should be avoided; desmopressin may be used to prevent complications.

Colitis

In patients with HPS, granulomatous inflammation of the intestines may occur, clinically and pathologically like Crohn's disease.[21] The most common symptoms of colitis associated with HPS are hematochezia, abdominal pain, and loose stools; approximately 15% of individuals may experience life-threatening gastrointestinal bleeding that may require surgical intervention such as colectomy. Granulomatous colitis has been identified in patients with HPS-1, HPS-4.[22] Treatment may involve anti-inflammatory agents, immunosuppressants, and anti-tumor necrosis factor alpha drugs, like Crohn's disease therapy. When all other treatments have failed, surgery may be applied as a last resort.[23]

Immunodeficiency, Neutropenia

Neutropenia is specific to HPS-2, but it has also been identified in HPS-9 and HPS-10, which are subtypes with mutations in subunits of the AP3 complex.[24] Neutropenia is chronic, and these patients are at high risk for recurrent viral and bacterial respiratory tract infections. Due to their neutropenia and abnormal cytotoxic activity of natural killer T (NKT) cells, these patients have increased susceptibility to certain malignancies, such as Hodgkin lymphoma.[25]

Pulmonary Fibrosis

Pulmonary fibrosis represents one of the most severe complications associated with HPS and is the primary cause of mortality among affected individuals. It predominantly occurs in the HPS-1, HPS-2, and HPS-4 subtypes. Specifically, pulmonary fibrosis is inevitable among individuals with the HPS-1 subtype, necessitating annual pulmonary function monitoring starting from adolescence in patients with HPS-1, HPS-2, and HPS-4.[16]

The exact mechanisms underlying pulmonary fibrosis development in HPS remain incompletely defined. Nonetheless, alveolar type II epithelial cells (AT2) have been identified as crucial components in the pathogenesis of pulmonary fibrosis.[26] Dysfunction of lamellar bodies, which represent LROs within type II pneumocytes that produce and store pulmonary surfactants, is believed to initiate macrophage-driven inflammation and fibroblast proliferation, leading ultimately to fibrosis.[10] AT2 cells in HPS demonstrate elevated expression levels of cytokines, chemokines such as CCL2 (also known as monocyte chemoattractant protein-1), inducible nitric oxide synthase, and galectin-3. In animal models of HPS, excessive CCL2 production by AT2 cells correlates with heightened alveolar macrophage infiltration, which subsequently elevates profibrotic factors like transforming growth factor-beta (TGF-β).[26-28] Additionally, galectin-3 promotes fibrosis through various mechanisms, including epithelial apoptosis, fibroblast proliferation, differentiation into myofibroblasts, and macrophage polarization toward an M2 phenotype. In HPS, galectin-3 intensifies tissue injury and aberrant fibroproliferative responses by modulating the action of chitinase-like protein 1, another established mediator in lung fibrosis.[29,30]

The clinical onset of pulmonary fibrosis varies among HPS subtypes: symptoms typically arise between the ages of 30 and 40 in patients with HPS-1 and HPS-4, while individuals with HPS-2 exhibit manifestations during childhood or early adulthood. Thus, clinical progression differs significantly from idiopathic pulmonary fibrosis (IPF).[31,32] Patients with HPS pulmonary fibrosis commonly present with exertional shortness of breath or chronic cough. On physical examination, oculocutaneous albinism with varying degrees of pigmentation, horizontal nystagmus, photophobia, reduced visual acuity, and bruising due to platelet dysfunction are commonly observed. Chest examinations often reveal coarse bilateral inspiratory crackles in lower lung fields, progressing over time. Severe cases may exhibit clubbing fingers and acrocyanosis. Pulmonary function tests (PFTs) in early, asymptomatic stages may appear normal; however, symptomatic patients typically show reduced forced vital capacity (FVC), decreased lung volumes indicative of a restrictive ventilatory defect, and impaired diffusion capacity for carbon monoxide (DLco), typical features of fibrotic lung disease.

Serial pulmonary function testing in severely affected individuals have demonstrated disease progression marked by a yearly decline in FVC percent predicted values ranging between 12% and 15%.[33]

Radiologically, chest X-rays in patients with advanced disease frequently display bilateral interstitial infiltrates with fibrosis and pleural thickening. High-resolution computed tomography (HRCT) remains the diagnostic modality of choice, initially demonstrating reticular patterns and subpleural septal thickening predominantly in basal lung regions. As fibrosis advances, findings extend diffusely into the pulmonary parenchyma, with characteristic abnormalities including ground-glass opacities, reticular interstitial thickening, lung volume reduction, honeycomb patterns, and traction bronchiectasis.[34] There is often concordance between HRCT progression and deteriorating pulmonary function parameters.[30]

Bronchoscopy provides limited diagnostic value for HPS-associated fibrosis, and lung biopsy is generally contraindicated due to heightened bleeding risk associated with platelet dysfunction.[30] Histopathologically, pulmonary fibrosis in HPS shares certain features with IPF, such as thickening of alveolar septa and interstitial spaces due to increased extracellular matrix, infiltration of immune cells, fibroblast proliferation, type II pneumocyte hyperplasia, fibroblastic foci, and temporal heterogeneity.[33] Unique features of HPS include alveolar macrophages exhibiting foamy cytoplasm filled with seroid lipofuscin granules, and vacuolated type II pneumocytes with enlarged lamellar bodies. Electron microscopy may reveal unusually large lamellar bodies within these cells. Overall, pulmonary fibrosis in HPS is characterized as a progressive, chronic interstitial lung disease.

Clinical trial results involving placebo groups investigating antifibrotic agents such as pirfenidone suggest that the rate of disease progression in patients with mild to moderate HPS pulmonary fibrosis is heterogeneous.35 However, survival data from severely affected individuals (aged between 37 and 47) indicate that survival typically does not exceed 20 months once FVC values drop below 50% of predicted levels.[36] Pediatric patients with HPS-2 have exhibited particularly rapid disease progression on HRCT imaging.[32]

DIAGNOSIS

As in many diseases, the diagnostic work-up begins with considering this disorder during the differential diagnosis. Clinical and laboratory indicators suggesting suspicion of HPS guide the clinician through the certain diagnosis.[6]

Clinical Characteristics

Skin and hair pigmentation is conspicuous, typically at least one shade lighter compared to other family members, ranging from white to light brown shades for hair and skin. Visual abnormalities including nystagmus, decreased iris and retinal pigmentation, significantly reduced visual acuity, and strabismus are key findings of physical examination.

Bleeding manifestations such as easy bruising, recurrent nosebleeds (epistaxis), gum bleeding, hematochezia, prolonged menstrual bleeding, significant postpartum hemorrhage, or extended bleeding following dental procedures, circumcision, or surgeries are evoking features for HPS diagnosis.[6,37]

Laboratory findings

Impaired secondary aggregation in platelet aggregation tests with normal test results for prothrombin time, partial thromboplastin time, and platelet counts are found. Absence of delta granules (dense bodies) within platelets, confirmed through electron microscopy is supporting the diagnosis.[6]

Genetic Counseling

The family history of similar features supports HPS suspicion. A clinical diagnosis of HPS in the proband can be established by observing characteristic hypopigmentation in hair and skin, typical ocular manifestations, and absence of platelet delta granules on electron microscopic examination.[6] Genetic analysis, through targeted or next-generation sequencing, is becoming an increasingly valuable tool to identify the responsible mutations and confirm a diagnosis in clinically suspected cases. Identification of biallelic pathogenic variants in AP3B1, AP3D1, BLOC1S3, BLOC1S5, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, or HPS6 genes can definitively establish the diagnosis, particularly when clinical presentation alone is inconclusive.[6]

MANAGEMENT, FOLLOW-UP AND TREATMENT

Following an initial diagnosis of HPS, a comprehensive evaluation of associated bleeding disorders is recommended, including detailed coagulation analy-

ses such as von Willebrand factor testing and platelet function assessments. Pulmonary fibrosis should be evaluated with regular PFT and HRCT. Colonoscopy may also be indicated if colitis symptoms are suspected. Genetic counseling should be provided to patients and their families to better understand the genetic nature, prognosis, and implications of HPS. Additionally, white blood cell counts and assessments of neutrophil function should be routinely performed to screen for immune deficiencies. Regular ophthalmologic care, including correction of refractive errors and interventions for strabismus, should be maintained, with surgery as an option when required. Annual follow-ups are essential.

Patients should take protective measures against excessive sun exposure to minimize skin damage, burns, and reduce the risk of skin cancer. Regular dermatological screening is advisable, regardless of symptom presence, and prompt management of skin cancer is necessary.

To manage the bleeding tendencies, it may be advisable for patients to use medical identification bracelets clearly indicating the platelet dysfunction. Additionally, patients are advised to avoid high-risk sports and activities likely to cause injury or trauma and should abstain from medications impairing platelet function, including aspirin, anticoagulants, and non-steroidal anti-inflammatory drugs (NSAIDs). Desmopressin can be employed as prophylaxis during invasive procedures. Platelet transfusions or red blood cell transfusions may become necessary for managing prolonged or significant bleeding episodes or during major surgical interventions.

For patients with colitis linked to HPS, treatment options include topical and systemic corticosteroids, anti-inflammatory agents, and immunomodulatory medications, though responses can vary. Severe cases unresponsive to conventional therapies may require anti-tumor necrosis factor-alpha (anti-TNF-alpha) treatments or even surgical bowel resection.[38]

Granulocyte colony-stimulating factor effectively treats neutropenia, and in severe cases, hematopoietic stem cell transplantation (HSCT) could be considered.[24]

For pulmonary fibrosis management, routine vaccinations against influenza, pneumococcus, and COVID-19 are recommended, alongside avoidance of exposure to respiratory irritants. Regular exercise and prompt treatment of respiratory infections or asthma exacerbations are critical. Although currently there are no officially approved pharmacological therapies specifically for HPS-related pulmonary fibrosis, supplemental oxygen therapy is recommended for symptomatic hypoxemic patients.[31] Lung transplantation remains the definitive therapeutic intervention, and early referral for lung transplantation is strongly recommended for HPS-PF patients.[38]

Pirfenidone and nintedanib, two FDA-approved medications for IPF, have been evaluated in HPS-PF. Pirfenidone, known to reduce pulmonary fibrosis via anti-inflammatory effects mediated by NF-κB, TGF-β, and Wnt signaling pathways, demonstrated in vitro reductions in inflammatory cytokines produced by alveolar macrophages from HPS-1 patients.[39,40] A long-term clinical trial indicated that pirfenidone treatment resulted in a slower annual decline (~8% per year) in pulmonary function over 44 months compared to placebo.[41] However, another study involving mild to moderate HPS-1 and HPS-4 patients showed no significant benefit at 12 months, leading to early termination.[32] Nintedanib, a tyrosine kinase inhibitor approved for IPF, poses a potential bleeding risk that could complicate its use in HPS-PF patients due to existing platelet abnormalities.[42] Nevertheless, there has been a reported case of progressive pulmonary fibrosis in an HPS patient who was treated successfully with nintedanib prior to undergoing lung transplantation.[43]

Combination therapy utilizing pirfenidone and nintedanib has demonstrated synergistic antifibrotic effects through modulation of macrophage and fibroblast signaling via the SPP1-AKT pathway.[44] This combination drug therapy may offer a promising avenue for the treatment of patients with HPS-PF. Other potential molecular therapeutic targets being investigated include thromboxane A2 receptor (TBXA2R), cannabinoid receptor type 1 (CB1R), inducible nitric oxide synthase (iNOS), and galectin-3.[15]

Given the genetic nature of HPS, gene therapy and gene-editing approaches are also under investigation. In vitro studies using lentiviral vectors have successfully reintroduced functional HPS1 genes into human dermal melanocytes, restoring proper gene expression and cellular function; however, challenges remain for effective gene delivery to alveolar epithelial cells.[45]

Considering these challenges, there is an urgent need for the development of safer and more effective treatments to comprehensively manage HPS.

CASE ANALYSIS

In our case, albinism and nystagmus are the most important findings that guide us. The patient first presented to the hospital at the age of 37 with complaints of dyspnea, which is consistent with the expected age range of 30-40 years for HPS pulmonary involvement in HPS-1 and HPS-4. The patient's dyspnea progressed rapidly. Although findings of pulmonary fibrosis were observed in the HPS-PF HRCT, the presence of cystic lesions in this patient may have caused difficulty in reaching the correct diagnosis at first. The cystic lesions were evaluated as emphysema due to the patient's smoking. However, the patient's PFT is consistent with a restrictive pattern. Bronchoscopy is not expected to lead to a diagnosis of the disease, and it did not help in this case either. The patient was consulted with other departments regarding other organ involvement and was referred for lung transplantation, which is currently the only proven treatment method. However, the patient died before undergoing transplantation.

CONCLUSION

HPS is an autosomal recessive, multisystemic disorder characterized primarily by oculocutaneous albinism, bleeding tendencies, and variable involvement of other organs including lungs, colon, and immune system. Although it is most seen on the Caribbean Island of Puerto Rico, the disease has been found in people of many different ethnic backgrounds. Caused by mutations in 11 different genes responsible for encoding proteins crucial for lysosome-related organelle (LRO) biogenesis. All patients with HPS, regardless of subtype, have tyrosinase-positive OCA and bleeding disorders ranging from mild to severe due to platelet dysfunction. Pulmonary fibrosis represents one of the most severe complications associated with HPS and is the primary cause of mortality among affected individuals. Clinical and laboratory indicators suggesting suspicion of HPS guide the clinician through certain diagnosis. After diagnosis, patients must be regularly monitored for hematology, ophthalmology, dermatology, chest diseases, neutropenia and gastroenterology. Treatments can be arranged according to the affected organ. Although antifibrotic treatments have been tried for HPS-PF, the only proven treatment method at present is lung transplantation, and early referral of patients is of great importance. Given the genetic nature of HPS, gene therapy and gene-editing approaches are also under investigation.

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CHAPTER 10

FAMILIAL INTERSTITIAL PNEUMONIAS (SP-C/TELOMERE SHORTENING/ABCA3)

AİLEVİ İNTERSTİSYEL PNÖMONİLER (SP-C/TELOMER KISALMASI/ABCA3)

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FAMILIAL INTERSTITIAL PNEUMONIAS (SP-C/TELOMERE SHORTENING/ABCA3)

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ABSTRACT

Familial interstitial pneumonia (FIP) represents one of the most intriguing frontiers in interstitial lung disease, lying at the intersection of clinical heterogeneity, genetic complexity, and therapeutic uncertainty. While idiopathic pulmonary fibrosis (IPF) remains the prototypical phenotype, patients with FIP often defy textbook definitions: presenting earlier, progressing faster, and exhibiting unexpected extrapulmonary manifestations such as macrocytosis or hepatic dysfunction.

Over the past two decades, a paradigm shift has occurred: from recognizing FIP as a clinical curiosity to understanding it as a genetically driven disorder rooted in mutations affecting surfactant homeostasis (e.g., *SFTPC*, *SFTPA1/2*, *ABCA3*) and telomere maintenance (e.g., TERT, TERC, RTEL1, PARN). These mutations not only alter epithelial cell integrity and regenerative capacity but also introduce critical questions about heritability, disease anticipation, and systemic involvement. Remarkably, in many families, these mutations reveal themselves not only through pulmonary fibrosis but through hematologic abnormalities, cryptogenic liver disease, and premature hair graying.

With the advent of accessible genetic sequencing and telomere length assays, FIP has become a diagnostically actionable entity. However, these developments have raised many questions: How frequently should an asymptomatic individual carrying a telomere mutation be monitored? Can standard immunosuppressive regimens be safely administered in patients with short telomeres? Should lung transplantation protocols be fundamentally restructured for this group?

Therapeutic decisions are no longer solely based on radiologic patterns or lung function decline. Instead, they must account for the molecular architecture of the disease. Emerging data suggest that antifibrotic therapies remain effective in patients with telomerase mutations, offering hope where traditional immunosuppression may increase harm. Additionally, lung transplantation, often considered the last resort, requires a nuanced approach in FIP due to heightened risk of complications in telomere syndromes.

In the future, the integration of genetic and clinical data may enable the development of a more predictable, safe, and effective monitoring-treatment model for both patients and asymptomatic individuals at risk. This chapter explores the evolving landscape of FIP, with a focus on gene-specific phenotypes, risk stratification strategies, and the expanding role of precision medicine.

Keywords: *Familial interstitial pneumonia; Surfactant protein mutations; Telomere shortening; Interstitial lung disease; Rare interstitial lung diseases; Monogenic fibrosis*

ÖZET

Ailesel intersitisyel pnömoni (AİP), interstisyel akciğer hastalıklarının en karmaşık ve dikkat çekici alt gruplarından birini oluşturur. Klinik varyasyonları, genetik çeşitliliği ve tedaviye verdiği değişken yanıtlarla, klasik intersitisyel akciğer hastalığı tanımlarının ötesine geçen bir tablo sunar. Olağan interstisyel pnömoni fenotipi bu hastalarda sık görülse de erken yaşta başlangıç, hızlı progresyon ve hematolojik ya da hepatik sistemleri içeren ekstratorasik bulgular AİP'nin, idyopatik pulmoner fibrozisten (İPF) ayırt edici özelliklerindendir.

Son yıllarda surfaktan metabolizmasından sorumlu genlerde (SFTPC, SFTPA1/2, ABCA3) ve telomer biyolojisiyle ilişkili genlerde (TERT, TERC, RTEL1, PARN) tanımlanan mutasyonlar, AİP'nin moleküler mekanizmalarını aydınlatmıştır. SP-C mutasyonları surfaktan protein yapısında bozulmaya

ve alveoler epitel bütünlüğünün zayıflamasına yol açarken; ABCA3 gen defektleri özellikle çocukluk çağında ağır ve hızlı ilerleyen tablolarla ilişkilidir. Telomer kısalması ise hücresel yaşlanmayı hızlandırarak fibrozis gelişimine zemin hazırlar ve hematolojik ya da hepatik sistem tutulumuyla seyreden geniş bir klinik spektrum ortaya çıkarır.

Klinik olarak hastalar asemptomatik bireylerden hızlı progresyon gösteren ağır fibrotik olgulara kadar değişen bir yelpazede karşımıza çıkar. Çocukluk çağında başlayan vakalar çoğunlukla surfaktan protein mutasyonları ile ilişkilendirilirken, erişkin yaşta görülen olgular daha çok telomer biyolojisi bozukluklarıyla bağlantılıdır. Erken saç beyazlaması, trombositopeni, makrositoz ya da kriptogenik siroz gibi akciğer dışı bulgular genetik temeli düşündüren ipuçlarıdır.

Tanıda aile öyküsü, genetik analizler, telomer uzunluğu ölçümleri, yüksek çözünürlüklü BT bulguları ve gerektiğinde histopatolojik inceleme birbirini tamamlayıcı şekilde kullanılmaktadır. Tedavide spesifik mutasyonlara yönelik küratif yaklaşımlar henüz geliştirilmemiş olsa da antifibrotik ajanlar (pirfenidon, nintedanib) telomer ilişkili olgularda dahi etkinlik göstermektedir. Buna karşın immünsüpresif tedaviler kısa telomerli hastalarda ciddi komplikasyon riski taşımaktadır. İleri evrede akciğer transplantasyonu önemli bir seçenektir; ancak bu hastalarda immünsüpresyonun yeniden yapılandırılması gereklidir.

Genetik analiz ve telomer uzunluğu ölçümünün rutin pratiğe entegre olması, AİP'nin yalnızca tanımlanabilir değil, aynı zamanda yönetilebilir bir hastalık hâline gelmesini sağlamıştır. Ancak bu gelişmeler beraberinde pek çok soruyu da getirmiştir: Telomer mutasyonu taşıyan asemptomatik bir birey ne sıklıkla izlenmelidir? Kısa telomerli hastalarda immünsupresif tedavi güvenli midir? Akciğer nakli sonrası immünosupresyon şeması bu grup için yeniden mi yapılandırılmalı mıdır?

Sonuç olarak AİP, heterojen yapısı, genetik temeli ve sistemik bulgularıyla kişiselleştirilmiş izlem ve tedavi yaklaşımı gerektiren kompleks bir hastalık grubudur. Gelecekte genetik verilerin rutin pratiğe entegrasyonu ile erken tanı olanaklarının artacağı ve hedefe yönelik tedavilerin geliştirileceği öngörülmektedir.

Bu bölümde, AİP'nin güncel genetik-moleküler altyapısı, gen-spesifik klinik özellikleri ve bireyselleştirilmiş yönetim yaklaşımları detaylı şekilde ele alınmıştır.

Anahtar Kelimeler: *Ailesel interstisyel pnömoni; Surfaktan protein mutasyonu; Telomer kısalması; Intersitisyel akciğer hastalığı; Nadir interstisyel akciğer hastalığı; Monogenik fibrozis*

CASE PRESENTATION

A 36-year-old married male, working as a restaurant owner, presented with progressive exertional dyspnea, fatigue, intermittent low-grade fever, and nocturnal burning and numbness in the lower extremities for over one year. The patient had no history of smoking or alcohol use. The family history revealed that the patient's mother died at the age of 65 due to interstitial lung disease (ILD). His medical history was notable for recurrent nephrolithiasis for more than 15 years and thrombocytopenia first detected in 2008. In late 2018, he was diagnosed with pulmonary embolism following complaints of shortness of breath and hemoptysis, and received low-molecular-weight heparin treatment. A thoracic computed tomography (CT) scan performed the same year revealed bilateral nodular infiltrates and ground-glass opacities, interpreted as pneumonia, and he was treated with intravenous antibiotics. Due to recurrent and persistent symptoms, the patient was referred to a tertiary center for further evaluation with a presumptive diagnosis of ILD.

On physical examination, bibasilar fine crackles, digital clubbing, palmar erythema, and poikilodermatous skin changes were noted. The skin showed scattered hypopigmented, erythematous, scaly plaques, and hyperkeratosis was present on toe-nails. The patient also reported diffuse body hair loss and premature graying of hair since childhood. Pulmonary function tests (PFTs) demonstrated a restrictive pattern (Forced Vital Capacity (FVC) 63%, Forced Expiratory Volume in 1 second (FEV_1) 66%) with a severely reduced Diffusing Capacity of the Lung for Carbon Monoxide (DLco) of 44%. High-resolution computed tomography (HRCT) imaging revealed lower-lobe predominant irregular reticulations and mosaic attenuation, suggesting fibrotic ILD (Figure 1). Bronchoalveolar lavage showed macrophage predominance (86%) with a low CD4/CD8 ratio (0.39). Bone marrow biopsy demonstrated hypocellularity. Laboratory testing revealed persistent thrombocytopenia (35.000/mm^3) and elevated INR. Abdominal imaging and upper GI endoscopy showed signs of liver cirrhosis and portal hypertension, including esophageal varices and ascites.

INTRODUCTION

Interstitial lung diseases (ILD) are a heterogeneous group of disorders characterized by abnormal inflammatory responses and tissue remodeling that affect the alveolar walls and interstitial compartments of the lung. This process may lead to fibrosis, resulting in impaired gas exchange, progressive loss of pulmo-

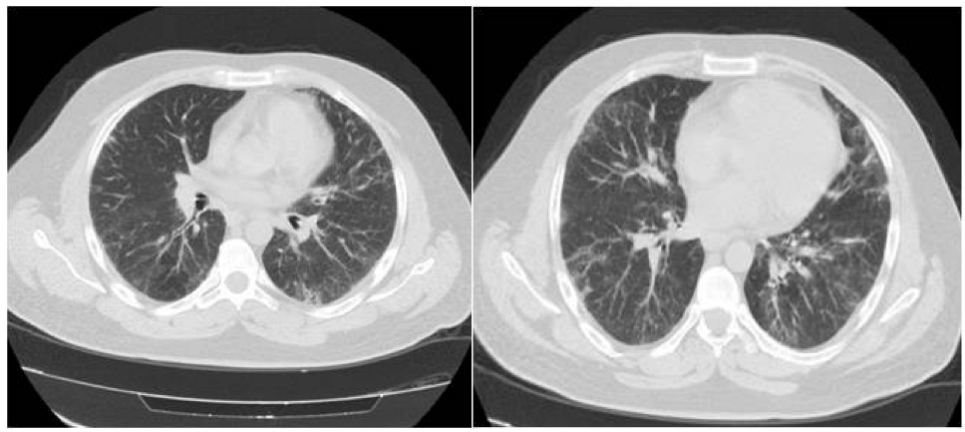


Figure 1. A thoracic computed tomography (CT) scan revealed bilateral nodular infiltrates and ground-glass opacities.

nary function, and, in some cases, irreversible lung damage.[1] Although the precise pathobiological mechanisms remain largely unclear, both environmental exposures and genetic susceptibility are believed to contribute significantly to disease development. While sporadic forms of interstitial pneumonia are more common, familial clustering has been increasingly recognized. For instance, the risk of pulmonary fibrosis is reported to be approximately ten fold higher among first-degree relatives of individuals diagnosed with idiopathic pulmonary fibrosis (IPF).[2]

Familial interstitial pneumonia (FIP) is defined as a condition in which at least two members of the same family have ILD, typically characterized by fibrotic changes. Although the phenomenon was first described over a century ago, it was not until the 1950s and 1960s that clinicians began to suspect a distinct, genetically driven subtype of fibrotic lung disease.[3,4] Recent advancements in genetic research have identified numerous risk variants associated with various pathogenic pathways, whose effects are particularly pronounced in hereditary forms of ILD. The study of ILD in familial contexts uncovered mutations affecting both telomere biology and surfactant metabolism.[3,5] These findings revealed that the clinical spectrum extended beyond IPF to include other progressive interstitial lung diseases such as non-specific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HSP), and ILD associated with rheumatoid arthritis.[6-8] Moreover, variants in TRGs and SRGs have been linked to diverse clinical parameters, including timing of symptom emergence, sex, pulmonary phenotype, extrapulmonary manifestations, and overall survival. The identification of a specific gene variant (e.g., in telomere-related genes (TRGs) or surfactant-related genes (SRGs)) segregating with ILD within a family provides strong evidence for a monogenic etiology of the disease.[2]

As public awareness of hereditary disorders increases and scientific literature continues to expand, genetic sequencing has begun to take a place in routine clinical care for patients with pulmonary fibrosis, with the potential to significantly impact disease management. Although numerous monogenic conditions have been linked to ILD, the scope of this chapter is limited to TRGs and SRGs, the most frequently implicated gene groups in FIP. Other rare diseases, such as Hermansky-Pudlak syndrome, pulmonary alveolar proteinosis, and pulmonary alveolar microlithiasis, present with distinct clinical features and are addressed separately in other chapters of the book.

EPIDEMIOLOGY

Accurately estimating the prevalence of FIP remains difficult. While IPF affects approximately 13.4-18.5 per 100,000 individuals, FIP is estimated at only 1.3-5.9 per million.[9,10] However, observational studies suggest that FIP may account for up to 20% of pulmonary fibrosis cases, likely due to underreporting or limited family history data.[11-13] Recent screening studies have revealed subclinical interstitial lung abnormalities in 15-31% of asymptomatic relatives of affected individuals.[14-17] Notably, such abnormalities were found even among relatives of patients with apparently sporadic disease.[16] These findings highlight

the potential underestimation of FIP prevalence and emphasize family history as a key risk factor. Familial interstitial pneumonia (FIP) encompasses a range of ILD subtypes, most commonly idiopathic pulmonary fibrosis, which accounts for approximately 50% of cases. Other forms include ILD associated with connective tissue diseases and chronic hypersensitivity pneumonitis. This clinical heterogeneity reflects the influence of underlying genetic predisposition.[3]

GENETIC AND MOLECULAR MECHANISMS

FIP represents a complex interplay between genetic predisposition and molecular dysregulation within lung tissue. Over the past two decades, significant advances in genomic profiling have identified key gene variants that contribute to disease susceptibility and progression. These genetic alterations fall broadly into two categories: surfactant protein homeostasis and telomere maintenance.[3]

Variants in surfactant-related genes, most notably *SFTPC*, *SFTPA1/2*, and *ABCA3*, confer susceptibility through mechanisms involving protein misfolding, impaired intracellular trafficking, and endoplasmic reticulum (ER) stress.[18-20] For instance, the *SFTPC* I73T missense mutation alters proSP-C processing and induces proteotoxicity, while BRICHOS domain mutations exacerbate ER stress and activate the unfolded protein response.[21] Biallelic loss-of-function mutations in *ABCA3* disrupt lamellar body formation and surfactant transport, resulting in alveolar epithelial cell injury.[20]

Concurrently, telomere biology disorders arising from mutations in TERT, TERC, RTEL1, PARN, NAF1, and related genes impair telomerase activity or telomere structure, leading to replicative senescence, genomic instability, and diminished regenerative capacity of alveolar epithelial type II cells.[22-25] These defects promote aberrant wound healing, fibrotic remodeling, and progressive decline in pulmonary function.

At the cellular level, both surfactant-related and telomere-related variants converge on critical pathogenic processes, including epithelial dysfunction, impaired alveolar repair, and dysregulated immune signaling. Furthermore, the penetrance and expressivity of these mutations are modulated by environmental exposures and additional genetic modifiers, contributing to interindividual variability in age of onset, disease severity, and extrapulmonary manifestations.[3]

Elucidation of these mechanisms not only facilitates more accurate risk stratification and early detection in at-risk individuals but also provides a rationale for emerging targeted therapies. In particular, the integration of comprehensive genomic analysis into clinical evaluation may inform prognostication and therapeutic decision-making in FIP, including consideration for antifibrotic therapy, and lung transplantation timing.

CLINICAL MANIFESTATIONS

Individuals affected by familial forms of pulmonary fibrosis often exhibit similar clinical symptoms, imaging characteristics, and histopathological patterns as seen in sporadic fibrotic ILDs. Nonetheless, FIP patients are typically diagnosed at a younger age and tend to experience a more aggressive disease course, often progressing to a fibrosing ILD phenotype associated with reduced survival.[26]

Hematologic abnormalities are commonly observed in FIP patients. Anemia, macrocytosis, and thrombocytopenia are notable findings, especially in those carrying mutations in TRGs.[27] Some patients may also develop myelodysplasia or acute leukemia, which are indicative of underlying genetic mutations.[28]

Liver involvement in FIP can manifest as elevated liver enzymes, cryptogenic cirrhosis, or hepato-pulmonary syndrome. These hepatic phenotypes may be linked to genetic variants and should be considered during clinical evaluation.[27] Certain cutaneous and hair-related signs, such as early-onset hair greying, may also be present and serve as clues to genetic predisposition.[27,29] Moreover, short telomere syndrome associated with FIP can present with systemic features, including compromised immune function, vision-related complications affecting the retina, and various neurological impairments.[23]

A significant proportion of individuals harboring mutations in telomere-related genes receive an ILD diagnosis around the average age of 58, which frequently prompts evaluation for lung transplantation as a treatment option.[30] Separate clinical studies have identified rare mutations in telomere-related genes in a notable proportion of IPF patients evaluated for lung transplantation, with reported prevalence rates reaching up to nearly one-quarter of cases.[31,32] Assessing the necessity of telomere length analysis and genetic testing in all individuals with fibrosing interstitial

lung diseases has become an area of growing clinical interest, especially before considering them for lung replacement procedures. While patients with familial pulmonary fibrosis remain eligible for transplant, coexisting short telomere syndromes may require tailored adjustments in immunosuppressive treatment strategies.[33]

Clinical course and prognosis vary according to the patient's genetic background, but progressive fibrosis and treatment resistance are common features. Therefore, early diagnosis and a multidisciplinary management approach are crucial for optimizing patient outcomes.

GENETIC TESTING AND COUNSELING

In families affected by FIP, genetic testing has become an increasingly valuable tool for identifying individuals at risk, especially in the presence of a confirmed monogenic cause. Given that FIP is most commonly inherited in an autosomal dominant manner, first-degree relatives of affected individuals have a substantial risk (approximately 50%) of inheriting a pathogenic variant. Therefore, once a (likely) pathogenic mutation is identified in an affected individual, cascade genetic testing in asymptomatic first-degree relatives can be considered.[34] The current recommendations for which individuals should be offered genetic sequencing and clinical genetic counselling are summarized in the Figure 2.[2] However, the decision to undergo genetic testing should be made carefully and with full understanding of the potential medical, psychological, and social implications. For this reason, genetic counseling is a critical part of the process. Counseling sessions provide an opportunity to discuss the inheritance patterns, the significance of test results, the possibility of disease anticipation in TRG mutations, and the potential impact of findings on insurance, family planning, and emotional well-being.[34,35] It is generally recommended that predictive genetic testing in as-

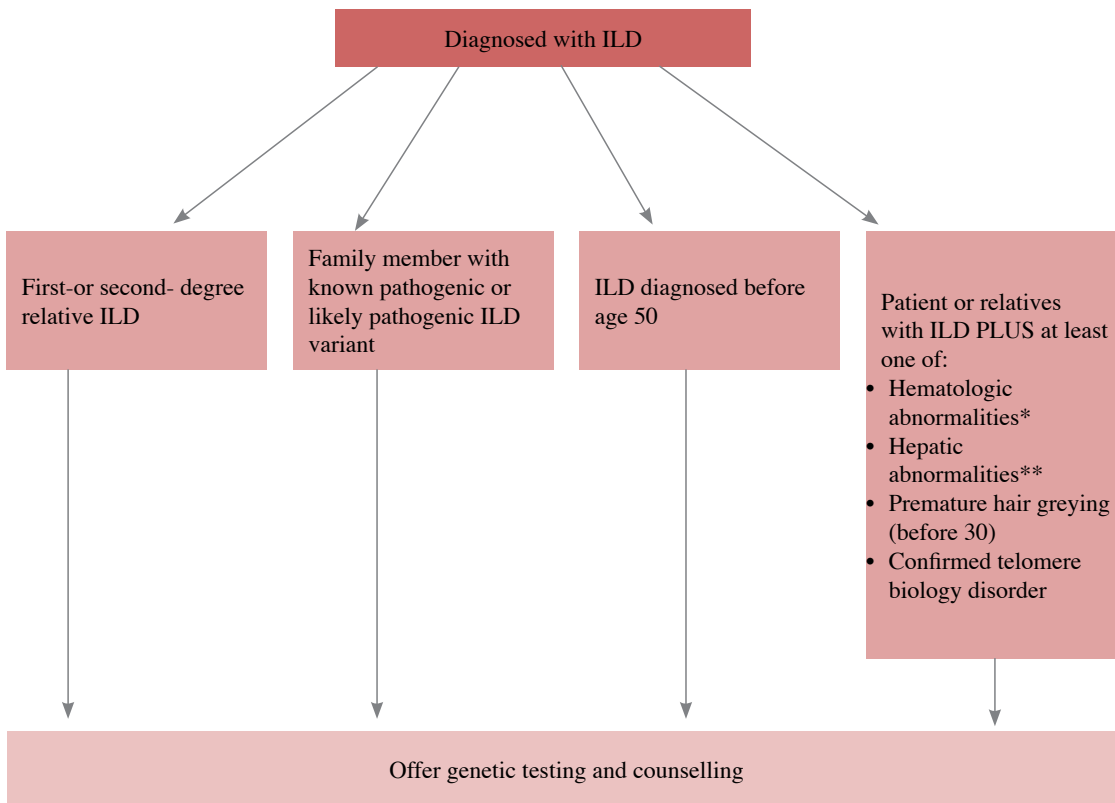


Figure 2. Algorithm for offering genetic sequencing and clinical genetic counseling in patients with ILD.[2]
***Hematological abnormalities:** macrocytosis, neutropenia, lymphoneia, thrombocytopenia, myelodysplasia, acute leukaemia.*
****Hepatic abnormalities:** cryptogenic elevated liver anzymes, portal hypertension, hepato-pulmonary syndrome, liver cirrhosis.*
***ILD:** Interstitial lung disease.*

ymptomatic individuals be deferred until they are of legal age and capable of making informed decisions, typically over 18 years of age. Additionally, national laws and healthcare policies may influence the accessibility and coverage of genetic testing, especially in individuals without clinical symptoms.[2]

While pathogenic variants in surfactant-related genes (SRG) often show high penetrance and thus strong predictive value, telomere-related gene mutations may present with variable expressivity and incomplete penetrance.[36] Moreover, risk assessment becomes more challenging due to genetic anticipation observed in families carrying telomere-associated mutations, where the disease may emerge at a younger age and present with increased severity in successive generations.[34] Importantly, the absence of a detected mutation does not always equate to the absence of risk, particularly in telomere biology disorders, where other non-genotyped mechanisms such as inherited short telomeres may still contribute to disease.[35]

In summary, genetic testing, when performed in a context of appropriate counseling and ethical oversight, can guide long-term clinical management and risk stratification for at-risk family members. However, interpretation of results must be individualized, considering the specific gene involved, family history, and the broader psychosocial context of the patient.

SCREENING AND FOLLOW-UP APPROACHES IN FAMILY MEMBERS

In individuals diagnosed with FIP, screening strategies aimed at the early detection of ILD in first-degree relatives, before the onset of symptoms, are gaining increasing importance. In clinical practice, it is considered that regular assessments in asymptomatic individuals may contribute to the early identification of disease. However, there is currently no consensus regarding the optimal frequency of such follow-up evaluations.[11,15,35]

When first-degree relatives present with persistent respiratory symptoms such as chronic cough or dyspnea, it is recommended that they undergo low-dose thoracic CT and pulmonary function testing.[26,37] In cases associated with short telomere syndrome, incorporating a complete blood count and liver enzyme testing into the follow-up protocol may be beneficial for the early detection of systemic manifestations.[36]

Early changes detected by high-resolution computed tomography (HRCT) have been linked to measurable reductions in lung function. For instance, asymptomatic relatives showing early ILD patterns on HRCT had a mean DLco of 97% predicted, whereas those with normal scans showed a higher mean of 105% predicted.[38] In a comparable manner, other studies reported DLco values of 89% compared to 93% in individuals presenting interstitial lung abnormalities and those lacking such findings, and 73% versus 87% in another cohort.[15,16] Despite these findings, forced vital capacity (FVC) typically remains within normal limits.[35] Thus, normal pulmonary function does not exclude early or subclinical disease, but pulmonary function testing continues to be a valuable tool for both baseline assessment and follow-up. Performing these tests annually may assist in identifying early functional decline.

Disease risk varies based on age, the type of genetic mutation, and, particularly in TRG mutations, the presence of genetic anticipation, where disease tends to occur earlier and more severely in successive generations.[39-41] While certain mutations (e.g., SFTPC, ABCA3) can cause disease in childhood, others such as SFTPA1/2 and TERT are typically associated with adult-onset ILD.[36]

There is growing evidence that genetic predisposition, advancing age, and environmental exposures, especially cigarette smoke, contribute to disease development. However, current evidence is insufficient to support gene- or age-specific screening guidelines. Nonetheless, regular clinical monitoring and minimizing exposure to environmental risk factors remain prudent approaches to facilitate earlier diagnosis and more effective management in individuals at risk.[2]

MANAGEMENT, FOLLOW-UP AND PROGNOSIS

In the treatment of FIP, while approaches similar to those for sporadic pulmonary fibrosis are generally followed, personalized treatment strategies based on genetic and clinical features are of particular importance. Current international guidelines recommend the use of antifibrotic therapies in patients diagnosed with IPF or progressive pulmonary fibrosis, regardless of whether the disease is familial or genetically based. In this context, nintedanib and pirfenidone are the cornerstone medications for patients with FIP.[42,43]

Retrospective studies have shown that antifibrotic

therapy slows the decline in lung function in patients carrying TRG mutations and is generally well tolerated. Moreover, pirfenidone has been reported to be effective regardless of telomere length.[42,43] In contrast, immunosuppressive drugs have been associated with adverse outcomes, particularly in patients with short telomere syndrome or those carrying TRG mutations. Therefore, the use of immunosuppressive therapy should be carefully considered.[44,45]

During follow-up, regular clinical assessments, pulmonary function testing, and radiological imaging are essential. In particular, annual repetition of PFTs enables early detection of disease progression.[37] In addition, to improve quality of life, patients should be encouraged to avoid environmental risk factors, especially exposure to inhaled agents such as cigarette smoke.

In terms of prognosis, disease progression in FIP can vary depending on the genetic mutation and the patient's overall condition. In patients with telomere-related mutations, the disease tends to follow a more aggressive course.[39,40] However, with appropriate treatment and close monitoring, both life expectancy and quality of life can be significantly improved.

The management of adult patients with FIP requires a multidisciplinary and personalized approach. Antifibrotic therapy, regular monitoring, and minimizing environmental risks are the cornerstones in slowing disease progression and reducing complications.[46,47]

CASE ANALYSIS

The presence of mucocutaneous findings (early graying, alopecia, poikiloderma), bone marrow failure, pulmonary fibrosis, and cryptogenic cirrhosis prompted further evaluation for an inherited telomere biology disorder. The patient was referred to the Department of Medical Genetics. Genetic testing revealed a pathogenic TERT variant, and telomere length was below the 10th percentile for age, confirming a telomeropathy diagnosis in the spectrum of FIP.

The patient was started on antifibrotic therapy, and his first-degree relatives were offered genetic counseling and screening. At one-year follow-up, a decline in PFT was observed (FVC 55%, DLco 34%), and he was referred to a lung transplant center for further evaluation.

This case highlights a complex multisystem telomeropathy manifesting with early-onset pulmonary fibrosis, bone marrow failure, cryptogenic cirrhosis, and characteristic mucocutaneous signs, fitting the extended phenotype of familial pulmonary fibrosis with telomere-related gene mutations. In such cases, early recognition of extrapulmonary features and genetic testing are crucial for diagnosis, family screening, and appropriate management, including timely referral for transplantation.

CONCLUSION

FIP is often inherited in an autosomal dominant pattern and may present with pulmonary and extrapulmonary signs, including hematologic and hepatic involvement. Mutations in surfactant-related genes (e.g., SFTPC, ABCA3) and telomere-related genes (e.g., TERT, TERC, RTEL1, PARN) are the most common monogenic causes of FIP. Genetic counseling and targeted testing should be offered to first-degree relatives of affected individuals, especially in the presence of early-onset disease or systemic findings.

Antifibrotic therapies are effective in slowing disease progression, even in patients with telomere-related mutations. Immunosuppressive therapy may carry increased risk in patients with short telomeres and should be used with caution. Lung transplantation remains a treatment option but requires special consideration of post-transplant immunosuppressive regimens in patients with telomeropathies.

Screening of asymptomatic relatives using HRCT, PFTs, blood counts, and liver function tests is recommended for early disease detection. Integration of genetic data into clinical management represents the future of personalized care in FIP.

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CHAPTER 11

PULMONARY AMYLOIDOSIS

PULMONER AMİLOİDOZ

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PULMONARY AMYLOIDOSIS

PULMONER AMİLOİDOZ

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ABSTRACT

Pulmonary amyloidosis is a rare and heterogeneous group of disorders characterized by the extracellular accumulation of misfolded and insoluble protein fibrils within the lung parenchyma and airways. While systemic amyloidosis and its pulmonary manifestations have been extensively discussed in the hematology literature, isolated pulmonary involvement remains exceedingly uncommon. In most instances, it has been described through case reports, small case series, or autopsy-based studies. From a clinical perspective, pulmonary amyloidosis is classified into three principal subtypes: tracheobronchial, nodular parenchymal, and diffuse alveolar-septal forms. Tracheobronchial amyloidosis is localized predominantly to the central airways and leads to progressive luminal narrowing, presenting with symptoms such as chronic cough, wheezing, recurrent respiratory infections, or hemoptysis. The nodular parenchymal type is often asymptomatic and is typically detected incidentally during thoracic imaging. It may appear as solitary or multiple nodules, occasionally demonstrating calcification, and can radiologically mimic primary or metastatic malignancies. The diffuse alveolar-septal subtype almost invariably reflects pulmonary involvement of systemic AL amyloidosis. Radiologically, this form closely resembles interstitial lung disease, with high-resolution computed tomography (HRCT) demonstrating ground-glass opacities, interlobular septal thickening, and a reduction in diffusing capacity as characteristic findings. Diagnostic evaluation requires an integrated approach combining clinical, radiologic, and histopathological modalities. HRCT represents the cornerstone of radiological assessment and diagnostic work-up. Definitive diagnosis, however, relies on histological demonstration of amyloid deposits using Congo red staining, which reveals the pathognomonic apple-green birefringence under polarized light. While immunohistochemistry may assist in fibril subtyping, laser microdissection coupled with mass spectrometry-based proteomic analysis is currently regarded as the gold standard. The differential diagnosis is broad, encompassing malignant neoplasms, granulomatous diseases, and a range of interstitial lung disorders, thereby underscoring the necessity of tissue confirmation in cases of clinical suspicion. Therapeutic strategies are closely related to the subtype. Localized tracheobronchial disease may be managed with bronchoscopic debulking, stent placement, or, in refractory cases, external beam radiotherapy. Nodular parenchymal amyloidosis generally requires no intervention unless progressive growth or symptomatic disease develops. In contrast, diffuse alveolar-septal involvement is almost invariably associated with systemic AL amyloidosis and necessitates hematology-directed regimens, including bortezomib-, daratumumab-, or lenalidomide-based protocols. Prognosis varies substantially: localized forms frequently pursue an indolent course, whereas pulmonary involvement in systemic AL amyloidosis is strongly associated with adverse outcomes. Future research priorities include the establishment of standardized diagnostic algorithms, the development of noninvasive biomarkers for earlier recognition, and the identification of novel therapeutic targets to improve long-term clinical outcomes in this rare but clinically important condition.

Keywords: *Pulmonary amyloidosis; Tracheobronchial amyloidosis; Lung nodules; Systemic amyloidosis; Immunoglobulin light chains*

ÖZET

Pulmoner amiloidoz, akciğer parankimi ve hava yollarında hatalı olarak katlanmış ve çözünmeyen protein fibrillerinin ekstrasellüler birikimi ile karakterize, nadir görülen, heterojen bir hastalık grubu içindedir. Sistemik amiloidoz ve pulmoner tutulumu hematoloji literatüründe ayrıntılı olarak incelen-

miştir ancak sadece pulmoner tutulum oldukça seyrektir görülmektedir. Literatürde olgu sunumları, küçük vaka serileri veya otopsi çalışmaları aracılığıyla tanımlanmıştır. Klinik olarak hastalık üç temel alt tipe ayrılmaktadır: trakeobronşiyal, nodüler parankimal ve diffüz alveoler-septal form. Trakeobronşiyal tutulum özellikle merkezi hava yollarında lokalizedir ve ilerleyici hava yolu daralmasına yol açarak kronik öksürük, hışıltı, tekrarlayan solunum yolu enfeksiyonları veya hemoptizi ile prezente olabilir. Nodüler parankimal form sıklıkla asemptomatik olup toraks görüntülemeleri sırasında tesadüfen saptanır. Tek veya çok sayıda nodül şeklinde izlenebilir, kalsifikasyon gösterebilir ve radyolojik olarak primer ya da metastatik maligniteyi taklit edebilir. Diffüz alveoler-septal tip genellikle sistemik AL amiloidozun akciğer tutulumu ile birlikte görülür. Bu tip radyolojik açıdan interstisyel akciğer hastalıklarına benzer; yüksek çözünürlüklü bilgisayarlı tomografide buzlu cam dansiteleri, interlobüler septal kalınlaşma ve difüzyon kapasitesinde azalma tipik olarak görülür. Tanısal yaklaşımda klinik, radyolojik ve histopatolojik yöntemlerin birlikte değerlendirilerek karar verilmelidir. HRCT, radyolojik değerlendirme ve tanıya yaklaşımda temel yöntem olarak mutlaka kullanılır. Kesin tanı, Kongo kırmızısı boyası ile polarize ışık altında tipik elma yeşili çift kırılma bulgusu veren amiloid birikimlerinin histolojik gösterilmesi ile konulur. Fibril alt tipinin belirlenmesi için immünohistokimya kullanılabilmekle birlikte, lazer mikrodiseksiyon ve kütle spektrometrisi tabanlı proteomik analiz günümüzde altın standart olarak kabul edilmektedir. Ayırıcı tanı yelpazesi oldukça geniştir ve malign neoplaziler, granülomatöz hastalıklar ve diğer interstisyel akciğer hastalıklarını içerir. Bu nedenle klinik şüphe durumunda doku tanısı gereklidir. Tedavi yaklaşımı alt tip ile yakından ilişkilidir. Lokalize trakeobronşiyal tutulumda bronkoskopik debulking, stent uygulaması veya dirençli olgularda eksternal radyoterapi düşünülebilir. Nodüler parankimal form genellikle tedavi gerektirmez; yalnızca progresif büyüme veya semptom gelişirse tedavi başlanır. Diffüz alveoler-septal tutulum ise neredeyse her zaman sistemik AL amiloidozun parçasıdır ve bortezomib, daratumumab veya lenalidomid temelli hematoloji odaklı protokoller gerektirir. Prognoz değişken olup lokalize formlar çoğunlukla indolent seyir gösterirken, sistemik AL amiloidozda pulmoner tutulum kötü prognoz ile ilişkilidir. Gelecekteki araştırmaların, standardize tanısal algoritmaların oluşturulmasına, noninvaziv biyobelirteçlerin geliştirilmesine ve uzun dönem klinik sonuçları iyileştirecek yeni tedavi hedeflerinin tanımlanmasına odaklanması gerekmektedir.

Anahtar Kelimeler: *Pulmoner amiloidoz; Trakeobronşiyal amiloidoz; Nodüler akciğer lezyonları; Sistemik amiloidoz; İmmünoglobulin hafif zincirleri*

CASE PRESENTATION

A 62-year-old female patient presented to the outpatient clinic with progressive exertional dyspnea over the past eight months, persistent dry cough, and worsening shortness of breath with exertion in recent weeks. She had no history of smoking. On physical examination, bilateral basal Velcro crackles were auscultated. Her oxygen saturation on room air was 90%.

Laboratory investigations revealed CRP: 4 mg/L, NT-proBNP: 1850 pg/mL, elevated serum free kappa light chains, and the presence of a monoclonal kappa band in both serum and urine immunofixation. A 24-hour urine collection showed proteinuria of 0.5 g/day. ANA, ENA, and ACE levels were within normal limits.

High-resolution computed tomography (HRCT) of the thorax showed diffuse interlobular septal thickening, bilateral basal-predominant ground-glass opacities (GGO), mild reticular infiltrates, and areas of polygonal arcades. No nodules, masses, or honeycombing were observed (Figure 1).

Echocardiography revealed increased left ventricular wall thickness with mild diastolic dysfunction. Cardiac MRI demonstrated diffuse gadolinium accumulation with subendocardial late enhancement. T1 mapping values were elevated.

A transbronchial biopsy performed for diagnostic purposes showed Congo red positivity with characteristic apple-green birefringence under polarized light microscopy. Immunohistochemical analysis confirmed AL (kappa) type amyloid deposition, establishing a diagnosis of diffuse alveolar-septal AL amyloidosis (or 'primary').

The patient was started on a chemotherapy regimen including bortezomib and daratumumab in collaboration with the hematology department. Supplemental oxygen therapy and infection prophylaxis were provided for pulmonary symptoms. Regular follow-up with NT-proBNP levels and echocardiography was recommended for cardiac involvement.

This case aims to illustrate the clinical, radiological, and histopathological characteristics of diffuse alveolar-septal amyloidosis. This form is frequently misinterpreted as interstitial lung disease and requires histopathological confirmation for a definitive diagnosis.

It represents pulmonary involvement of systemic AL amyloidosis, and treatment should primarily focus on hematologic control.

INTRODUCTION

Amyloidosis is a rare group of diseases characterized by the misfolding of proteins into β-pleated sheet fibrillar structures that accumulate in various tissues.

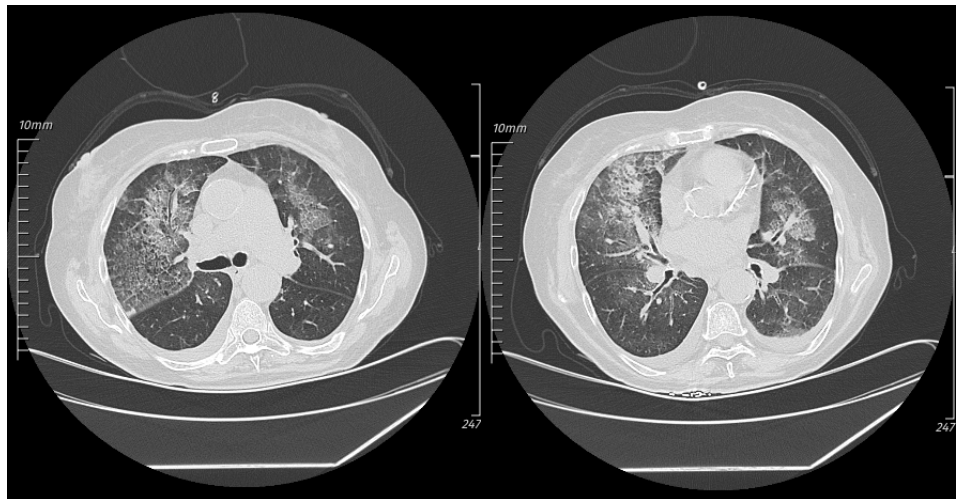


Figure 1. Thorax HRCT reveals diffuse interlobular septal thickening, bilateral basal-predominant ground-glass opacities (GGO), mild reticular infiltrates, and areas of polygonal arcades.

Publications after 2020 have increasingly referred to this process as a "systemic proteopathy resulting from impaired protein homeostasis." This aberrant protein accumulation not only alters tissue morphology but also causes significant functional impairment.[1]

Although awareness of amyloidosis has grown in recent years, its historical roots trace back to the mid-19th century. In 1854, Rudolf Virchow observed a starch-like substance under the microscope and termed it "amyloid." At the time, it was believed to be of carbohydrate origin and was thus named after the Greek word amylum, meaning starch. Subsequent histochemical and biochemical analyses later confirmed that the amyloid substance was actually of proteinaceous nature. The classical Congo red staining method, along with the identification of "apple-green birefringence" under polarized light microscopy, was first described in the mid-20th century. Today, immunohistochemical analysis and proteomic techniques serve as the gold standard for the precise identification of amyloid subtype.[2]

PATHOGENESIS

In the process of amyloid formation, proteins misfold into β-pleated sheet structures due to instability in their native three-dimensional conformation. These misfolded proteins aggregate into insoluble fibrils, which deposit extracellularly in tissues and lead to organ dysfunction.[3]

Different precursor proteins give rise to distinct fibril types upon misfolding, resulting in various forms of amyloidosis. For example, in AL (light-chain) amyloidosis, immunoglobulin light chains (either kappa or lambda) secreted by monoclonal plasma cells undergo conformational changes and aggregate into amyloid fibrils.[3] In localized pulmonary forms, it is believed that this deposition originates from plasma cells within the respiratory tract.[4] In ATTR (transthyretin) amyloidosis, either wild-type or mutant transthyretin molecules misfold and form amyloid fibrils. Recent studies emphasize the role of the local microenvironment and immune response, particularly in the pathogenesis of localized amyloidosis.[5]

CLASSIFICATION

Amyloidosis is classified based on the biochemical nature of the deposited protein. AL (primary) amyloidosis is caused by the deposition of immunoglobulin light chains and can present in either systemic or localized forms. AA amyloidosis is characterized by the accumulation of serum amyloid A protein, typically in the context of chronic inflammation. ATTR amyloidosis involves the deposition of transthyretin-derived fibrils.

Amyloid proteins are classified according to the following criteria in Table 1.[2-6]

Pulmonary amyloidosis is further subclassified based on clinical presentation into three major forms:

Table 1. Classification of amyloid proteins.[2,6]

Category	Subtypes / Examples	Key Features
a. Molecular Origin	• AL (Light chains) • AA (Serum Amyloid A) • ATTRwt (wild-type) • ATTRv (variant) • Others: $A\beta_2M$, ALECT2, AApoAI, AGel, etc.	• AL: Most common systemic type • AA: Inflammatory diseases • ATTRwt: Age-related • ATTRv: Hereditary mutations
b. Distribution Pattern	• Systemic: AL, AA, ATTR • Localized: Tracheobronchial, bladder, skin, lung parenchyma	• Systemic: Multiorgan involvement • Localized: Single organ only
c. Genetic Characteristics	• Hereditary: ATTRv, AApoAI, AGel • Acquired: AL, AA, ATTRwt	• Hereditary: Autosomal dominant mutations • Acquired: Plasma cell/inflammatory basis
d. Diagnostic Techniques	• Conventional: Congo red staining, IHC • Advanced: LMD-MS/MS	• Congo red: Green birefringence • IHC: May be inconclusive • MS: Gold standard

AA: *Amyloid A,* ***AApoAI:*** *Amyloid from Apolipoprotein A-I,* ***$A\beta_2M$:*** *Amyloid from Beta-2 Microglobulin,* ***AGel:*** *Amyloid from Gelsolin,* ***AL:*** *Amyloid Light Chain,* ***ALECT2:*** *Amyloid from Leukocyte Chemotactic Factor 2,* ***ATTR:*** *Amyloid from Transthyretin,* ***ATTRwt:*** *Wild-type Transthyretin,* ***ATTRv:*** *Variant Transthyretin,* ***CR:*** *Congo Red,* ***IHC:*** *Immunohistochemistry,* ***LMD-MS/MS:*** *Laser Microdissection with Tandem Mass Spectrometry,* ***MGUS:*** *Monoclonal Gammopathy of Undetermined Significance,* ***TTR:*** *Transthyretin.*

- Tracheobronchial type
- Nodular parenchymal type
- Diffuse alveolar-septal type (usually associated with systemic disease)

This classification has important implications for both diagnosis and therapeutic strategy.[2] An overview of the subtypes of pulmonary amyloidosis is given in Table 2.[7-9]

CLINICAL MANIFESTATION

Pulmonary amyloidosis manifests with a wide spectrum of clinical signs and symptoms depending on the site and extent of involvement. The disease course may range from asymptomatic to severe forms presenting with progressive dyspnea, recurrent infections, or even massive hemoptysis.

Although rare, pulmonary amyloidosis may be associated with autoimmune diseases (e.g., Sjögren's syndrome, systemic lupus erythematosus) and lymphoproliferative disorders (particularly MALT lymphoma), suggesting a potential link between local amyloid deposition and underlying clonal B-cell proliferation in certain cases.[10]

Localized Tracheobronchial Amyloidosis

This form usually presents with symptoms due to mechanical airway obstruction. The most common clinical findings include:[11,12]

- Chronic cough
- Exertional dyspnea
- Recurrent bronchopulmonary infections
- Hemoptysis
- Dysphonia (especially in upper tracheal involvement)

Tracheobronchial amyloidosis is more commonly seen in individuals over 50 years of age. Thorax HRCT may reveal irregular thickening and calcifications of the tracheal and bronchial walls, contributing significantly to the diagnostic work-up.[11,13]

Localized Pulmonary Parenchymal Amyloidosis

This form is often asymptomatic and is typically discovered incidentally during imaging for unrelated reasons. When symptoms are present, they tend to be mild:

- Cough (in 20-30% of cases)
- Mild-to-moderate dyspnea

Table 2. Classification of amyloid proteins.[2,6]

Subtype	Clinical and Radiological Features	Diagnosis and Management
Tracheobronchial Type	• Amyloid confined to submucosa of trachea and large bronchi • Symptoms: chronic cough, wheezing, hemoptysis, dyspnea • Physical exam: rhonchi, wheezing, stridor • HRCT: airway wall thickening, nodular calcifications, luminal narrowing	• Diagnosis: bronchoscopy + endobronchial biopsy • Treatment: bronchoscopic debulking, argon plasma coagulation, or laser therapy • No systemic treatment typically needed
Nodular Parenchymal Type	• Often asymptomatic; incidentally found • Single or multiple well-defined nodules (often peripheral, may be calcified) • HRCT: well-defined, frequently calcified nodules • Differential: metastases, granulomatous disease, infections	• Diagnosis: transthoracic needle biopsy or surgical wedge resection • Treatment: usually none; excision in select cases
Diffuse Alveolar-Septal Type	• Rarest form; often part of systemic AL amyloidosis • Symptoms: progressive dyspnea, hypoxemia, restrictive respiratory failure • HRCT: diffuse reticular opacities, interlobular septal thickening, ground-glass opacities • PFT: restrictive pattern with ↓ DLco	• Diagnosis: surgical lung biopsy • Treatment: systemic chemotherapy (e.g., bortezomib, daratumumab)

DLco: *Diffusing capacity of the lung for carbon monoxide,* ***HRCT:*** *High-resolution computed tomography,* ***PFT:*** *Pulmonary function test.*

- Chest pain (rare)
- Hemoptysis (uncommon)

Radiologically, findings may include solitary or multiple nodules, masses, or ground-glass opacities. These lesions may mimic malignancy. No systemic features are typically present. Histopathologically, localized parenchymal amyloidosis is most often of the AL type, with light chain deposition.[11]

This subtype is frequently associated with autoimmune diseases (e.g., Sjögren's syndrome, systemic lupus erythematosus) and lymphoproliferative disorders (e.g., MALT lymphoma), further supporting a role for immune mechanisms in its pathogenesis.[11]

Pulmonary Involvement in Systemic Amyloidosis

In systemic AL amyloidosis, pulmonary involvement is often clinically silent and identified primarily as an autopsy. If symptomatic, patients may present with:[12]

- Progressive dyspnea
- Hypoxemia due to diffuse alveolar infiltrates
- Signs of pulmonary congestion secondary to heart failure
- Rarely, hemoptysis

Involvement of the alveolar septa can lead to clinical and radiological findings resembling interstitial lung disease (ILD). Pulmonary symptoms may often be misinterpreted as due to heart failure or pulmonary infections.[13]

Systemic Manifestations and Associated Conditions

Systemic amyloidosis is frequently accompanied by multisystemic symptoms. The most common symptoms are as below:[13]

- Fatigue, weight loss
- Proteinuria or nephrotic syndrome
- Congestive heart failure due to restrictive cardiomyopathy
- Macroglossia, periorbital purpura, peripheral neuropathy

RADIOLOGICAL FINDINGS

Thoracic computed tomography (CT) is the most valuable imaging modality in the diagnostic work-up of

pulmonary amyloidosis. Radiologic features vary according to the localization of amyloid deposition.[14]

Localized Pulmonary Parenchymal Amyloidosis

In this subtype, nodular involvement is the most frequently observed radiologic finding. These features may resemble malignancies, granulomatous diseases, or infectious lesions, complicating differential diagnosis. Typical CT findings include:[15]

- Solitary or multiple solid nodules
- Mass-like lesions
- Calcified nodules
- Subpleural nodules or masses
- Pulmonary cysts, often associated with nodules
- Spiculated, lobulated, or well-defined contours
- Mediastinal or hilar lymphadenopathy, sometimes with calcifications
- Pleural plaques

Nodular lesions accompanied by cystic changes may be associated with underlying conditions such as Sjögren's syndrome, lymphoma, or lymphoid interstitial pneumonia (LIP). Therefore, imaging findings alone are insufficient for definitive diagnosis, and histopathologic confirmation is required.[15]

Localized Tracheobronchial Amyloidosis

Radiologic findings in this form primarily reflect airway wall involvement and typically include:[15]

- Thickening of the tracheal wall
- Bronchial wall thickening
- Tracheobronchial calcifications
- Tracheal lumen narrowing, with distal atelectasis
- Bronchiectasis, often secondary to infection
- Post-obstructive pneumonia, parenchymal destruction, and cyst formation
- Classic "nodular tracheal surface" appearance on CT

Pulmonary Involvement in Systemic Amyloidosis

Systemic amyloidosis typically demonstrates an alveolar septal pattern in the lungs. Imaging findings often resemble those seen in ILDs:[15]

- Diffuse interlobular septal thickening
- Widespread ground-glass opacities (GGO)
- Reticular infiltrates
- Bilateral, diffuse distribution
- Polygonal arcades and interlobular septal prominence
- Rarely, nodular involvement

PET-CT and Other Imaging Modalities

- **FDG-PET/CT:** Nodular lesions generally exhibit low or heterogeneous fluorodeoxyglucose (FDG) uptake. High and homogeneous uptake may raise suspicion for malignancy.[16]
- **Magnetic Resonance Imaging (MRI):** While highly valuable for assessing cardiac amyloidosis, MRI plays a limited role in pulmonary involvement and is generally not preferred.[17]
- **Routine Chest Radiography:** Often appears normal or may show non-specific nodular opacities. Although of limited diagnostic value, it remains widely used in initial evaluations.[18]

DIAGNOSTIC APPROACH

The diagnosis of pulmonary amyloidosis is based on the integration of clinical presentation, imaging findings, and histopathological confirmation. The primary goal is to distinguish between localized and systemic forms and to determine the underlying etiology.

Clinical Suspicion Based on Imaging

Although nonspecific, certain findings on thoracic CT should raise suspicion for amyloidosis, particularly in appropriate clinical contexts. These include:[19]

- Single or multiple calcified nodules or masses
- Tracheobronchial wall thickening with calcifications
- **In systemic forms:** diffuse septal thickening, ground-glass opacities, and reticular patterns

Amyloidosis should be included in the differential diagnosis, especially in patients with underlying Sjögren's syndrome, MALT lymphoma, or systemic AL amyloidosis.[20]

Tissue Diagnosis: Biopsy Techniques

The gold standard for diagnosing amyloidosis is the demonstration of amyloid deposits in tissue samples. The choice of biopsy method depends on lesion localization:[20,21]

- **Transbronchial biopsy:** Preferred in cases of tracheobronchial involvement
- **CT-guided transthoracic needle biopsy:** Suitable for deep parenchymal or subpleural nodules
- **Video-assisted thoracoscopic surgery (VATS) biopsy:** Used in patients with diffuse, small, or diagnostically challenging lesions
- **Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA):** A safe and effective option for diagnosing mediastinal lymphadenopathy

Histopathological Evaluation

- Congo red staining demonstrating apple-green birefringence under polarized light microscopy is the diagnostic hallmark of amyloid deposition.[6]
- Immunohistochemistry may aid in typing amyloid (e.g., AL, AA, ATTR).[6]
- Laser microdissection and mass spectrometry (LMD-MS) is the most sensitive method for accurate amyloid typing and is preferred when immunohistochemistry is inconclusive.[6]

Systemic Evaluation

To distinguish localized disease from systemic amyloidosis, the following assessments are recommended:[1]

- Serum free light chain assay (sFLC)
- Immunofixation electrophoresis (IFE) of serum and urine
- Bone marrow aspiration and biopsy to rule out plasma cell dyscrasia
- Echocardiography and cardiac MRI, especially to evaluate for restrictive cardiomyopathy

TREATMENT AND FOLLOW-UP

Due to its rarity, there are no randomized controlled trials specifically addressing the treatment of pulmonary amyloidosis. Current management strategies are primarily based on retrospective data, case series, and expert opinion.

Localized Tracheobronchial Amyloidosis

Treatment in this form is typically symptomatic. Interventions are warranted in the presence of airway obstruction or recurrent infections.

Treatment options include:[22]

- **Endobronchial debulking:** Techniques such as mechanical resection, laser photocoagulation (Nd:YAG), cryotherapy, or argon plasma coagulation (APC) can be employed.
- **Stent placement:** Temporary symptomatic relief can be achieved in cases with severe tracheal or main bronchial stenosis.
- **Radiotherapy:** In refractory or recurrent cases, low-dose localized radiotherapy (~20–30 Gy) may be beneficial, although the risk of tissue necrosis should be considered.
- **Medical therapy:** The role of corticosteroids, colchicine, or immunomodulatory agents is limited and generally not recommended.

Follow-up:[22]

- Symptomatic patients should be monitored every 6-12 months with thoracic CT and pulmonary function tests (PFTs).
- Clinical vigilance is essential for infection risk, and antibiotic therapy should be guided by cultures when necessary.

Localized Pulmonary Parenchymal Amyloidosis

Most cases are asymptomatic and incidentally detected; treatment is not indicated in asymptomatic individuals.

Indications for treatment include:[23]

- Progressive dyspnea, hemoptysis, or recurrent infections
- Suspicion of malignancy (e.g., rapidly enlarging, spiculated, or FDG-avid lesions)
- Structural complications related to nodules or masses

Treatment options:[23]

- **Surgical resection:** Can be both diagnostic and therapeutic in solitary peripheral nodules.
- **Post-biopsy observation:** In cases with confirmed diagnosis and absence of symptoms, clinical and radiological follow-up after thoracoscopic or transbronchial biopsy is usually sufficient.

Follow-up:

- Annual thoracic CT imaging is recommended in clinically stable patients.

- More frequent follow-up may be necessary in symptomatic patients or when lesion growth is observed.

Pulmonary Involvement in Systemic Amyloidosis

Since this form reflects pulmonary involvement of systemic disease, treatment is primarily directed at the underlying systemic pathology.

Targeted therapies:[24]

- **For AL-type systemic amyloidosis:**
  - Agents such as bortezomib, lenalidomide, daratumumab, and melphalan are commonly used.
  - High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) is recommended for eligible patients.
- **For ATTR-type amyloidosis:**
  - Systemic control can be achieved using transthyretin stabilizers (e.g., tafamidis, diflunisal) or RNA-based therapies (e.g., patisiran, inotersen), although pulmonary involvement is rare in this form.

Supportive care:[25]

- Oxygen therapy for chronic hypoxemia
- Infection prophylaxis (especially pneumococcal and influenza vaccination)
- Diuretics in cases of heart failure or pulmonary congestion

Multidisciplinary follow-up is essential in systemic cases with pulmonary involvement and should involve pulmonology, hematology, cardiology, and nephrology teams.

GENERAL FOLLOW-UP RECOMMENDATIONS

Follow-up strategies differ depending on whether the disease is localized or systemic.[25,26]

- **Localized cases:**
  - In clinically stable patients, low-dose thoracic CT every 6-12 months and annual PFTs are recommended.
  - Although the risk of progression to systemic disease is low, long-term surveillance is advised.
- **Systemic amyloidosis:**
  - **NT-proBNP and echocardiography:** Critical for early detection of cardiac involvement.
  - **Urine and serum immunofixation:** Used to monitor hematologic progression.
  - **Bone marrow biopsy:** May be repeated to assess remission following treatment.

CASE ANALYSIS

The presented case represents a rare form of diffuse alveolar septal amyloidosis.

The presence of inspiratory "Velcro-type" crackles on auscultation is a key clinical indicator of interstitial involvement.[27]

High-resolution computed tomography (HRCT) revealed bilateral, basally predominant ground-glass opacities (GGO), diffuse interlobular septal thickening, and polygonal arcades. This radiological appearance is consistent with the diffuse alveolar septal amyloidosis (DASA) pattern described in interstitial lung literature.[28] Notably, this imaging pattern, as described in the case reported by Moin et al., should prompt careful consideration of diffuse alveolar septal amyloidosis in the differential diagnosis.[27,29]

Laboratory findings, including elevated NT-proBNP levels, abnormal serum free light chain (sFLC) ratio, and the presence of monoclonal kappa bands in serum and urine, are strongly indicative of systemic AL-type amyloidosis.[30] This constellation of findings supports the systemic nature of the disease and guides further diagnostic and therapeutic planning.

Histopathological confirmation was obtained via transbronchial biopsy, which revealed Congo red positivity and green birefringence under polarized light microscopy, hallmarks of amyloid deposition.[5]

The patient was initiated on a chemotherapy regimen comprising bortezomib and daratumumab, consistent with current protocols for systemic AL amyloidosis. This therapeutic approach underscores the fact that diffuse alveolar septal involvement represents a manifestation of systemic disease requiring hematologic-directed therapy.[7]

This case highlights the following diagnostic and management considerations in diffuse alveolar septal amyloidosis:

- HRCT findings such as ground-glass opacities and septal thickening may mimic other interstitial lung diseases
- Systemic screening, including kappa-sFLC ratio, NT-proBNP levels, and electrophoretic studies, plays a critical diagnostic role
- Accurate biopsy technique and implementation

of appropriate treatment regimens are essential in AL-type systemic amyloidosis.[30]

CONCLUSION

Pulmonary amyloidosis is a rare disease classified clinically into tracheobronchial, nodular, and diffuse parenchymal forms. While dyspnea, cough, and hemoptysis are common in the tracheobronchial form, the nodular type is often asymptomatic and detected incidentally. Diagnosis requires a combined assessment with HRCT, bronchoscopy, and endobronchial biopsy. Congo red staining with apple-green birefringence under polarized light microscopy is the classical diagnostic hallmark of amyloidosis. Immunohistochemistry and mass spectrometry are used to determine the amyloid subtype. Distinguishing between AL and ATTR types is critical for treatment decisions. In symptomatic patients with tracheobronchial amyloidosis, bronchoscopic debulking is the first-line therapeutic approach. In systemic AL amyloidosis, chemotherapy (e.g., daratumumab, bortezomib) and hematologic assessment are required. In ATTR amyloidosis, transthyretin stabilizers such as tafamidis are utilized. The differential diagnosis should exclude infections, malignancies, vasculitis, and granulomatous diseases.

Accurate and timely identification of pulmonary amyloidosis, together with meticulous subclassification, remains pivotal for guiding evidence-based clinical management and improving patient outcomes; however, given the disease's rarity, clinical heterogeneity, and diagnostic complexity, further prospective studies are essential to elucidate its underlying pathophysiology, refine diagnostic algorithms, and assess the long-term efficacy of emerging therapeutic interventions.

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CHAPTER 12

PLEUROPARENCHYMAL FIBROELASTOSIS

PLÖROPARENKİMAL FİBROELASTOZ

Prof. Dr. Özlem Özdemir Kumbasar

PLEUROPARENCHYMAL FIBROELASTOSIS

PLÖROPARENKİMAL FİBROELASTOZ

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ABSTRACT

Pleuroparenchymal fibroelastosis (PPFE) is a serious type of interstitial lung disease (ILD) described with predominant upper lobe pleural and parenchymal fibroelastosis. PPFE is divided into two groups: idiopathic and secondary PPFE. Idiopathic PPFE (iPPFE) was classified in the rare idiopathic interstitial pneumonia (IIP) group in 2013 "American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias". Secondary PPFE is related to different causes such as medications, hematopoietic stem cell or bone marrow transplantation, lung transplantation, radiation therapy, autoimmune diseases, exposures, infections.

Actual incidence and prevalence of PPFE is not known . Patients with PPFE may occur at any age, it is more frequent between the ages of 30-60 years. The onset of the disease is usually insidious and progressive; the main symptoms are exertional dyspnea, dry cough, weight loss; platythorax is an important physical finding. Pneumothorax is a frequent complication. Clubbing is rare, fine cracles may be heard in some patients. Pulmonary function test reveals restrictive defects. Residual volume (RV) and ratio of RV to total lung capacity (RV/TLC) may increase. Diffusion capacity (DLco) is less decreased than forced vital vapacity. Hypercapnia is a frequent finding and hypoxemia is less prominent; hypoxemia and hypercapnia may coexit in advanced stages. High PCO_2 level is associated with poorer prognosis. Chest x-ray shows apical thickening, subpleural reticular densities in the upper lung areas, upward shift of hilar structures due to progressive volume loss. Typical computed tomography findings are pleural thickening, subpleural dense consolidation and reticulations, dense fibrotic bands adjacent to pleura predominantly localized in upper lobes. Pathological findings of PPFE are dense subpleural, intraalveolar fibrosis with the deposition of elastic fibers; fibrous visceral pleural thickening, mild lymphocytic inflammation, fibroblastic foci (rare). The lung parenchyma far from pleura is usually preserved. Diagnostic methods for PPFE are clinical, radiological, physiological and histopathological evaluation.

Risk of pleural complications and acute exacerbation of interstitial lung disease limits the use of surgical biopsy. There is no effective treatment for PPFE. Prognosis of patients with iPPFE was found poorer than those of patients with IPF, most important cause of death is chronic respiratory failure. Psychological support and pulmonary rehabilitation are important for supportive care methods, but pneumothorax and pneumomediastinum may interrupt exercise programs. Oxygen therapy should be given to hypoxemic patients, monitoring for hypercapnia is important. Noninvasive positive pressure ventilation is administered to hypercapnic patients with chronic respiratory disease, but risk of pneumothorax limits the use of positive pressure ventilation. High flow nasal oxygen therapy may be an option for hypercapnic PPFE patients.

Keywords: *Interstitial lung diseases; Idiopathic interstitial pneumonia, Pleuraparenchymal fibroelastosis; Bone marrow transplantation; Lung transplantation*

ÖZET

Plöroparankimal fibroelastozis (PPFE), üst lob baskın plevral ve parankimal fibroelastoz ile karakterize ağır bir interstisyel akciğer hastalığıdır. İdyopatik ve sekonder olarak iki gruba ayrılır. İdyopatik PPFE (iPPFE), 2013 "Amerikan Toraks Derneği/Avrupa Solunum Derneği İdyopatik İnterstisyel Pnömonilerin Uluslararası Multidisipliner Sınıflamasında" nadir idyopatik interstisyel pnömoniler (İİP)

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grubunda yer almıştır. Sekonder PPFE ise ilaçlar, hematopoetik kök hücre veya kemik iliği nakli, akciğer nakli, radyoterapi, otoimmün hastalıklar, maruziyetler, enfeksiyonlar gibi farklı nedenlere bağlı olarak ortaya çıkar.

PPFE'un gerçek insidansı ve prevalansı bilinmemektedir. PPFE olguları her yaştan olabilirse de hastalık 30-60 yaş arasında daha sıktır. Hastalığın başlaması genellikle sinsi ve ilerleyicidir, ana belirtiler eforla nefes darlığı, kuru öksürük, kilo kaybıdır; platitoraks önemli bir fizik bulgudur. Pnömotoraks sık görülen bir komplikasyondur. Çomak parmak nadirdir, bazı hastalarda ince raller duyulabilir. Solunum fonksiyon testlerinde restriktif defekt saptanır. Rezidü hacim (RH), RH/total akciğer kapasitesi oranı (RH/TAK) artabilir. Difüzyon kapasitesi (DLco), zorlu vital kapasiteye (ZVK) göre daha az düşer. Hiperkapni sık bir bulgudur, hipoksemi daha az belirgindir; ileri evrelerde hipoksemi, hiperkapni birlikte bulunabilir. Yüksek PCO_2 düzeyleri daha kötü prognozla ilişkilendirilir. Akciğer filminde apikal kalınlaşma, üst akciğer alanlarında subplevral retiküler dansiteler, ilerleyici hacim kaybına bağlı hiler yapıların yukarı yer değiştirmesi görülür. Tipik bilgisayarlı tomografi bulguları baskın olarak üst loblarda yer alan plevral kalınlaşma, subplevral yoğun konsolidasyon ve retikülasyonlar, plevraya komşu yoğun fibrotik bantlardır. PPFE'un patolojik bulguları elastik liflerin birikimi ile yoğun subplevral, intraalveoler fibrozis, visseral plevrada fibröz kalınlaşma, hafif lenfositik inflamasyon, fibroblastik odaklar (nadir) şeklinde özetlenebilir. Plevraya uzak akciğer parankimi genellikle korunmuştur. PPFE tanısı klinik, radyolojik, fizyolojik ve histopatolojik bulguların kombinasyonu ile konur.

Plevral komplikasyonlar ve akciğer fibrozisinin akut alevlenmesi riski cerrahi biyopsi kullanımını sınırlamaktadır. PPFE'in etkin bir tedavisi yoktur. İPPFE olgularının prognozu İPF olgularından daha kötüdür, iPPFE'li olguların en önemli ölüm nedeni kronik solunum yetmezliğidir. Destekleyici tedavi yöntemleri olarak psikososyal destek ve pulmoner rehabilitasyon önemlidir, ancak pnömotoraks ve pnömomediasten egzersiz programlarını kesintiye uğratabilir. Hipoksemik hastalara oksijen verilmelidir, hiperkapni için monitörizasyon önemlidir. Kronik solunum sistemi hastalığı olan hiperkapnik hastalarda noninvazif pozitif basınçlı ventilasyon uygulanır, ancak PPFE olgularında pnömotoraks riski pozitif basınçlı ventilasyon kullanımını sınırlar. Yüksek akımlı nazal oksijen tedavisi hiperkapnik PPFE olguları için bir seçenek olabilir.

Anahtar Kelimeler: *İnterstisyel akciğer hastalıkları; İdyopatik interstisyel pnömoni; Plöroparankimal fibroelastoz; Kemik iliği nakli; Akciğer nakli*

CASE PRESENTATION

A 31-year-old, newly married, female patient presented with fatigue, palpitation and exertional dyspne. Her complaints started two years ago, but she thought her complaints were related to her low weight. She had no history of previous respiratory illness, smoking or inhalational exposure. Her family history was unremarkable. She was thin (body mass index:18kg/m^2), blood pressure was 110/70 mmHg, pulse rate was 104/min, respiratory rate was 18/min; oxygen saturation was 93%. There was platythorax, very few cracles were heard on auscultation. On chest X-ray, diaphragma was elevated bilaterally, bilateral apical pleural thickening and reticular shadows in the upper lung zones and pneumothorax in the right lung were observed; on the lateral radiograph, narrowing of the anteroposterior diameter of the thoracic cage was noticed (Figure 1).

Thoracic computed tomography (CT) showed bilateral apical irregular pleural thickening, pneumothorax on the right side, subpleural consolidations and fibrotic changes (Figure 2).

Complete blood count, CRP, eryhrocyte sedimantation rate, blood glucose, liver and renal function tests were normal; autoantibodies were negative. Arterial blood gases revealed mild hypoxemia.

Diagnosis of pleuroparenchymal fibroelastosis was considered. While her partner was supportively present at the beginning of the process, the patient soon had to continue the battle without her partner, accompanied instead by the healthcare providers.

INTRODUCTION

Pleuroparenchymal fibroelastosis (PPFE) is a serious type of interstitial lung disease (ILD) described with predominant upper lobe pleural and parenchymal fibroelastosis. It was first described in 1992 in Japan by Amitani; it was named as 'Amitani's disease' or 'upper lobe pulmonary fibrosis'.[1]

In 2004 Frankel et al. reported five cases with similar features and suggested the term 'pleuroparenchymal fibroelastosis'. Surgical biopsy findings of these cases didn't fit with any of the known interstitial pneumonias. The reported pathological findings were fibrosis of the visceral pleura, prominent subpleural fibroelastosis, sparing of the areas far from the pleura, mild and patchy lymphoplasmocytic infiltrates, and rare fibroblastic foci between the fibrotic areas and surrounding unaffected parenchyma.[2]

"American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias" was updated in 2013. Idiopathic interstitial pneumonias (IIPs) were divided into three subgroups in this new statement as major IIPs, rare IIPs and unclassifiable IIP. Idiopathic PPFE was classified as a rare IIP.[3]

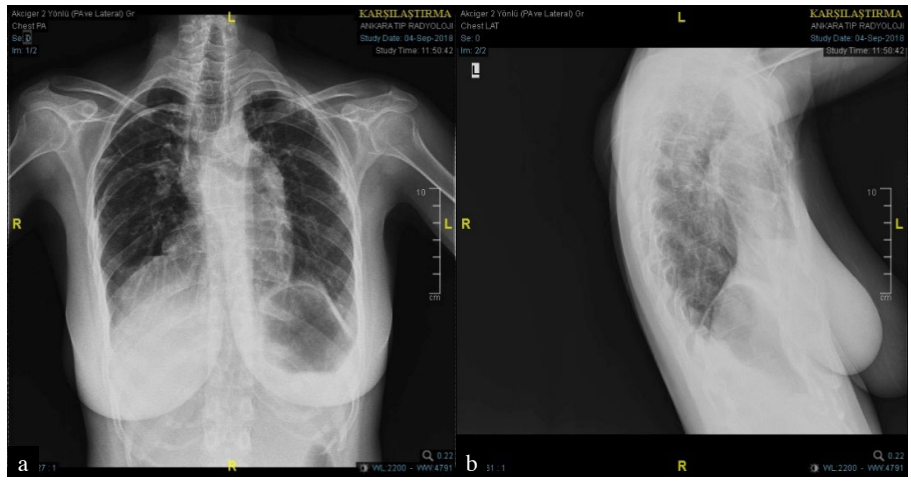


Figure 1. Posteroanterio and lateral radiographs of chest, respectively, demonstrating mainly a right-sided pneumothorax and narrowing of the width of thorax.

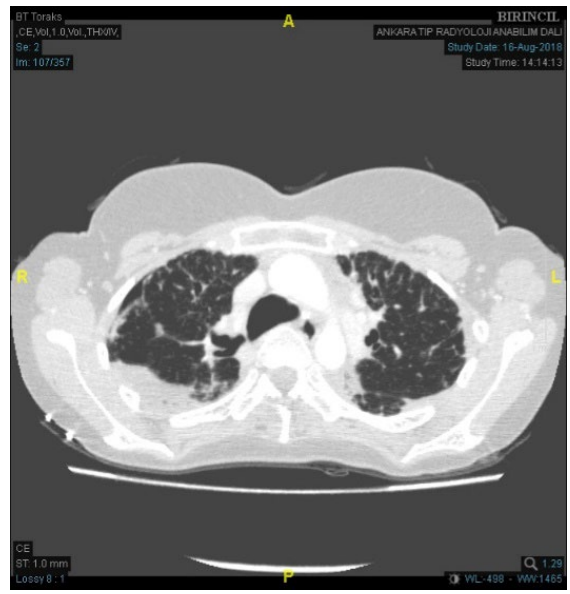


Figure 2. An image of thorax computerized tomography from the upper lobes reveals bilateral irregular pleural thickening, mainly in right apicoposterior localization, minimal right pneumothorax.

PPFE is still a rare disease, but it is increasingly recognised.

EPIDEMIOLOGY

Actual incidence and prevalence of PPFE is not known, because there isn't a consensus for diagnostic criteria. Studies estimate the prevalence of idiopathic PPFE among IIPs as 0.5-10.4%; this wide variation depends on the study population and dignostic criteria used.[4] Nakatani et al. reviewed retrospectively their database of diagnostic pathology archives; evaluated 205 patients diagnosed interstitial lung disease with surgical lung biopsy and 12 cases (5.9%) were identified as PPFE after reevaluation with multidisciplinary discussion. Seven cases (58%) were male, seven patients were nonsmoker, median age was 62 years. Eight patients were idiopathic PPFE, four pa-

tients were secondary PPFE. Of 205 patients 77 were IIP, thus the frequency of idiopathic PPFE was 10.4% among IIPs.[5] PPFE is more common amog severe ILD cases, in a series including 118 fibrotic ILD patients registered for lung transplantation, 25% of patients had radiological findings compatible with PPFE.[6]

The age range in different series was 18-85 years. There was a bimodal distrubition of presentation, with a peak in the third decade and another peak in the sixth decade.[7] There was slight male or female predominance in some series, and no sex difference in some others. Idiopathic PPFE was often reported in middle aged to elderly patients with a median age at diagnosis about 60 years.[4] However most the cases followed in our center are young patients, age range of our patients is 19-50 years, and there is no sex difference in them.

ETIOLOGY AND PATHOGENESIS

PPFE is divided into two groups: idiopathic and secondary PPFE. Idiopathic PPFE is included in rare IIP group. Secondary PPFE is associated with different conditions.[8] Pathogenesis is not clearly defined. Lung injury may trigger the pathological cascade causing fibrotic changes. Some genetic mutations are important for the development of fibrotic interstitial lung disease. Telomere gene mutations were identified in patients with PPFE.[8,9] Newton et al. evaluated 115 ILD cases with telomere gene mutations and found that 46% of these cases were IPF patients and 10% had PPFE. Mutations of patients with PPFE in this cohort were related to TERT, TERC or RTEL1.[10] Nunes et al. investigated 10 patients with PPFE for TERT and TERC mutations, TERT mutations were identified in five of them.[11] Genetic mutations may occur without family history, but there are familial PPFE cases.[7,9] Our first cases were two sisters, 19 and 21 years old, they had bilateral apical pleural and parenchymal fibrosis. These cases presented in early 1990s before PPFE was described and recognized in retrospective evaluation.

Secondary PPFE may be related to medications, hematopoietic stem cell or bone marrow transplantation, lung transplantation, radiation therapy, autoimmune diseases, exposures, infections.[12] In 2011, four cases with PPFE related to bone marrow transplantation were reported. All of them presented with recurrent pneumothoraces and histological findings of bronchiolitis obliterans.[13] Chronic graft versus host disease and alkylating agents have been considered as possible causes of PPFE after hematopoietic stem cell transplantation.[14] PPFE was found to have a major histopathological pattern of restrictive allograft dysfunction after lung transplantation.[15] PPFE cases were described after treatment with alkylating agents.[16] PPFE was reported as a late complication of childhood cancer therapy especially with high dose alkylating agents.[17] In one study, marked PPFE was detected in 23% of hypersensitivity pneumonitis cases, and was associated with reduced forced vital capacity (FVC) and predictive of mortality.[18] Sari et al. detected PPFE in 18.1% of patients with systemic sclerosis associated interstitial lung disease, and patients with PPFE had higher age and longer disease duration than patients without PPFE.[19] In a systematic review and meta analysis, it was reported that 20.5% of patients with rheumatic autoimmune disease had PPFE, and the most common PPFE-associated disease was systemic sclerosis, followed by rheumatoid arthritis.[20] Infections (pulmonary aspergiollosis or Mycobactrium avium complex), exposures (asbestos, aluminium or silica) or radiation are strogly suspected for development of PPFE.[12,21]

CLINICAL MANIFESTATIONS

Patients with PPFE may present at any age, but it is more frequent between the ages of 30-60 years. There is no relation to smoking. The onset of the disease is usually insidious and progressive, and main symptoms are exertional dyspnea, dry cough, weight loss. Nonspecific chest discomfort and pleuritic pain are reported. Most patients have low body mass index (BMI); platythorax or flat chest (reduced anteroposterior to transverse diameter ratio of the thoracic cage) is an important physical finding. This deformity may develop because of the upper lobe fibrosis and progress with disease severity, or it may be a congenital deformity. A deep suprasternal notch may be detected in some patients. Clubbing is rare, fine cracles may be heard in some patients.[4,8,21-23] Five PPFE cases with vocal cord paralysis were reported, pneumothorax was noted in three of them, aspiration pneumonia occurred in three patients.[24]

Pneumothorax is a frequent complication; it may be recurrent and usually small in size and asymptomatic; sometimes chest drainage may be required.[4,8]

PULMONARY FUNCTION TESTS

Pulmonary function tests (PFT) reveal decreased forced vital capacity (FVC), total lung capacity (TLC),

and increased ratio of forced expiratory volume in one second (FEV1) to FVC (FEV1/FVC). Residual volume (RV) may relatively increase because of the hyperinflation of lower lobes, air trapping, chest wall restriction due to platythorax, and ratio of RV to total lung capacity (RV/TLC) ratio may increase. Diffusion capacity for carbon monoxide (DLco) is less decreased than FVC. Relative preservation of DLco according to FVC might be explained with less involvement of lower lobes where blood perfusion is more, in addition alveolar carbon monoxide uptake may be increased because of extrapulmonary restriction.[4,8,21,22,25]

Interstitial lung diseases usually lead to gas exchange abnormalities resulting hypoxemia and hypocapnia. Patients with ILD rarely have hypercapnia even in advanced stages. But hypercapnia is a frequent finding in patients with PPFE, and hypoxemia is less prominent. Hypoxemia and hypercapnia may coexit in advanced stages. The PCO_2 level is inversely correlated with FVC, flat chest index (the ratio of anteroposterior diameter to transverse diameter of the thoracic cage) and BMI, and positively correlated with RV/TLC ratio. High PCO_2 level is associated with poorer prognosis.[25,26]

LABORATORY FINDINGS

There isn't any specific diagnostic blood test for PPFE. Elevated levels of surfactant protein D (SP-D) and Krebs von der Lungen 6 (KL-6) may be found in patients with PPFE. These biomarkers are correlated with diseae severity and prognosis in fibrotic ILDs.[4,22]

In patients with an underlying connective tissue disease, serological abnormalities related to their connective tissue diseases may be detected.[2]

RADIOLOGICAL FINDINGS

The diagnosis of PPFE can often be suspected on chest x-ray. Chest x-ray shows apical thickening, subpleural reticular densities in the upper lung areas, upward shift of hilar structures due to progressive volume loss. In advanced stages, consolidation and reticular opacities extend adjacent lobes. Tracheal deviation may develop (Figure1, 3a).[4,8,21,22]

Computed tomography (CT) findings are important, both standart axial and coronal reconstruction images should be evaluated. Typical CT findings are pleural thickening, subpleural dense consolidation and reticulations, dense fibrotic bands adjacent to pleura predominantly localized in upper lobes. Traction bronchiectasis and significant volume loss of upper lobes may be found. Subpleural cysts may develop in advanced stages. In some cases, a pattern of usual interstitial pneumonia (UIP), or inconsistent with UIP, less frequently nonspecific interstitial pneumonia (NSIP) may coexit in the lower lobes (Figure 2, 3b).[4,21,22,24]

Deepening of the suprasternal notch is a physical finding in patients with PPFE. In a study, the depth of

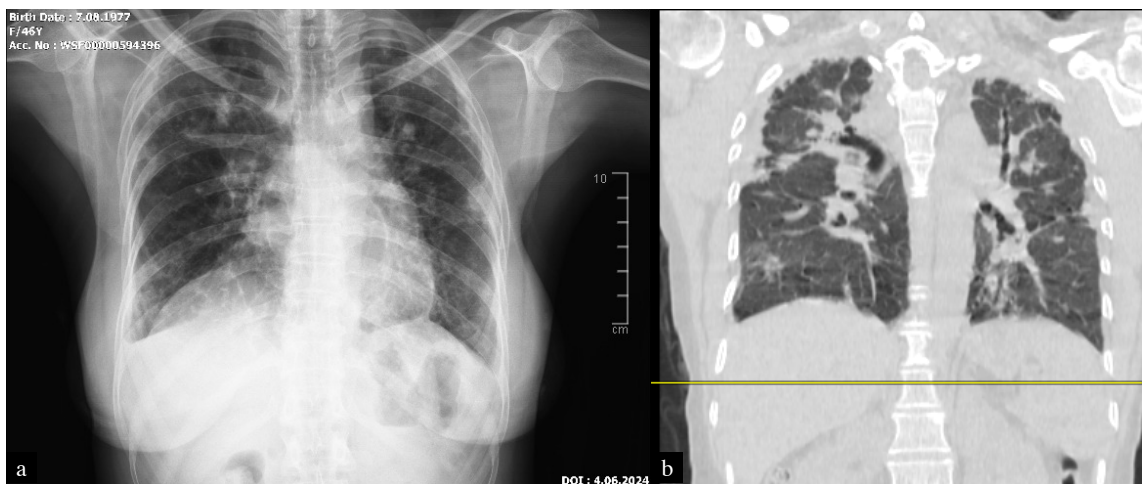


Figure 3. a) chest x-ray, **b)** coronal reconstruction image of thoracic CT scan of a patient with PPFE. The patient is a 47-year-old female patient. Radiologically apical thickening, reticulations especially in the upper and middle lung areas are observed. PFT results were as FVC:47%, FEV1:46%, FEV1/FVC:81%, DLco:60%

the suprasternal notch was measured on CT of the patients with PPFE, IPF, chronic hypersensitivity pneumonitis and non ILD patients. The depth of the suprasternal notch effectively differentiated patients with PPFE from other groups, and it was an independent prognostic factor in patients with PPFE.[27]

PATHOLOGICAL FINDINGS

Pathological findings of PPFE are dense subpleural, intraalveolar fibrosis with the deposition of elastic fibers; fibrous visceral pleural thickening, mild lymphocytic inflammation, fibroblastic foci (rare). Elastic fibers randomly distributed in the extracellular matrix can be confirmed by elastin specific stains. The lung parenchyma far from pleura is usually preserved. The border between fibroelastosis and underlying normal parenchyma is relatively abrupt; rare fibroblastic foci are noted at the edge of the fibrosis. Bronchocentric intraalveolar fibrosis is occasionally observed.[7,22,28]

In a study with 12 patients, seven patients had histopathologically coexistent ILD in lower lobes, three of them had usual interstitial pneumonia pattern.[28]

DIAGNOSIS

The diagnosis of PPFE is based on a combination of clinical, radiological, physiological and histopathological findings. Histopathological findings are important; but risk of relapsing pneumothorax, pleural complications and acute exacerbation of pulmonary fibrosis limits the use of surgical biopsy.[8]

Reddy et al. proposed histopathological and radiological criteria for diagnosis of PPFE (Table 1).[28]

Enomoto proposed diagnostic criteria without histopathological findings in 2017.[29]

1. "Radiological PPFE pattern on thoracic CT scan (bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes and less marked or no involvement of the lower lobes-definite radiological crtiteria proposed by Reddy et al)."
2. "Radiologic confirmation of disease progression (defined as an increase in the upper lobe consolidation with or without pleural thickening and/or a decrease in upper lobe volume on serial radiologic assessment)"
3. "Exclusion of other lung diseases with identifiable causes (such as connective tissue disease-related ILD, chronic hypersensitivity pneumonitis, pulmonary sarcoidosis, pneumoconiosis, and active pulmonary infection)."

In 2019 the Study Group on Diffuse Pulmonary Disorders in Japan proposed more comprehensive diagnostic criteria for idiopathic PPFE (iPPFE). They divided PPFE into four groups: 1-Definite iPPFE (pathological confirmation is needed). 2-Radiologically and physiologically probabale iPPFE. 3-Radiologically probable iPFFE. 4-Possible iPPFE. Physiological criteria were RV/TLC percent predicted ≥115% or BMI≤20 and RV/TLC percent predicted ≥80%.[30]

Secondary causes of PPFE should be excluded in patients with PPFE. Lung transplantation, bone mar-

Table 1. Proposed diagnostic criteria for PPFE.[28]

	Pathology	**CT**
Definite with PPFE	"Upper zone pleural fibrosis with subjacent intraalveolar fibrosis accompanied by alveolar septal elastosis"	"Pleural thickening with associated subpleural fibrosis concentrated in the upper lobes, with less marked or no lower lobe involvement"
Consistent with PPFE	"Intra-alveolar fibrosis present but not associated with significant pleural fibrosis, not predominantly beneath the pleura, or not in an upper lobe biopsy"	"Upper lobe pleural thickening with associated subpleural fibrosis present but distribution of these changes not concentrated in the upper lobes or no features of coexistent disease elsewhere"
Inconsistent with PPFE	"Absence of features of definite or consistent diagnosis"	"Absence of features of definite or consistent diagnosis"

row or hematopoietic stem cell transplantation, radiotherapy, chemotherapy history, and presence of connective tissue disease should be investigated.[4]

Some patients may have genetic disorder. Genetic testing may provide additional information beyond radiological and pathological findings; and may avoid unnecessary tests and invasive procedures. If telomere biology disorders detected, genetic counseling should be given; and this information might affect treatments plans.[31]

Differential diagnosis includes pulmonary apical cap, fibrotic hypersensitivity pneumonitis, connective tissue disease associated ILD, sarcoidosis, asbestosis, infections (nontuberculous mycobacteria, pulmonary aspergillosis). Apical caps occur in older smokers, and typically asymptomatic and nonprogressive. Apical cabs tend to be localised small mass lesions in the apices of upper lobes.[7,22]

DISEASE COURSE AND PROGNOSIS

Some patients may have involvement at the lung apex long before the diagnosis and might be asymptomatic during this period. The prediagnostic phase of PPFE may be misdiagnosed as pulmonary apical cap on short term observation.[32]

Survival of patients with iPPFE was found worse than those of patients with IPF. Five years survival rate for PPFE was 38.5%. Occurence of lung cancer was lower in patients with PPFE, acute exacerbation incidence was similar.[33] Most common cause of death in patients with iPPFE is chronic respiratory failure. Acute exacerbation and infection are other causes of mortality.[22] Chronic pulmonary infection with Aspergillus spp., nontuberculous mycobacteria, Pseudomonas aeruginosa is associated poor prognosis.[21]

Pneumothorax is a frequent complication during the course of PPFE. Pneumothorax is often recurrent and asymptomatic.[34] History of pneumothorax was more common (more than three times) in patients with PPFE among patients with ILD who were registered for lung transplantation.[6]

Progressive weight loss, low BMI, rapid FVC decline, pneumothorax, coexiting lower lobe fibrosis, hypercapnia are associated with poor prognosis.[4]

Lung volume in different lobes can be quantitatively measured with 3D-CT. In a study standardized lung volume was calculated by dividing the lung volume measured with 3D-CT by the predicted FVC. Patients with lower standardized upper lobe volume had shorter survival time than those with higher standardized uppler lobe volume. Increased annual decline of standardized upper lung volume was significantly associated with mortality.[35]

MANAGEMENT

There is no curative and effective treatment for PPFE. Low dose steroids may be used empirically, but its effect isn't known. High dose steroids or immunosuppressive agents is usually avoided because of infection risk. Efficacy of antifibrotic agents remains uncertain.[4,23]

Effect of pirfenidone was retrospectively evaluated in patients with "typical idiopathic pulmonary fibrosis" (IPF-32 patients), or "usual interstitial pneumonia+pleuroparenchymal fibroelastosis like lesions" (UIP+PPFELL-12 patients) or "usual interstitial pneumonia + nonspecific interstitial pneumonia" (UIP+NSIP-14 patients). Pirfenidone decreased FVC decline in all three groups, but outcomes were worse in patients with UIP+PPFELL. Overall survival was shorter for "UIP+PPFELL" than for "UIP+NSIP" and "typical IPF".[36]

Nasser et al. evaluated the effect of nintedanib in patients with PPFE. Nine (seven idiopathic, two secondary) of 21 patients with PPFE had received nintedanib. A slower FVC decline was observed in these nine patients.[37] On the other hand, in another retrospective study, annual %FVC decline in patients with iPPFE was greater during nintedanib treatment than that before treatment.[38] Additionally weight loss due to gastrointestinal side effects of antifibrotics may be a problem for PPFE patients with low BMI.[22]

Psychological support and pulmonary rehabilitation are important for supportive care methods, but pneumothorax and pneumomediastinum may interrupt exercise programs.[4,22]

Oxygen therapy should be given to hypoxemic patients, monitoring for hypercapnia is important. Noninvasive positive pressure ventilation is administered to hypercapnic patients with chronic respiratory disease, but risk of pneumothorax limits the use of positive pressure ventilation. High flow nasal oxygen therapy may be an option for hypercapnic PPFE patients.[4,26]

Low body weight and weight loss are poor prog-

nostic factors, so nutrition is important for these patients. Nutritional therapy may help to prevent weight loss and preserve lung function.[39]

Lung transplantation is only curative treatment for patients with end stage interstitial lung diseases. In patients with PPFE, severe malnutrition, chest deformities and recurrent pneumothorax may limit lung transplantation. In a nation wide, multicenter study from France, 31 patients who underwent lung or heart-lung transplantation were evaluated. Lung transplantation for PPFE caused high postoperative morbidity and mortality rates. Patients requiring emergency lung transplantation with advanced disease, malnutrition, or critical clinical status had poor prognosis.[40]

CASE ANALYSIS

Radiological findings of this young, nonsmoker female were compatible with PPFE. There was no etiological agent or underlying disease. Therefore, it was accepted as idiopathic PPFE. We didn't plan biopsy, because of penumothorax risk. Pulmonary function tests (PFT) performed after resolution of pneumothorax, PFT showed restrictive ventilatory impairment. We planned low dose corticosteroid treatment and low dose metoprolol for sinus tachycardia. Pulmonary rehabilitation was started after the resolution of pneumothorax.

Low dose steroid treatment didn't work; we stopped it. We continued low dose metoprolol. Three months after diagnosis, oxygen desaturation during exercise developed; portable oxygen support was started. She lost weight, five months after diagnosis, she was given enteral nutrition support. Eighteen months after diagnosis she was hypoxemic and hypercapnic at rest, she was admitted to the hospital and high flow nasal oxygen was applied, and long-term oxygen treatment at home was planned. Three months later hypercapnia progressed; she was admitted to the hospital and noninvasive mechanical ventilation was started despite the pneumothorax risk. Pneumothorax didn't develop; noninvasive mechanical ventilation continued at home. Thirty months after diagnosis she died because of hypercapnic respiratory failure.

CONCLUSION

PPFE is a rare interstitial lung disease with poor prognosis. PPFE may be idiopathic or secondary; some cases may be familial. Chemotherapy, bone marrow transplantation, lung transplantation or connetive tissue diseases may cause PPFE. Platythorax is an important finding, and pneumothorax is a frequent complication. Unlike other interstitial lung diseases hypercapnia may occur; most important cause of death is chronic repiratory failure. Diagnosis is based on clinical, radiological, physiological and histopathological findings. Surgical lung biopsy may be dangerous for some patients. Diagnostic criteria without histopathology were proposed. There is no effective treatment for PPFE. Future research should be focused on defining exact diagnostic criteria and finding effective treatment.

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CHAPTER 13

THORACIC INVOLVEMENT IN IGG4-RELATED DISEASES

IGG4 İLE İLİŞKİLİ HASTALIKLARDA TORAKS TUTULUMU

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THORACIC INVOLVEMENT IN IGG4-RELATED DISEASES

IGG4 İLE İLİŞKİLİ HASTALIKLARDA TORAKS TUTULUMU

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is a rare, systemic, immune-mediated, fibroinflammatory disorder that can affect multiple organs. In recent years, thoracic involvement has been increasingly recognized. The disease typically occurs in middle-aged and older men; in patients with thoracic involvement, the diagnosis is most often established around 60 years of age. Concomitant extrathoracic organ disease raises diagnostic suspicion. Thoracic involvement may encompass the lungs, mediastinal and hilar lymph nodes, pleura, and airways, as well as vascular structures and the posterior mediastinum. The most frequent respiratory manifestations are nonspecific, including dyspnea, cough, and chest pain, although some patients remain asymptomatic.

Diagnosis requires integration of clinical findings with imaging, serology, and histopathology. Imaging features in thoracic IgG4-RD are non-pathognomonic and heterogeneous. Common radiologic findings include mediastinal lymphadenopathy, pulmonary nodules, bronchovascular bundle thickening, and pleural abnormalities. Serologically, elevated serum IgG4 concentrations (typically ≥135 mg/dL) and increased circulating plasmablast counts (>900/mL) are characteristic; however, normal serum IgG4 does not exclude the diagnosis. The distinctive histopathologic and immunohistochemical hallmarks include a dense lymphoplasmacytic infiltrate, storiform-pattern fibrosis, obliterative phlebitis or arteritis, and an increased IgG4+/IgG+ plasma-cell ratio (>40%), together with high tissue counts of IgG4+ plasma cells. Although thresholds vary by organ, for pulmonary and pleural disease the recommended cutoffs are >50 IgG4+ cells per high-power field (HPF) in surgical biopsies and >20 cells/HPF in nonsurgical biopsies.

Treatment is indicated for symptomatic thoracic disease; asymptomatic individuals (such as those with isolated mediastinal lymphadenopathy or incidentally detected small lung nodules) may be managed with close surveillance. Corticosteroids remain first-line therapy, whereas rituximab or inebilizumab are effective options for refractory or steroid-dependent cases. Although initial therapeutic responses are often robust, relapses are common, underscoring the need for structured, long-term follow-up that includes clinical and laboratory assessment and interval imaging when appropriate. In the diagnostic workup of IgG4-RD, exclusion of alternative diagnoses is fundamental. Accordingly, multidisciplinary evaluation improves diagnostic accuracy, excludes mimickers, and guides early treatment planning. Future research should focus on refining diagnostic criteria, identifying prognostic biomarkers, and developing targeted, durable therapies for IgG4-RD with thoracic involvement.

Keywords: *Immunoglobulin G4-related disease; Rare interstitial lung diseases; Thoracic diseases*

ÖZET

İmmünoglobulin G4 ilişkili hastalık (IgG4 İH), birden fazla organı etkileyebilen sistemik, immün aracılı, fibroinflamatuvar nadir bir hastalıktır. Son yıllarda torasik tutulum giderek daha fazla tanınmaktadır. Hastalık genellikle orta ve ileri yaş erkeklerde görülür; torasik tutulumu olan IgG4 İH'nin tanısı sıklıkla 60 yaş civarında konur. Toraks dışı organ tutulumunun eşlik etmesi tanısal şüpheyi artırır. Torasik tutulum akciğerleri, mediastinal lenf düğümlerini, plevrayı ve hava yollarını, ayrıca vasküler yapılar ile posterior mediasten dokularını içerebilir. Bu tutulum sonucunda en sık dispne, öksürük ve göğüs ağrısı gibi spesifik olmayan solunumsal semptomlar gelişir; ancak bazı hastalar asemptomatik olabilir.

Tanı, klinik bulguların görüntüleme, seroloji ve histopatoloji ile entegrasyonuna dayanır. Torasik tutu-

lumu olan IgG4 İH'de görüntüleme bulguları patognomonik değildir ve değişkenlik gösterir. En sık saptanan radyolojik bulgular mediastinal ve hiler lenfadenopati, pulmoner nodüller, bronkovasküler kalınlaşma ve plevral anormalliklerdir. Serolojik olarak, yüksek serum IgG4 düzeyleri (genellikle ≥135 mg/dL) ve artmış dolaşımdaki plazmablast sayıları (>900/mL) karakteristiktir; bununla birlikte, serum IgG4 düzeylerinin normal olması hastalığı dışlamaz. IgG4 İH'nin ayırt edici histopatolojik ve immünohistokimyasal özellikleri arasında yoğun lenfoplazmasitik infiltrasyon, storiform paternli fibrozis, obliteratif flebit veya arterit ve IgG4+/IgG+ plazma hücre oranında artış (> %40) ile yüksek IgG4+ plazma hücresi sayıları yer alır. Eşikler organa göre değişmekle birlikte, pulmoner ve plevral tutulumda önerilen eşikler cerrahi biyopsiler için >50 hücre/yüksek büyütme alanı (BBA) ve cerrahi dışı biyopsiler için >20 hücre/BBA'dır.

Semptomatik torasik tutulumda tedavi endikedir; izole mediastinal lenfadenopati veya tesadüfen saptanmış küçük akciğer nodülleri gibi asemptomatik olgular yakın izlemle yönetilebilir. Kortikosteroidler birinci basamak tedavidir; refrakter veya steroide bağımlı olgularda rituksimab ya da inebilizumab etkili seçeneklerdir. Başlangıç tedavi yanıtları yüksek olmakla birlikte relaps sıktır, bu durum düzenli takip gerekliliğini ortaya koymaktadır. IgG4 İH tanısında öncelikle ayırıcı tanıdaki hastalıkların dışlanması esastır. Bu nedenle multidisipliner değerlendirme tanısal doğruluğu artırır ve erken tedavi planlamasını yönlendirir. Gelecekteki araştırmalar, tanısal kriterlerin geliştirilmesi, prognostik belirteçlerin tanımlanması ve torasik tutulumu olan IgG4 İH için hedefe yönelik, kalıcı tedavilerin geliştirilmesine odaklanmalıdır.

Anahtar Kelimeler: *Immunoglobulin G4-related disease; Rare interstitial lung diseases; Thoracic diseases*

CASE PRESENTATION

A 69-year-old woman presented with dyspnea and productive cough. Radiological imaging revealed diffuse lymphadenopathy, a left hilar mass, pleural and pericardial effusions, and gastric wall thickening (Figure 1-3). ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) showed multiple FDG-avid lymph nodes and a hypermetabolic gastric lesion. Inguinal lymph node and nasopharyngeal biopsies showed plasma cell-rich chronic inflammation with increased IgG4-positive plasma cells. Laboratory findings included hypergammaglobulinemia, borderline IgG4 elevation, high erythrocyte sedimentation rate (ESR), and polyclonal gammopathy. Despite initial suspicion of lymphoma, histopathological and clinical findings supported systemic immunoglobulin G4-related disease (IgG4-RD). Immunosuppressive treatment was planned.

INTRODUCTION

Immunoglobulin G4-related disease is a systemic, immune-mediated fibroinflammatory disorder affecting multiple organs.[1,2] Most frequently effected organs are pancreas, biliary tree, orbits, lacrimal and major salivary glands, aorta and retroperitoneum, lungs, kidneys, meninges, and thyroid gland.[3,4] IgG4-RD man-



Figure 1. PA Chest radiography showed left sided pleural pathology.



Figure 2. Thoracic CT showed parenchymal infiltration and pleural effusion.

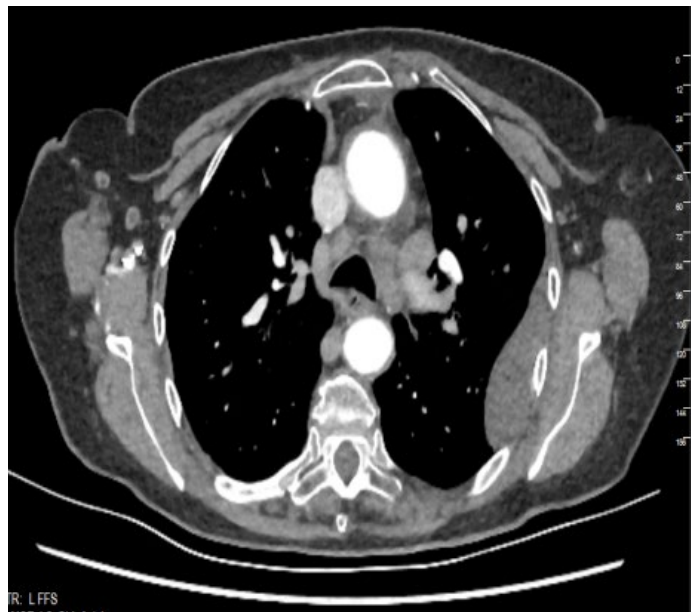


Figure 3. Thoracic CT showed mediastinal lymph nodes and pleural effusion.

ifests as a subacute mass in the affected organ or as diffuse enlargement of the organ, which may present in a synchronous or metachronous manner.[2,4-6] The number of studies specifically investigating thoracic involvement remains limited. IgG4-RD can affect any thoracic organ, including the lungs, pleura, lymph nodes, mediastinum, vascular structures, heart, posterior mediastinum, and even bones.[7,8]

PATHOGENESIS

The pathogenesis of IgG4-RD remains incompletely understood. IgG4, which comprises approximately

4-6% of total IgG, is notable for its relatively low inflammatory activity due to its poor capacity to bind activating Fc receptors and fix complement.[9] Initially, it was presumed that patients with IgG4-RD invariably exhibited elevated serum IgG4 levels; however, subsequent investigations revealed that approximately 30 percent of these patients maintain normal serum IgG4 concentrations.[10] Furthermore, patients with other conditions characterized by raised serum IgG4 concentrations, such as IgG4 myeloma, typically lack the hallmark features of IgG4-RD.[11]

Recent studies have identified oligoclonal expansions of activated B cells and cytotoxic CD4+ T cells as central contributors in IgG4-RD.[12-14] IgG4+ plasma blasts display pronounced oligoclonality and extensive somatic hypermutations, reflecting activation driven by T-cell signals.[14] T follicular helper (Tfh) cells, primarily the Tfh2 subset, produce IL-4, facilitating class-switching to IgG4.[11,15] Additionally, IL-10-producing follicular T regulatory cells further support IgG4 production and align with disease severity and organ involvement.[16]

Fibrosis in IgG4-RD is caused by multiple interactions between activated B cells, CD4+ cytotoxic T lymphocytes, M2 macrophages and fibroblasts.[17] By presenting antigens, activated B cells induce CD4+ T cells to adopt a cytotoxic phenotype (release of perforin and granzyme), leading to apoptosis.[18] M2 macrophages (activated by transforming growth factor-beta [TGF-β]) clear apoptotic cells though efferocytosis.[19] Multiple immune cells converge on fibroblasts by releasing platelet-derived growth factor (PDGF) from B cells, IL-1β, TGF-β, and interferon gamma (IFN-γ) from CD4+ cytotoxic T lymphocytes, and IL-10, CC-chemokine 18, and IL-33 from M2 macrophages, which collectively stimulate fibroblast activation and further fibrosis.[12] The space created by apoptotic cell death leads to tissue remodeling and fibrosis, tumor-like masses and organ enlargement. These changes are histopathologically seen as lymphoplasmacytic infiltrate and storiform fibrosis. Regulatory T cells secrete IL-10, IFN-γ and TGF-β, which can increase B-cell IgG4 production and supports fibrosis development.[20] Genetic factors increase susceptibility, but the mechanism has not been explained.[21]

EPIDEMIOLOGY

Epidemiological data on IgG4-RD remain limited. Retrospective evaluations are difficult and incomplete as the diagnosis usually requires pathological confirmation and clinicopathological correlation.[19] According to Japanese data, the estimated incidence ranges from 0.28 to 1.08 per 100,000.[22] Another US-based study reported the total incidence of IgG4-RD to be between 0.78 and 1.39 cases per 100,000 annually, with a prevalence of 5.3 per 100,000 individuals.[23] However, the prevalence of IgG4-RD is thought to be increasing with better recognition of the disease.[24]

Immunoglobulin G4-RD is more frequently diagnosed among middle-aged and older males. The majority of patients were males and 90% were diagnosed after the age of 40 years.[3,4,25-28] Typical onset after age 50, coupled with a higher prevalence in men, is unusual for an autoimmune disease. The male-to-female ratio and age at onset may vary depending on the primary organ affected at presentation.[24] In the Japanese study, the mean age at diagnosis was 58 years, and the male-to-female ratio was 1:0.77.22 Analysis of data from two international cross-sectional studies has showed that being Asian or female may predispose individuals to head and neck-limited disease.[29]

Similar to IgG4-RD, thoracic involvement occurs predominantly in middle-aged to elderly men, typically diagnosed at approximately 60 years of age.[24] Previously published data suggest that thoracic involvement may be seen in anywhere between 10 and 50% of patients.[30] However, the lower frequency of involvement in some reports may be because they do not include mediastinal and airway manifestations. Lung involvement has been reported in approximately 18-23% of patients.[3,31] The majority of patients with intrathoracic involvement also exhibit extrathoracic manifestations. A Japanese study of 4,304 patients estimated that isolated lung involvement occurred in 8% of cases.[22]

CLINICAL MANIFESTATIONS

It is difficult to diagnose patients with IgG4-RD who lack specific symptoms. Several studies have identified IgG4-related respiratory disease, which may be asymptomatic or present with dyspnea, cough, hemoptysis, chest pain or pleurisy.[10,11,24] In a recent study, 48 patients with thoracic involvement were evaluated, of whom 14 exhibited respiratory symptoms such as wheezing (64%), cough (21%), thoracic pain (14%) and dyspnea (14%).[32] Fever is an atypical symptom of IgG4-RD and is an exclusion criterion in the 2019

American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) classification.[7]

RADIOLOGICAL FINDINGS

No imaging features are pathognomonic for IgG4-RD, and radiological appearances alone are insufficient to differentiate IgG4-RD from alternative diagnoses.[10] Chest computed tomography (CT) scan is the most commonly employed imaging modality for assessing thoracic involvement in IgG4-RD. Inoue et al. classified four distinct lung involvement patterns based on predominant thoracic CT findings: (1) a solid nodular pattern (multiple solid nodules), (2) a round-shaped ground- glass opacity (GGO) pattern (multiple GGO lesions), (3) an alveolar-interstitial pattern (septal thickening, honeycombing, reticulations, or architectural distortion), and (4) a bronchovascular pattern (bronchiolitis, consolidation, peribronchovascular thickening or mucoid impaction).[10] Lymph node involvement (bilateral mediastinal), pleural disease (thickening or effusion) and posterior mediastinal patterns (fibrosis) were included, defining seven distinct patterns of thoracic involvement.[8] A recent systematic review of 18 studies reported that the predominant CT findings of thoracic involvement were mediastinal lymphadenopathy (48.8%), pulmonary nodules (39.6%), and bronchovascular thickening (22.3%).[33] If assessed according to the defined classification, the second most common finding is bronchovascular changes.[33]

Parenchymal involvement of the lung in IgG4-RD is manifesting as one or more focal opacities that may mimic neoplasms.[15,34] Parenchymal lesions typically demonstrate increased uptake on 18F-FDG PET imaging, however, in IgG4-RD such uptake usually represents benign lymphoplasmacytic inflammation.[35] Although IgG4-RD is characterized by both fibrotic and inflammatory processes, a systematic review of this condition reported that interstitial lung disease was present in only 9.4% of definitively diagnosed cases.[33]

Mediastinal involvement in IgG4-RD commonly presents as bilateral mediastinal lymphadenopathy, often accompanied by hilar node enlargement.[11] Lymph nodes are generally well-defined and < 2 cm in diameter, although larger nodes up to 5 cm have been reported.[35] Mediastinal lymphadenopathy can occasionally be the initial or only radiological manifestation of IgG4-RD.[10] Posterior mediastinal involvement in IgG4-RD has been observed in around 3-6% of cases.[11,30,32,36] Posterior mediastinal infiltration or fibrotic involvement may result in vascular narrowing or stenosis.

Pleural involvement in IgG4-RD has been reported in approximately 8-15% of cases, with pleural manifestations including diffuse or nodular pleural thickening with occasional exudative effusions.[11,30,32,33,36] Histopathologically, these correspond to a fibrinous pleuritis that can progress to pleural fibrosis and lung entrapment if untreated.[37] Kasashima et al. reported that pleural effusion is the most frequent manifestation of pleural involvement in IgG4-RD, with histopathologically marked eosinophilic infiltration and abundant IgG4+ plasma cells.[38]

IgG4-RD pulmonary vascular disease; uncommonly lymphoplasmacytic infiltration of pulmonary arterial walls may lead to pulmonary hypertension that can mimic chronic thromboembolism or idiopathic pulmonary arterial hypertension.[39,40]

Airway involvement in IgG4-RD is another uncommon manifestation, with lymphoplasmacytic infiltration and fibrotic remodeling potentially causing airway stenosis, leading to atelectasis or asthma-like symptoms.[11,41] Symptoms indicative of asthma or allergic conditions are observed in approximately 40% of patients.[10]

Corcoran et al. developed classification criteria to distinguish the role of the disease in thoracic lesions attributable to IgG4-RD.[30] According to this diagnostic criteria, thoracic involvement in IgG4-RD is classified into four categories: definite (confirmed by histopathologically), highly probable (characteristic imaging features, absence of alternative diagnoses, and documented clinical improvement with targeted therapy), probable (typical imaging findings without alternative explanations, but lacking therapeutic confirmation), and possible (radiological findings consistent with IgG4-RD, although a plausible alternative cause exists). Additionally, even in the absence of biopsy or evaluation of therapeutic response, the coexistence of two or more characteristic thoracic imaging patterns in a single patient may indicate IgG4-RD.[33]

LABORATORY AND PULMONARY FUNCTION TESTS

In IgG4-RD, no single biomarker has been definitive-

ly established for diagnosis.[10] However, serum IgG4 levels and the enumeration of circulating plasmablasts are the most informative indicators, particularly when integrated with clinical, radiologic, and histopathologic data.[11] Although the 2019 ACR–EULAR criteria highlight an elevated serum IgG4 concentration (>135 mg/dL), which is detected in approximately two-thirds of patients, as an important diagnostic indicator, the optimal cut-off value for diagnosing IgG4-RD remains uncertain.[7,10] In patients with multi-organ involvement, IgG4 concentrations often increase, and extremely elevated serum IgG4 values (e.g., >5 g/L) have been associated with higher diagnostic specificity.[42] However, markedly elevated serum IgG4 concentrations do not exclude alternative diagnoses.[10] In an analysis of 32,206 cases, 191 patients had serum IgG4 levels greater than five times the upper limit of normal, and 25% of these individuals were ultimately diagnosed with other conditions, including malignancies, infections, and other autoimmune diseases.[43] Additionally, low serum IgG4 measurements that can occur in patients with markedly elevated IgG4 concentrations.10 In one analysis, 10 of 38 individuals with IgG4-RD had falsely low serum IgG4 levels attributable to this phenomenon.[44] It should be recognized that serum IgG4 concentrations are influenced by several factors, including ethnic background, organ involvement, and disease severity.[31,45] Although some investigators have advocated using the serum IgG4-to-IgG ratio to refine diagnostic accuracy in IgG4-RD, subsequent evaluations suggest that this measure provides no discernible advantage over serum IgG4 concentration alone.[46-48]

Flow cytometric detection of circulating plasmablasts at a cut-off exceeding 900 cells per mL has emerged as a useful biomarker for IgG4-RD.[49] In some patients with active IgG4-RD, plasmablast counts are high even when serum IgG4 levels are normal, suggesting that monitoring these cells could be useful as an additional biomarker and enhance existing diagnostics and assessment of disease activity.[49,50] In addition to serum IgG4 and circulating plasmablast counts, several biological markers have been identified. These include elevated ESR or C-reactive protein (CRP), polyclonal hypergammaglobulinaemia (total serum IgG levels >1800 mg/dL, with elevated IgG subclasses and IgE), and hypocomplementaemia (low serum levels of C3 <86 mg/dL and C4 <17 mg/dL).[10,11,21,28]

Most patients with thoracic involvement in IgG4-RD exhibit elevated serum IgG4 concentrations, reported in approximately 80-85% of cases.[51,52] Co-occurrence of asthma, moderate hypereosinophilia, and elevated IgE levels is relatively common and associated with an increased risk of disease relapse, but pronounced hypereosinophilia is an exclusion criterion for IgG4-RD under the ACR-EULAR classification criteria. These serological abnormalities can aid in differentiating thoracic involvement in IgG4-RD from other pulmonary pathologies; for example, an unexplained lung nodule or pleural effusion accompanied by an elevated serum IgG4 (with normal tumor markers) strongly suggests IgG4-RD.[52] Nonetheless, no laboratory finding is pathognomonic, and definitive diagnosis of thoracic involvement in IgG4-RD requires correlation of serology with characteristic imaging and histopathological features.[40]

Pulmonary function tests in IgG4-RD most often reflect a restrictive pattern or near-normal spirometry.[40,53] Obstructive abnormalities are less common.[53] In a study diffusing capacity of the lung for carbon monoxide per liter of alveolar volume was found to be pivotal in detecting pulmonary involvement.[54]

HISTOPATHOLOGY OF THORACIC LESIONS

The histological triad of IgG4-RD consists of: (1) a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, (2) a storiform (whorled) pattern of fibrosis, and (3) obliterative phlebitis (venous obliteration by inflammatory fibrosis).[55] Verification of abundant IgG4+ plasma cells in tissue is essential.[56,57] Additionally, measurement of the IgG4+/IgG+ plasma cell ratio is recommended, with a ratio greater than 40% generally considered abnormal.[56,58]

Histopathological features associated with IgG4-RD lack specificity; therefore, a probability-based histological classification has been proposed, categorizing findings into three groups: histologically highly suggestive of IgG4-RD (presence of at least two of the three characteristic features), probable histological features of IgG4-RD (presence of only one feature), and insufficient histopathological evidence (absence of characteristic features).[56] The 2019 ACR/EULAR classification criteria assign progressively higher scores based on specific histopathological findings: a dense lymphoplasmacytic infiltrate carries the lowest score, the presence of obliterative phlebitis increases this scoring further, and storiform fibrosis,

regardless of the presence of phlebitis, contributes the highest weight to classification.[29] Additionally, immunohistochemical findings, including assessment of IgG4+ plasma cells per high-power field (hpf) and the IgG4+/IgG+ plasma cell ratio, contribute further to the classification criteria.[29]

In pulmonary manifestations of IgG4-RD, infiltration by IgG4+ plasma cells is commonly observed, but characteristic storiform fibrosis may be absent on histopathological examination.[30,57] Additionally, neutrophilic aggregates, which are generally uncommon in IgG4-RD lesions from other organs, can occasionally be detected in lung tissue.[30] In the lungs, IgG4-RD produces a diffuse lymphoplasmacytic infiltrate with fibrosis and occasional eosinophils, often distributed in a lymphangitic pattern (along the bronchovascular bundles/septa, resulting in thickening of the bronchial walls and surrounding tissue).[52] A notable feature of IgG4-related lung lesions is obliterative arteritis, characterized by lymphoplasmacytic inflammation of small arteries resulting in luminal obliteration.[36,56] Unlike most other affected organs, in the lung, obliterative arteritis predominates over obliterative phlebitis.[11,56] For pulmonary and pleural involvement, the consensus statement recommends thresholds of IgG4+ plasma cells>50 cells/hpf for surgical biopsies and IgG4+ plasma cells >20 cells / hpf for nonsurgical biopsies.[56] For both biopsy types, the IgG4+/IgG+ plasma cell ratio should be >40%, in accordance with the consensus statement.[56]

Five histopathological patterns of IgG4-RD lymph nodes have been described:[59] (1) multicentric Castleman disease-like, (2) reactive follicular hyperplasia, (3) interfollicular expansion, (4) progressive transformation of germinal centers, and (5) inflammatory pseudotumor-like changes. The most common findings are reactive follicular hyperplasia and interfollicular plasmacytosis, which are relatively non-specific.[60] The pseudotumour-like pattern (with focal fibrosis) is least common but more suggestive of IgG4-RD.[60] Storiform fibrosis is usually absent in IgG4-related lymphadenopathy (except focally in the pseudotumour form), and obliterative phlebitis is rare in lymph nodes.[11,60] In lymphadenopathy, the diagnostic threshold for IgG4+ plasma cells is defined as >50 cells/hpf. However, given the infrequent presence of key histopathological features such as storiform fibrosis and obliterative phlebitis, combined with the limited specificity of elevated IgG4+ plasma cell counts, lymph node biopsy alone should not be considered definitive for diagnosing IgG4-RD. Nonetheless, biopsy of lymph nodes remains valuable for ruling out alternative diagnoses, particularly lymphoma or infections.[10] IgG4-RD may be mistaken for sarcoidosis in patients presenting with bilateral hilar lymphadenopathy.[61,62] Moreover, significantly elevated IgG4 concentrations and increased IgG4/IgG and IgG4/IgG3 ratios detected in bronchoalveolar lavage fluid from patients with IgG4-RD could aid in the differential diagnosis between these two conditions.[61]

IgG4-related pleural disease is uncommon; notably, the characteristic storiform fibrosis and obliterative phlebitis may be subtle or absent in pleural involvement.[63] Pleural biopsies typically show a thick fibroinflammatory tissue with dense lymphoplasmacytic infiltration enriched in IgG4-positive plasma cells and varying degrees of fibrosis.[64] Other fibrosing pleuritis etiologies such as tuberculosis, rheumatoid pleurisy, or empyema-associated fibrosis generally lack this IgG4+ predominance. Diagnosis therefore depends on identifying IgG4+ plasma cell-rich fibrosis and excluding alternative etiologies.[63,64]

In the mediastinum, histopathology of lesions usually exhibit the full triad of IgG4-RD.[65] These features resemble IgG4-RD in other organs but are not pathognomonic, also occurring in conditions such as histoplasmosis or granulomatous fibrosing mediastinitis.[66]

DIAGNOSIS

Suspicion of thoracic involvement in IgG4-RD is essential for a certain diagnosis, and occurs in the situations given below:

1. **Clinical Presentation:**
    - Constitutional symptoms: Fatigue, weight loss (substantial in IgG4-related autoimmune pancreatitis mild in other cases), unexplained fever (atypical, exclusion criterion in ACR/EULAR criteria).[7]
    - Respiratory symptoms: May be asymptomatic or vary according to lesion location; common symptoms include wheezing, cough, thoracic pain and dyspnea.[10,11,24]
2. **Laboratory Indicators:**
    - **Two key markers for diagnosis are:**
        - **Elevated serum IgG4 levels (>135 mg/dL):** Normal levels do not exclude the dis-

ease, but very high serum IgG4 levels are associated with higher diagnostic specificity. According to the ACR/EULAR classification criteria, higher serum IgG4 concentrations correspond to increased diagnostic scores.[7]

- Increased circulating plasmablasts (>900/mL).[49]

- **Nonspecific laboratory abnormalities are:**
  - Peripheral eosinophilia (>3000 cells/mm^3 suggests alternative diagnoses such as hypereosinophilic syndrome, antineutrophil cytoplasmic antibody (ANCA) vasculitis, or allergic bronchopulmonary aspergillosis, and is an exclusion criterion per ACR/EULAR criteria).[7]
  - **Hypergammaglobulinemia (total serum IgG >1800 mg/dL;** often accompanied by elevated IgG2 and IgE, and decreased IgA levels).[10,11]
  - Hypocomplementemia.[21]
  - Mildly elevated CRP and ESR.[28]

3. Radiological Findings:

According to current literature, the radiological manifestations of thoracic IgG4-RD are summarised in Table 1.

4. Extra-thoracic Assessment:

- **Clinical evaluation:** Careful assessment for extra-thoracic involvement, with particular attention to idiopathic pancreatitis, cholangitis with fibrosis, symmetrical enlargement of salivary or lacrimal glands, fibrosis of the retroperitoneum, orbital inflammatory lesions or protrusion, and unexplained masses involving pancreas, biliary tract, kidneys, orbits, and major salivary and lacrimal glands.[7,8]
- **Whole-body imaging:** Whole-body CT or 18F-FDG PET/CT.[10]
- **Laboratory evaluation:** Renal and hepatic function tests, assessment for proteinuria.[10]

5. Histopathological Confirmation:

- Characteristic histopathologic and immunostaining features.[55,56]
  - Dense lymphoplasmacytic infiltrates
  - Storiform pattern of fibrosis
  - Obliterative phlebitis or arteritis
  - Elevated IgG4+/IgG+ plasma cell ratio (>40%) or elevated IgG4+ plasma cell counts per hpf (threshold varies by organ; for pulmonary and pleural involvement, >50 cells/hpf for surgical biopsies and >20 cells/hpf for nonsurgical biopsies)

Table 1. Radiological manifestations in thoracic IgG4-RD.

Common manifestations
Lymph nodes: Mediastinal and hilar lymphadenopathy, typically well-defined, usually <2 cm but occasionally up to 5 cm. Nodes may show fibrosis, often with multiple enlarged lymph nodes.
Lung: Four characteristic CT patterns-solid nodular, bronchovascular (thickening of bronchovascular bundles and interlobular septa), alveolar-interstitial (diffuse ground-glass opacities, bronchiectasis, honeycombing), and round-shaped ground-glass opacities. Pulmonary nodules and bronchovascular thickening are the most observed findings.
Pleura: Pleural thickening (nodular or diffuse), occasionally associated with pleural effusion and fibrosis.
Uncommon manifestations
Pulmonary vessels: Pulmonary arterial infiltration or fibrosis, potentially causing pulmonary hypertension.
Airways: Airway wall infiltration or fibrosis, potentially resulting in narrowing, atelectasis, or asthma-like symptoms.
Posterior mediastinum: Fibrosis or infiltrative lesions in the posterior mediastinum, potentially causing vascular compression or stenosis.
Other: Involvement of the thoracic aorta, heart (coronary artery stenosis, valvular abnormalities, myocardial/pericardial involvement), and bones (bone erosions adjacent to pseudotumors).
IgG4-RD: *Immunoglobulin G4-related disease,* ***CT:*** *Computed tomography,* ***GGO:*** *Ground-glass opacity.*

6. **Rule out Alternative Diagnoses:** Consider differential diagnoses based on clinical context, serum IgG4 levels, plasmablast counts, and histopathological features.

Final Diagnosis: Confirm thoracic IgG4-RD based on integrated clinical, radiological, laboratory, and histopathological evidence.[67]

TREATMENT

Treatment is recommended for symptomatic thoracic IgG4-RD. Asymptomatic individuals, such as those with isolated chest lymphadenopathy, or incidentally detected lung nodules may not require immediate intervention. Early-stage disease that initially appears non-progressive necessitating regular monitoring. In these cases, a policy of watchful waiting may be appropriate, with intervals of at least 6 months provided patients remain asymptomatic.[68] In other instances, management of thoracic manifestations of IgG4-related disease primarily involves immunosuppressive treatment regimens.

Current international consensus suggests glucocorticoids as first-line therapy, typically oral prednisone at a dosage of 0.6 mg/kg/day.[69] Efficacy is usually observed within the first 2-4 weeks of treatment; many patients respond even earlier.[70] Some authors have proposed initiating prednisone at 0.6 mg/kg daily for 2-4 weeks, followed by dose reductions of 10 mg every 2 weeks until a daily dose of 20 mg is reached, and subsequently tapering by 5 mg every 2 weeks, aiming to discontinue prednisone within 3-6 months.[69] Steroid non-responsiveness is rare (<5%) and suggests an alternative diagnosis. Conversely, relapses following corticosteroid tapering are frequently observed, with reported recurrence rates ranging from 60% to 80% among patients.[71]

Patients with inadequate response to glucocorticoids commonly experience disease flares when doses are reduced below 10-15 mg/day of prednisone or equivalent.[33] Therefore, in selected patients exhibiting extensive disease involvement (such as involvement of three or more organs) or markedly elevated serum IgG4 levels (exceeding five-fold the upper normal threshold), initiating combination therapy comprising glucocorticoids and rituximab may be appropriate.[68]

Patients demonstrating steroid dependence might benefit from adjunctive immunosuppressive therapy to mitigate adverse effects associated with prolonged corticosteroid exposure. Alternatively, maintaining patients on minimal corticosteroid dosages (e.g., approximately 5 mg/day) could be necessary, given its efficacy in reducing relapse risk relative to placebo.[71]

In patients who show resistance to glucocorticoid therapy or who cannot sufficiently reduce their prednisone dose (typically below 5 mg/day), rituximab (1 g intravenously every 15 days, two doses in total) or inebilizumab (300 mg intravenously every 15 days, two doses in total) could be considered.[68,72] A meta-analysis evaluating rituximab treatment outcomes in IgG4-related disease reported an aggregated complete response rate of 88.9% at six months, with relapse occurring in approximately 21% of patients.[73] Regular maintenance therapy (dose of 1 g every 6 months) can prevent late relapses but may result in secondary hypogammaglobulinemia and respiratory infections.[74] Inebilizumab was U.S. Food and Drug Administration approved for IgG4-RD based on a randomized trial of 135 patients assigned to inebilizumab (300 mg IV on days 1, 15, and week 26) or placebo.[72] At 52 weeks, flares were significantly lower with inebilizumab (10%) than placebo (60%), and more patients achieved flare-free, glucocorticoid-free complete remission.[73]

Conventional immunosuppressive agents such as azathioprine, mycophenolate mofetil, ciclosporin, and methotrexate, show limited efficacy in inducing remission but are beneficial for steroid-sparing purposes.[69] If rituximab therapy is contraindicated or otherwise not feasible, alternative immunosuppressive agents such as mycophenolate mofetil (up to a maximum tolerated dose of 2.5 g/day) or azathioprine (approximately 2 mg/kg per day) represent suitable options.[68] Multiple clinical trials are currently underway, aiming to elucidate optimal therapeutic strategies for IgG4-related disease.[32,68]

PROGNOSIS AND FOLLOW-UP

Clinical and laboratory evaluations are recommended every 3-6 months for stable, treated patients, and more frequently for active disease cases.68 Essential monitoring parameters include complete blood count, biochemical profile, IgG subclass concentrations (particularly IgG4), baseline IgE levels, and complement components C3 and C4 when these have correlated with disease activity.[12,40,68] Baseline elevations in serum IgG4, IgE, and eosinophil counts predict a higher relapse risk.[68]

Periodic imaging (every 6-12 months) may be indicated for patients whose disease activity cannot be fully assessed by clinical and laboratory parameters alone.[11,68] CT alone might not reliably differentiate active disease from residual fibrosis, and supplemental 18F-FDG PET/CT may offer additional insights.[75,76]

The IgG4-RD responder index, a recently introduced assessment tool, has demonstrated promising reliability in evaluating comprehensive disease activity and associated organ damage.[77] Disease activity across 14 organs is graded on a scale from 0 to 4, incorporating evaluations of organ-specific damage severity, sequelae, and serum IgG4 concentrations. Thoracic involvement specifically includes assessments of the lung, lymphadenopathy, large vessels (including the aorta), and mediastinum.[77] This scoring system is increasingly utilized in randomized clinical trials to systematically evaluate therapeutic responses and longitudinal disease monitoring.[40]

The potential association between IgG4-RD and an elevated risk of malignancy warrants further investigation through rigorous prospective studies. While some studies indicate a higher cancer risk in IgG4-RD, others have not confirmed this association.[78-81] Additionally, a history of malignancy may predispose individuals to IgG4-RD.[68] A recent meta-analysis reported increased risks specifically for pancreatic cancer and lymphoma, but not for respiratory or gastric malignancies.[82]

CASE ANALYSIS

This case taught us that we should also keep in mind Ig4- RD in the presence of a disease affecting more than one component in the lung with multi-organ involvement. For our patient despite initial suspicion of lymphoma, the clinical, radiological, and histopathological features were consistent with IgG4-RD.

CONCLUSION

IgG4-RD represents a systemic fibroinflammatory condition predominantly affecting middle-aged to elderly men, capable of involving virtually all thoracic structures, often concomitantly with extrathoracic manifestations. Clinical presentation is nonspecific, with diagnosis relying on integrating clinical, radiological, biological, and histopathological evidence, as no single marker is pathognomonic. Recognition of thoracic IgG4-RD is complicated by numerous differential diagnoses, particularly when isolated thoracic involvement occurs.

Management primarily involves corticosteroids and rituximab, yielding high initial response rates but significant relapse risks, necessitating ongoing vigilance. Further research is essential to enhance understanding of disease pathogenesis, improve diagnostic precision, identify prognostic indicators, and develop targeted therapies with sustained efficacy.

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CHAPTER 14

RARE INTERSTITIAL LUNG DISEASES IN MEDICAL AND POSTGRADUATE EDUCATION

TIP EĞİTİMİ VE MEZUNİYET SONRASI EĞİTİMDE NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARI

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ABSTRACT

Rare interstitial lung diseases (ILDs) are often not adequately covered in medical education due to their low prevalence, yet they create major challenges for patients and healthcare providers. Many physicians may first encounter these diseases in clinical settings without having received proper training, which can lead to delayed diagnoses and negative impacts on patients. Educational programs often include rare ILDs under broader topics, without focusing on their specific features. New methods such as telemedicine, pre-recorded patient-physician video consultations, and narrative medicine can help improve awareness, diagnostic thinking, and empathy. Involving patients directly in educational activities also supports better understanding. International organizations and patient foundations contribute valuable resources and training programs. Strengthening education on rare ILDs will help future doctors recognize these diseases earlier and provide better care. Practical, focused, and patient-centered approaches are essential to improve outcomes for patients with rare ILDs and to close existing gaps in medical training.

The educational framework for rare ILDs is shaped by the educators' interests and experiences, as well as the institutions' available resources. However, at the very least, basic knowledge is mandatory for any doctor who is guiding patients in managing rare ILDs or other health conditions. Medical education curricula should be reviewed from this perspective.

For pulmonologists who will provide healthcare to patients with rare ILDs, a satisfactory level of education must be ensured in terms of early diagnosis, optimal disease management, and communication skills specific to rare ILDs. From this perspective, the situation in different countries should be reviewed and appropriate adjustments should be made. To achieve this, both undergraduate medical education and pulmonology residency training should be standardized in coordination not only with relevant institutions but also with professional societies in pulmonology. Since rare ILD patients are generally referred to specialized centers, referring postgraduate pulmonology students to these centers for education on rare ILDs may be a viable option.

The methods used for educational purposes must be enriched to effectively reach target audiences, including medical students, physicians, patients, their relatives, and the general public. The needs must be revealed first, and innovative options need to be implemented and validated.

This chapter reviews how rare ILDs are addressed in undergraduate and postgraduate medical training and suggests innovative ways to improve and enrich education in this field.

Keywords: *Interstitial lung diseases; Rare interstitial lung diseases; Medical education; Undergraduate; Postgraduate; Telemedicine; Narrative medicine; Curriculum*

ÖZET

Nadir interstisyel akciğer hastalıkları (İAH), prevalansları düşük olduğundan tıp eğitiminde çoğunlukla yeterince ele alınmamaktadır ve bu durum hem hastalar hem de sağlık çalışanları açısından önemli zorluklar yaratmaktadır. Pek çok hekim bu hastalıklarla klinik pratikleri sırasında, öncesinde yeterli eğitim almadan karşılaşmakta ve bu durum, tanıda gecikmelere ve hasta açısından da stresli bir sürece yol açabilmektedir. Eğitim programlarında nadir İAH'lara genellikle ana başlıklar altında, hastalıkların kendine özgü özelliklerine odaklanılmadan yer verilmektedir. Tele-tıp uygulamaları, video ile hasta görüşmelerinin kaydedilerek eğitim materyali olarak kullanılması ve anlatısal tıp gibi yeni yöntemler

farkındalığı artırmaya, tanısal süreçlere ve empatiyi artırmaya katkı sağlamaktadır. Hastaların eğitimsel süreçlere doğrudan dâhil edilmesi de daha kapsamlı bir anlayış gelişmesi açısından yararlı olacaktır. Ayrıca, uluslararası kuruluşlar ve hasta dernekleri, bu alanda eğitim programları ve değerli eğitim kaynakları sunmaktadır. Nadir İAH'lara yönelik eğitimin güçlendirilmesi, geleceğin hekimlerinin bu hastalıkları daha erken tanımasına ve daha nitelikli sağlık hizmeti sunmasına olanak tanıyacaktır. Hasta merkezli, pratiğe dönük ve odaklı yaklaşımlar hem hastalık yönetimini iyileştirmek hem de tıp eğitimindeki boşlukları kapatmak açısından önemlidir.

Nadir İAH için eğitim çerçevesi, eğiticilerin ilgi alanları ve deneyimlerinin yanı sıra kurumların mevcut kaynakları tarafından şekillendirilmektedir. Bununla birlikte, bu tanıları olan hastalara rehberlik eden her hekim için asgari düzeyde nadir İAH'lar ve ilişkili diğer sağlık sorunlarının yönetiminde kullanacakları temel bilgilerin edinilmesi zorunludur. Bu nedenle tıp eğitimi müfredatlarının bu bakış açısıyla gözden geçirilmesi gerekmektedir.

Nadir İAH hastalarına sağlık hizmeti sunacak göğüs hastalıkları uzmanları için erken tanı, hastalığın optimal yönetimi ve nadir İAH'larda iletişim becerileri açısından tatmin edici bir eğitim düzeyi sağlanmalıdır. Bu açıdan farklı ülkelerdeki durum gözden geçirilip uygun düzenlemeler yapılmalıdır. Bunun için mezuniyet öncesi tıp eğitimi kadar göğüs hastalıkları uzmanlık eğitimi, ilgili kurumlar yanında uzmanlık dernekleri ile de eşgüdümlü standartlaştırılmalıdır. Nadir İAH hastaları genellikle uzmanlaşmış merkezlere yönlendirildiğinden, uzmanlık sonrası göğüs hastalıkları öğrencilerinin bu merkezlere yönlendirilerek nadir İAH'lar konusunda eğitim almaları uygulanabilir bir seçenek olabilir.

Eğitim amaçlı kullanılan yöntemler; tıp öğrencileri, hekimler, hastalar, hasta yakınları ve genel toplum dahil olmak üzere hedef kitlelere etkin biçimde ulaşabilmek için zenginleştirilmelidir. Öncelikle ihtiyaçlar ortaya konmalı, ardından yenilikçi seçenekler hayata geçirilmeli ve geçerliliği test edilmelidir.

Kitabın bu bölümünde, nadir İAH'ların mezuniyet öncesi ve sonrası tıp eğitiminde nasıl ele alındığı gözden geçirilmekte ve bu alandaki eğitimin iyileştirilmesine yönelik öneriler sunulmaktadır.

Anahtar Kelimeler: *İnterstisyel akciğer hastalıklar; Nadir interstisyel akciğer hastalıkları; Tıp eğitimi; Mezuniyet öncesi; Mezuniyet sonrası; Tele-tıp; Anlatı tıbbı; Müfredat*

INTRODUCTION

Rare interstitial lung diseases (ILDs) are often neglected due to their extremely low prevalence. Undoubtedly, patients with rare ILDs require healthcare support throughout the entire clinical journey, from initial consideration during the differential diagnosis process to the management of the confirmed disease. Even when a lung disease occurs in only one in a million individuals, the chest physician who encounters such a patient must provide appropriate guidance, ensuring access to effective treatment and addressing any coexisting pulmonary conditions. This challenge is not limited to pulmonologists but applies to all physicians who encounter patients with rare diseases in clinical settings. Jean-François Cordier opposed the perception that rare or orphan lung diseases are reserved solely for specialized chest physicians working in university centers. He emphasized that patients with such conditions often begin their diagnostic journey close to where they live. Furthermore, he noted that any chest physician is likely to encounter several patients with rare diseases throughout their career.[1] Recognizing and considering rare lung diseases, including rare ILDs, in differential diagnoses is only possible if these conditions are addressed during medical education whether at the undergraduate, postgraduate, or vocational training levels. In this book, The LAM Story chapter illustrates a journey marked by underestimation, neglect, dismissiveness, and unawareness on the part of physicians before the final diagnosis of LAM. It is striking to see what patients and their families endure during times filled with uncertainty. Although these examples date back thirty years, the lack of awareness and knowledge about rare diseases continues to pose a significant barrier to timely and accurate diagnosis. Patients may experience delays and struggle to find specialists with sufficient expertise in their condition. When physicians are unfamiliar with these diseases, they may unintentionally cause patients to feel confused, anxious, or hopeless. Proper training can improve both diagnostic accuracy and the quality of communication with patients. Limited medical knowledge in this area may often lead to poor communication, particularly a lack of empathy toward patients with rare ILDs. For this reason, the book includes a chapter dedicated to the educational aspects of rare ILDs, a group of serious lung conditions that are often difficult to recognize and treat.

A European survey showed that 95% of healthcare professionals think there is a need for more detailed education on rare lung disease. Coincidentally, 95% of the patients were very interested in contributing to medical education and being involved in clinician training.[2] These results demonstrate that there is a mutual need for more educational resources and collaborations. Recently, Aldora and colleagues have discussed the educational aspects in rare lung diseases

in general, including rare ILDs. They pointed out that the patients with rare and orphan lung diseases often experienced significant delays in getting a correct diagnosis and struggled to find experienced physicians. Furthermore, reaching expert centers, usually located at large university hospitals, might cause long and expensive travel for appointments. They suggest improving education for rare lung disorders to increase the knowledge and awareness of these topics through international collaboration and networking.[3]

This chapter aims to discuss how rare ILDs are currently included in medical and postgraduate education and suggest ways to improve and vary educational activities in this field.

CURRENT EDUCATIONAL STATUS

Jean-François Cordier noted in the introduction to a monograph on orphan diseases: "As teaching in medical schools cannot cover the many rare diseases, it is unavoidable that general practitioners do not know all of the estimated 8,000 rare diseases. Therefore, the specialist must have the capacity to suspect the diagnosis in their field and further orient the patient towards expert centers, where the final diagnosis may be confirmed and the management defined, if necessary."[1] From this perspective, clinical suspicion must begin at the very first step of patient evaluation, and the diagnostic process should follow a systematic, guided approach. While a definitive diagnosis depends on clinical suspicion, a physician must possess relevant knowledge in order to suspect a rare condition in the first place.

The inclusion of rare ILDs in undergraduate and postgraduate medical curricula varies widely between countries and institutions. In most medical school programs, rare ILDs occupy only a minimal place. This approach is often based on the rationale that primary care graduates should be well-versed in the most common health conditions encountered nationally, with an emphasis on prevention and treatment. Rare diseases, by contrast, are typically listed only by name, often at the end of disease lists arranged by prevalence, or appear on the differential diagnosis discussions, mentioned only briefly. They are generally introduced during postgraduate training, where fellows may encounter only a handful of cases during specific rotations. As a result, awareness and familiarity with these diseases remain lower than expected, not only among general practitioners but also among some pulmonology trainees. Due to their limited presence in medical education, many physicians are unfamiliar with rare ILDs when they encounter them in real-life clinical practice. A pulmonologist may even retire without having seen a single case; yet if they do, patients with rare ILDs reasonably expect to receive care aligned with best medical practices.

Critically examining the current status of rare ILDs in medical education can serve as a valuable guide in addressing existing gaps and shaping more inclusive and effective curricula.

Rare ILDs in Medical Education

In the United States, the USMLE examination is essential for obtaining an ECFMG certification. The USMLE content outline reflects the content of the medical school curriculum, including rare ILDs, only in general terms. In the Respiratory Diseases chapter, under the section titled "Pneumoconiosis/fibrosing/restrictive pulmonary disorders/interstitial lung disease", the exam content mentions conditions such as pneumoconiosis, asbestosis, silicosis, and interstitial pneumonias like usual interstitial pneumonia (UIP). However, many rare ILDs (including Pulmonary Alveolar Proteinosis (PAP), Pulmonary Amyloidosis, Langerhans Cell Histiocytosis (LCH), and Lymphangioleiomyomatosis (LAM), etc.) are not specifically addressed.[4]

Since the European countries might have different curricula for undergraduate medical education, it is not possible to discuss their contents in relation to rare ILDs on a country-by-country basis.

The core curriculum for undergraduate medical education in Turkey is known as UÇEP (Ulusal Çekirdek Eğitim Programı – National Core Education Guide), with its most recent update published in 2020.[5] This guide outlines five fundamental pillars: (1) Outcomes/Competency Areas, which define the knowledge, skills, and attitudes that medical students are expected to acquire; (2) a list of Clinical Symptoms/Signs/Conditions that students should be able to recognize; (3) a Core Diseases/Clinical Problems list that sets expectations for mastery of essential conditions and clinical issues; (4) a list of Basic Medical Practices specifying the procedures students must be competent to perform; and (5) the Behavioral, Social, and Human Sciences component, which emphasizes the human-

istic and societal dimensions of medical education. UÇEP serves as a key reference for medical schools, academic departments, and educators in the planning and development of curricula. For each disease listed in the guide, the required level of competency is defined: diagnosing, treating, and managing acute problems (e.g., asthma); diagnosing, treating, and preventing conditions (e.g., pneumonia); or referring patients to appropriate specialists with a differential diagnosis (e.g., interstitial lung diseases). It is evident that this general framework allows flexibility for each medical school and pulmonary medicine department, depending on the expertise of their academic staff.

Education in Postgraduate/Residency/ Fellowship Programs

The American Board of Internal Medicine-Pulmonary Diseases exam content outline (Pulmonary Diseases Blueprint) defines the knowledge areas required for board certification in pulmonology in the United States of America. Although there is no rare ILD-specific category, the section on diffuse parenchymal lung disease, which accounts for 10% of the exam, includes several rare conditions. These include IgG4-related disease, pleuroparenchymal fibroelastosis, LAM, LCH, Birt-Hogg-Dubé Syndrome, PAP, and a general group labeled as genetic and other rare interstitial lung diseases.[6] This structure suggests a more integrated and comprehensive recognition of rare ILDs in specialist education.

The HERMES *(Harmonised Education in Respiratory Medicine for European Specialists)* syllabus, developed by the European Respiratory Society (ERS), serves as a guideline for standardized postgraduate education across Europe. It does not include a separate heading for rare ILDs but distributes relevant diseases under broader categories. LCH, LAM, PAP, and amyloidosis appear under diffuse parenchymal lung diseases (DPLD), while silicosis is covered within occupational diseases. Birt-Hogg-Dubé Syndrome and familial interstitial pneumonias are also included.7 Despite its detailed structure, the absence of a unified rare ILD section may limit the visibility of these diseases during training.

The TUKMOS curriculum defines the national framework for pulmonology residency training in Turkey. It includes a specific section on rare lung diseases, naming four rare ILDs: LCH, LAM, PAP, and pulmonary amyloidosis. In addition, it refers to pulmonary involvement of hematological diseases, which may imply the inclusion of conditions such as IgG4-related disease and Hermansky-Pudlak Syndrome.8 Although only a few diseases are explicitly listed, the inclusion of rare ILDs in the program is a promising attempt.

In pulmonology training, rare ILDs can be included under the broader category DPLD. This approach allows trainees to learn about these conditions within a unified framework, making it easier to understand them collectively. In addition to theoretical education, it is essential to emphasize that managing rare ILDs often requires a biopsychosocial approach that addresses the physical, emotional, and social needs of patients. This type of training is only feasible if the educational institution accepts and manages rare ILD patients. Otherwise, a structured rotation system involving expert centers (national or international) may help pulmonary medicine trainees gain the necessary exposure to these rare conditions.

Alternative Methods Through Telemedicine

Telemedicine-based methods have created new opportunities for enhancing clinical education in rare ILDs, particularly in postgraduate and specialty training programs. Due to the very low prevalence of these diseases, many medical students and fellows may not encounter such patients during routine clinical rotations. In a previous article, the use of pre-recorded video consultations, as implemented in a panel session at the Turkish Thoracic Society Congress, allowed clinicians to observe real patients with LAM, BHD, PAM, and PAP. Participants reported that this method improved their understanding of the biopsychosocial dimensions of rare ILDs and positively influenced their clinical practice.[9]

Similarly, undergraduate students who participated in structured telemedicine sessions conducted via video counseling showed improvements in medical history-taking, diagnostic approaches, and communication skills, while also gaining early exposure to patient-centered and holistic care principles.[10] Additionally, a pre-recorded video consultation with a PAM patient was watched in the classroom during the pulmonary medicine clerkship (Figure 1). This provided an opportunity to discuss not only the medical aspects but also the holistic approaches to patient care. Although the in-person presence of a rare ILD patient



Figure 1. A Pre-recorded video consultation with a patient watched in the classroom.
With the permission of the patient and students.

may not always be feasible during educational activities due to many limitations, pre-recorded telemedicine video consultations offer an opportunity to meet patients independent of time, availability, and distance limitations.

These experiences with innovative methods, such as using telemedicine in medical education, support the integration of video-based telemedicine tools into medical and postgraduate training programs to enhance practical experience and communication skills. These methods allow all trainees to engage with rare ILD patients and clinical scenarios, regardless of patient availability in their clinical settings. As rare diseases are often underrepresented in healthcare systems, these methods provide a valuable solution to enhance awareness and ensure adequate training for future doctors, including pulmonologists.[9]

International Societies, Foundations, and Guidelines

Education on rare ILDs can only be expanded through inclusive organizations and integrative strategies. In this section, the roles of professional societies, foundations, and clinical guidelines will be discussed. Some of these initiatives have the potential to serve as models that can be adapted and implemented at the national level. In this way, global comprehensiveness may be achieved through the integration of local efforts.

One of the most important international non-profit organizations in Europe focusing on rare lung diseases is ERN-LUNG (European Reference Network on Rare Respiratory Diseases). This network was launched in 2017 by the European Union to improve the care of people with rare diseases. Its education committee aims to ensure that both professionals and patients have access to up-to-date and relevant educational materials to support the diagnosis, treatment, and management of rare lung conditions. Rare ILDs are included among the nine rare lung disease areas covered by this program. Powell et al. conducted a survey-based study to assess the educational landscape in Europe from both physician and patient perspectives. The data provided valuable insights into existing limitations and potential future directions. A notable finding from the survey revealed that patients identified several barriers to accessing education, including language limitations, travel costs, and poor health that restricted their ability to travel. According to the results, 88.5% of patient respondents believed there was a need for patient education at the European level, yet only 34.8% were aware of existing activities.[2] These barriers must be taken into account when planning educational initiatives for patients. Additionally, an overwhelming majority (95%) of respondents emphasized the importance of involving patients in the education of healthcare professionals.[2] The responses to this survey should be regarded as an instructive and guiding signal for future planning.

ERN-LUNG organizes educational activities such as webinars, online training courses, and international meetings for both clinicians and patients. The goal is to increase knowledge, raise awareness, and support healthcare professionals in managing these rare conditions. ERN-LUNG also offers a dedicated training program, the ERN-LUNG Academy, which provides webinars, clinical e-cases, and on-site training at ERN-LUNG member hospitals.[3]

The ERS supports continuing education and professional development programs for respiratory professionals, which include content on rare lung diseases. This lifelong learning initiative has covered several orphan and rare lung conditions.[11] In addition, ERS has established an international, multi-center network called Clinical Research Collaborations (CRCs), which brings together researchers and patients to advance science in specific disease areas. Some CRCs have focused on rare conditions such as idiopathic pulmonary fibrosis (IPF), childhood ILD, and pulmonary hypertension.[3] Considering that even IPF is classified as a rare disease, it is important to recognize that other rare ILDs also deserve similar attention and support through CRCs.

The ERS launched a project called Harmonised Education in Respiratory Medicine for European Specialists (HERMES) with the aim of promoting the standardization of postgraduate training for respiratory medicine specialists across Europe. A mandatory module on orphan lung diseases in the HERMES core syllabus ensures that specialists who undertake the HERMES examination receive training in these conditions.[12]

The American Thoracic Society (ATS), one of the largest respiratory health organizations, offers a wide range of resources on rare lung diseases for both healthcare professionals and patients. These include official clinical statements, articles published in the Annals of the ATS, case reports, and accessible patient fact sheets on conditions such as LAM, sarcoidosis, alpha-1 antitrypsin deficiency (AATD), and Hermansky-Pudlak syndrome. ATS also organizes special events such as Lung Disease Week and collaborates with patient groups to raise awareness. Through webinars, clinical case discussions, and educational materials, ATS actively supports education and improved care in rare ILDs.[13]

The European Lung Foundation (ELF), established by ERS in 2000, focuses on improving education and communication between patients and healthcare professionals. For rare lung diseases, ELF has created several fact sheets and online resources in different languages to help patients better understand their condition. It also involves patients directly through Patient Advisory Groups and Patient Priorities websites, supporting conditions like LAM, bronchiectasis, sarcoidosis, and childhood ILDs.[14] Patient education is important, but it should be supported by the education of healthcare professionals as well. While patients aim to learn how to live with their disease, clinicians have the responsibility to support them with a biopsychosocial, patient-centered approach.

The LAM Foundation is a remarkable example of building something from nothing. Exactly 30 years ago, the mother of a patient with LAM brought together other patients and their families to raise awareness of this rare ILD and to support scientific research aimed at finding effective treatments. The details of the LAM story can be found in the relevant chapter of this book. The LAM Foundation's website offers a wide range of information. LAMposium, the Foundation's flagship scientific meeting, is a unique event that brings together two target groups (physicians/scientists and patients and their families) who learn from one another: patients benefit from expert insights, while experts gain valuable perspectives from the individuals they serve and care for. Information about the Foundation and the symposium is available on its website.[15]

CONSEQUENCES OF EDUCATIONAL GAP AND LACK OF AWARENESS

Misdiagnosis, Delay in Diagnosis, and Treatment Errors

When rare ILDs are not adequately covered during undergraduate or postgraduate medical training, clinicians may fail to consider them in the differential diagnosis of abnormal lung findings. In clinical practice, this lack of awareness can lead to unnecessary investigations or referrals to unrelated specialties, ultimately delay in diagnosis and struggling with uncertainties. Early recognition of these diseases can help avoid excessive testing, reduce both physical and mental stress for patients and clinicians, and enable timely intervention, often before disease progression occurs. Accurate and early consideration of rare ILDs

supports more efficient, targeted care and contributes to improved clinical outcomes.

Patients' Perspective

For patients with rare ILDs, the diagnostic journey is often prolonged and emotionally challenging. Many reports do not receive clear or detailed explanations about their condition, which prevents them from understanding the cause of their symptoms. This lack of information can lead to fear, anxiety, and a sense of helplessness. Several studies have shown that patients often feel lost and unsupported, particularly when they are unable to access reliable information about their disease or what to expect in the future.[16,17] Without adequate education, managing both the illness and its emotional impact becomes significantly more difficult. A chapter of this book, dedicated to patient perspective in ILD, provides a broader spectrum on the topic.

When healthcare professionals are unaware of rare ILDs, the diagnostic process is often delayed. Patients may undergo numerous tests, receive incorrect referrals, or be told that their symptoms are not serious, even emotional. During this period, many feel that their concerns are being dismissed or ignored. Some describe this phase as one marked by uncertainty and emotional distress.[18] These experiences highlight that education is essential not only for patients, but also for clinicians. A better understanding of rare ILDs on both sides can enhance communication, reduce anxiety, and enable earlier diagnosis and more effective treatment.

Patient-Doctor Communication and Trust

True communication and trust are fundamental parts of patient care, even more so for rare ILD patients. When clinicians are uncertain or unfamiliar with a disease, it can affect the way they interact with patients. However, when clinicians are well-educated about a disease, they will feel more confident in managing it, and this confidence will be transferred to the patient. A lack of clear explanations or hesitant language may increase the patient's anxiety and diminish their trust in the healthcare system. In contrast, a well-informed and empathetic clinician can foster the trust that the patient needs. Patients are more likely to trust doctors who take the time to listen and explain the challenges of living with a rare disease. This trust also enhances patients' adherence to treatment and follow-up.

RECOMMENDATIONS AND FUTURE DIRECTIONS

A survey study demonstrated that patients with rare diseases are generally willing to share their health data for research and healthcare purposes, as long as the privacy of their data is respected, and they can control the shared information. One of the main reasons patients supported data sharing was the opportunity to learn more about their condition and discuss it with healthcare professionals.[19] These findings suggest that patient involvement in medical education can be valuable. Incorporating patients by case-based video consultations and telemedicine tools into medical undergraduate and postgraduate training programs may enhance clinicians' understanding of rare ILDs by exposing them to real patient experiences. These approaches may strengthen clinical knowledge and improve patient-centered care. The same study also highlights the importance of clear data protection and privacy policies.[19] Patients are more likely to participate in educational and clinical activities when they trust that their information will be used responsibly. This respect will support the trust between clinicians and patients, improve the incorporation, which will be beneficial for both sides.

A panel presented at the Turkish Thoracic Society Congress introduced an innovative approach by integrating pre-recorded video consultations with patients diagnosed with rare ILDs, including LAM, PAP, PAM, and BHD Syndrome. Patients had consented to video recordings in a telemedicine session while they talked about their experiences, and afterwards, the video recordings were presented to congress attendees with patient consent. A questionnaire after the session was used to evaluate the participants' perspectives, and responses indicated that this method was effective in increasing awareness of the bio-psycho-social aspects of rare ILDs. Many reported that the experience positively influenced their clinical practice and emphasized the potential of telemedicine as a tool for education. The majority of participants addressed the video consultations as either equally or more effective than in-person patient presentations.[9] These findings support the integration of even the recorded materials of patients' experiences into both medical and postgraduate medical education as a way to promote awareness, empathy, and a more comprehensive approach to rare ILDs.

Narrative Medicine is an important tool for teaching and learning medicine, with many advantages cited in relevant literature. As Milota et al. highlighted in

a systematic review, narratives in the clinical setting can help doctors bridge the gap between their pathophysiological knowledge and the experiential knowledge contained in their patients' stories. In medical education, narratives serve as a crucial means of preparing medical students to engage in the shared decision-making process with their patients, help students hone their listening and observation skills, stimulate their empathetic abilities, and, in general, increase their capacity for reflection and perspective-taking. This approach also leads to a better sense of self as well as better and more meaningful relationships with colleagues and the public.[20] Recently, a scoping review was published to promote the power of narrative medicine in theoretical and clinical practice, education, and training, while supporting the development of methods to evaluate and measure its impact.[21] A pulmonologist, a writer, and a medical teacher simultaneously, feels responsible for collecting patients' stories and publishing them as a supplementary educational resource. Since the storybook consists of real patients' stories, including those of LAM, PAP, and Primary Pulmonary Hypertension cases among the rare lung diseases, through their unique experiences, it could be incorporated into rare ILD education. As an e-book, it can be used to expand its educational features for global use.[22] Raising awareness and promoting the use of narrative medicine in medical education may contribute to a more holistic understanding and teaching of diseases.

CONCLUSION

The educational framework for rare ILDs is shaped by the educators' interests and experiences, as well as the institutions' available resources. However, at the very least, basic knowledge is mandatory for any doctor who is guiding patients in managing rare ILDs or other health conditions. Medical education curricula should be reviewed from this perspective.

For pulmonologists who will provide healthcare to rare ILD patients, a satisfactory level of education is essential for early diagnosis, optimal disease management, and communication skills in rare ILDs. Since rare ILD patients are generally referred to specialized centers, referring postgraduate pulmonology students to these centers for education on rare ILDs may be a viable option.

The methods used for educational purposes must be enriched to effectively reach target audiences, including medical students, physicians, patients, their relatives, and the general public. The needs must be revealed first, and innovative options need to be implemented and validated.

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CHAPTER 15

PATIENT PERSPECTIVE IN RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARINDA HASTANIN BAKIŞ AÇISI

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PATIENT PERSPECTIVE IN RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARINDA HASTANIN BAKIŞ AÇISI

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ABSTRACT

Rare interstitial lung diseases (ILDs) encompass a diverse group of conditions with low prevalence, including lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), pulmonary alveolar proteinosis (PAP), and others. These diseases often involve multisystem manifestations and are characterized by prolonged diagnostic delays, limited treatment options, and a significant psychosocial burden. The rarity and clinical heterogeneity of these ILDs lead to their exclusion from large-scale trials, resulting in insufficient evidence-based guidelines and contributing to a sense of orphanity among patients. This chapter explores the diagnostic journey, emotional experiences, treatment expectations, and healthcare system interactions from the perspective of patients with rare ILDs. It highlights how misdiagnoses and long diagnostic delays exacerbate feelings of frustration and isolation in patients and their relatives. In many cases, patients report needing years to receive an accurate diagnosis, often after being misclassified as having more common diseases such as asthma. Emotional burdens such as anxiety, depression, and loss of identity are prevalent, particularly among women with LAM and patients with PAP and PLCH. Health-related quality of life (HRQoL) is consistently impaired in rare ILDs, even in patients with preserved lung function. Patient-reported outcome measures (PROMs) provide valuable insight into the lived experience of these conditions yet remain underutilized. The scarcity of disease-specific data limits the ability to tailor management strategies to patient needs. Patients consistently express expectations for symptom control, disease stabilization, manageable side effects, and access to clinical trials or future curative therapies. Their experiences with healthcare systems are often marked by limited access to specialized centers and a lack of disease-specific education and support resources. Multidisciplinary care and patient-centered approaches are emphasized as essential to improving care and quality of life. In conclusion, understanding patient perspective is crucial in the management of rare ILDs. In conclusion, physicians should address not only the medical but also the emotional and social needs of patients. Bridging the gap between clinical expertise and patient experience requires an empathetic, multidisciplinary, and holistic approach to care, which can ultimately enhance outcomes and patient satisfaction.

Keywords: *Patient centered medicine; Interstitial lung diseases; Rare interstitial lung diseases; Diagnostic delay; Quality of life; Patient perspective; Orphan disease*

ÖZET

Nadir interstisyel akciğer hastalıkları (İAH), Lenfanjiyoleyomiyomatozis (LAM), pulmoner Langerhans hücreli histiyositoz (PLHH), pulmoner alveolar proteinozis (PAP) gibi düşük prevalanslı, klinik olarak heterojen hastalıklardan oluşan heterojen bir gruptur. Multisistem tutulum, tanı gecikmeleri, sınırlı tedavi seçenekleri, yaşam kalitesinde düşme ve belirgin psikososyal yük ile karakterize bu hastalıklar, sıklıkla büyük klinik çalışmaların dışında kalmakta ve yetkin merkezlere erişimde sorunlar yaşanmaktadır. Bu durum hem bilimsel hem duygusal anlamda "yetim hastalık" algısını güçlendirmektedir. Bu bölümde, nadir interstisyel akciğer hastalıklarına sahip bireylerin tanı süreci, duygusal deneyimleri, tedavi beklentileri ve sağlık sistemiyle etkileşimleri hasta perspektifinden ele alınmaktadır. Özellikle doğru tanı almaktaki zorlukların ve uzun tanı sürelerinin, hastalarda ve ailelerinde gerginlik, umutsuzluk ve dışlanmışlık duygularını nasıl artırdığını ortaya koymaktadır. Hastalar sıklıkla astım, kronik obstrüktif akciğer hastalığı (KOAH) veya enfeksiyon gibi daha yaygın hastalıklarla karıştırılmakta ve doğru tanıya ulaşmaları ortalama birkaç yılı bulmaktadır. Bu süreçte yaşanan belirsizlik,

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yalnızlık hissi, anksiyete ve kimlik kaybı gibi duygusal zorluklar, hastalık yükünü artırmaktadır. Özellikle LAM, PAP ve PLHH hastalarında depresyon ve anksiyete sık bildirilen duygusal durumlardır. Sağlıkla ilişkili yaşam kalitesi (SİYK), nadir İAH hastalarında belirgin şekilde bozulmuştur. Hasta tarafından bildirilen sonuç ölçümleri, bu deneyimi yansıtmada önemli araçlar olup halen yetersiz kullanılmaktadır. Tedaviyle ilgili beklentiler; semptom kontrolü, hastalığın ilerlemesinin durdurulması, yönetilebilir yan etkiler ve gelecekte geliştirilecek küratif tedavilere erişim yönündedir. Klinik deneyim kadar hasta deneyiminin de karar süreçlerine entegre edilmesi gerekliliği vurgulanmaktadır. Hastalar, tanı ve tedavi sürecinde multidisipliner merkezlerde, konusunda uzman hekimlerce izlenmek istemekte; tanıdaki belirsizlik, bilgiye erişim zorluğu ve sağlık sistemindeki parçalı yapı, hasta deneyimini olumsuz etkilemektedir. Destek grupları ve hasta dernekleri, bilgiye erişim ve sosyal destek açısından önemli katkılar sunmaktadır. Sonuç olarak, nadir İAH'lı hastalarda hasta bakımı yalnızca medikal tedavi ile sınırlı olmamalı, duygusal ve sosyal ihtiyaçları da kapsayan bütüncül, empatik bir yaklaşım benimsenmelidir. Hasta sesinin duyulduğu, yaşam kalitesine odaklanan ve multidisipliner anlayışı temel alan bir sağlık hizmeti, bu alandaki en önemli ihtiyaçlardan biridir.

Anahtar Kelimeler: *Hasta merkezli bakım; İnterstisyel akciğer hastalıkları; Nadir interstisyel akciğer hastalıkları; Tanı gecikmesi; Yaşam kalitesi; Hasta perspektifi; Öksürük hastalık*

INTRODUCTION

Rare interstitial lung diseases (ILDs) represent a small but clinically significant subset of diffuse parenchymal lung diseases. Conditions such as lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Hermansky-Pudlak syndrome-associated ILD (HPS-ILD), Birt–Hogg–Dubé syndrome (BHDS), pulmonary alveolar proteinosis (PAP), pulmonary alveolar microlithiasis (PAM), familial interstitial pneumonias (FIP), pleuroparenchymal fibroelastosis (PPFE), and IgG4-related ILD present unique diagnostic, therapeutic, and psychosocial challenges due to their rarity, multisystem involvement, and frequent diagnostic delays.[1] Although there is no universally accepted or clearly defined criterion established by the World Health Organization (WHO), diseases with a prevalence of less than 1 in 2,000 in Europe, and those affecting fewer than 200,000 individuals in the United States, are defined as "rare diseases."[1,2] Rare ILDs are a subset of ILDs that have low prevalence and are often poorly characterized due to limited patient numbers, clinical heterogeneity, and lack of large-scale studies.[2] Despite advancements in imaging and genetics, patients with these diseases frequently face substantial burdens in accessing accurate diagnosis, disease-specific information, and specialized care. This chapter explores patient experiences in these rare ILDs, highlighting their diagnostic journeys, emotional responses, treatment expectations, and the broader implications of orphan disease status.

LIMITED DATA IN THE LITERATURE AND ORPHANITY OF RARE ILDS

Rare ILDs, by virtue of their low prevalence and clinical heterogeneity, are often excluded from large-scale clinical trials and epidemiological studies. The number of publications indexed in PubMed, including clinical trials, randomized controlled trials (RCTs), and case reports, related to both rare and more common ILDs, are presented in Table 1 (last updated on June 24, 2025). This scarcity of robust, generalizable data contributes to their classification as orphan diseases, a designation that not only reflects a lack of therapeutic development but also underscores the systemic neglect these conditions face within research and healthcare infrastructures. The limited evidence base impedes the establishment of standardized diagnostic pathways, prognostic markers, and treatment algorithms. As a consequence, healthcare professionals may encounter significant uncertainty when managing these conditions, which in turn exacerbates the challenges patients face in obtaining a timely diagnosis and effective care. From the patient's perspective, this scientific and clinical marginalization often translates into feelings of neglect, isolation, and diminished hope. Many patients with rare ILDs describe a prolonged diagnostic journey involving misdiagnoses, insufficient information, and fragmented care.[1-3] The absence of disease-specific support resources, clinical guidelines, and educational materials further amplifies the sense of invisibility. Unlike patients with more prevalent forms of ILD, such as idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD) related ILDs, or sarcoidosis, those affected by rare types frequently express frustration over the paucity of attention their conditions receive from both the medical community and the pharmaceutical industry.[4]

This sense of orphanity seems not only emotional but also structural. This table reflects a broader inequity in how research priorities are set and how healthcare systems allocate resources. Without targeted advocacy and dedicated funding for rare ILDs, progress in un-

Table 1. Number of all published articles, clinical trials, randomized clinical trials and case reports about interstitial lung diseases in the PubMed (personal brief analysis).

	Overall number of articles	Clinical trial	RCT	Case report
IPF	17,677	504	302	1,779
Sarcoidosis	36,424	367	120	12,467
HP	6,448	68	14	1,669
PLCH	12,903	92	15	6,777
LAM	2,238	39	14	895
PAP	2,539	28	7	1,027
PAM	470	0	0	282
Acute silicosis	339	5	2	74
BHDS	920	2	1	354
HPS	844	7	2	231
FIP	2,825	23	6	546
Pulmonary Amyloidosis	2,458	28	9	1,085
PPFE	348	2	1	119
IgG4-related pulmonary disease	550	0	0	317

Table preparation method: *Electronic search of PubMed using specific keywords (disease names given in table) were conducted. Clinical trials, randomised clinical trials, and case reports were also screened individually by using filters. The data included was limited to English publications.* ***BHDS:*** *Birt-Hogg-Dubé syndrome,* ***FIP:*** *Familial interstitial pneumonias,* ***HP:*** *Hypersensitivity pneumonitis,* ***HPS:*** *Hermansky-Pudlak syndrome,* ***IPF:*** *Idiopathic pulmonary fibrosis,* ***ILD:*** *Interstitial lung disease,* ***LAM:*** *Lymphangioleiomyomatosis,* ***PPFE:*** *Pleuroparenchymal fibroelastosis,* ***PAM:*** *Pulmonary alveolar microlithiasis,* ***PAP:*** *Pulmonary alveolar proteinosis,* ***PLCH:*** *Pulmonary Langerhans cell histiocytosis.*

derstanding and managing these diseases may remain slow. Importantly, this reality calls for a concerted effort to integrate the voices of patients into the research agenda, ensuring that the unique challenges they face are acknowledged and addressed in both clinical care and scientific investigation.

Perspective of patients in rare ILDs is a very neglected subject. Studies investigating patient perspectives in ILDs are more scarce than clinical trials and vast majority of these studies were conducted in IPF.[5-7] A small study conducted in China delves into the personal experiences of IPF patients. Through semi-structured interviews, it uncovers themes such as the prolonged and confusing journey to diagnosis, daily life challenges, emotional distress, and the desire for continuous care.[5] The findings highlight the

necessity for improved healthcare delivery and patient education, especially in remote areas. A broader, multinational study revealed significant diagnostic and treatment delays in IPF (0.8-2 years from symptom onset), frequent underreporting of symptoms by physicians compared to patients, high healthcare utilization (average 7-10 tests before diagnosis, annual hospitalization rate 24-64%), suboptimal treatment satisfaction (50% in moderate-severe IPF), and poor quality of life despite (mean EuroQol-5 Dimensions score: 61.7/100) increased antifibrotic use.[6] Several studies have investigated the patient perspective in individuals with LAM.[8-10] One study explored both the physical and emotional burdens experienced by patients and assessed that frustration, anxiety, identity loss, difficulty accepting the disease, and guilt were common among LAM patients.[8] In a study investigating the priorities of women living with LAM, the top three identified were the development of improved diagnostic assays, broader availability of treatment options, particularly sirolimus, and enhanced access to specialized LAM centers.[9] A recent study focusing on the psychosocial experiences of patients with LAM concluded that feeling of helplessness were associated with longer disease duration and greater limitations in daily activities, contributing to a more negative perception of the disease.[10] High levels of anxiety (31%), impulsivity (14%) and cannabis use disorder (8%) were reported in patients with PLCH.[11] A review which examined coping strategies of patients with PAP revealed that many PAP patients seek social support and connect with peer networks; joining support groups or online communities provides "a sense of camaraderie and empowerment" that helps counteract isolation.[12]

DIAGNOSTIC JOURNEY AND DELAYS

Diagnostic delay is a pervasive challenge in all types of ILDs, with profound implications for both clinical outcomes and patient well-being. It often takes months to years for patients to receive a correct diagnosis, contributing to psychological distress, frustration, and diminished quality of life. In a multinational European survey, 40% of patients with pulmonary fibrosis reported waiting over a year for a final diagnosis, with significant emotional burden during the process, including fear, confusion, and a perceived lack of support from the healthcare system.[13] Similarly, Lyu et al. found that Chinese patients with IPF described their diagnostic journey as long and confusing, often involving multiple misdiagnoses and feelings of disconnection from healthcare services.[5] Lancaster et al. reported that the time from symptom onset to diagnosis ranged from 0.8 to 2 years across countries and highlighted the disconnect between physician and patient perceptions of disease symptoms and severity, further compounding patient dissatisfaction and treatment delay.[6] Diagnostic errors in ILD, particularly due to the nonspecific nature of early symptoms and the rarity of the diseases, have been identified as critical contributors to delayed care and poor outcomes, reinforcing patients' sense of being overlooked and misunderstood.[3]

Patients with rare ILDs commonly report a prolonged and fragmented diagnostic pathway, often involving multiple misdiagnoses. For example, LAM is frequently mistaken for asthma, COPD, or spontaneous pneumothorax in young women before appropriate high-resolution computed tomography (HRCT) and vascular endothelial growth factor-D (VEGF-D) testing confirm the diagnosis.[14-16] Similarly, PLCH may be confused with emphysema or asthma in smokers, and BHDS is often underdiagnosed due to its dermatologic and renal manifestations overshadowing pulmonary cysts.[17,18] Diseases such as PAM and PAP are often misidentified as infectious or autoimmune processes, and PPFE is frequently misclassified as advanced fibrosis or sequelae of prior lung injury.[19-22] Average diagnostic delay and common misdiagnoses of rare ILDs are shown in Table 2.[16,18-22] These findings highlight the necessity of enhancing early recognition, healthcare professional education, and patient-centered diagnostic pathways in rare ILDs.

HOW TO MEASURE PATIENT PERSPECTIVE IN RARE ILDS

Biological and molecular insights are advancing personalized treatment and true personalization requires incorporating patient perspectives. The authors of a review article argue for integrating patient-reported outcomes, preferences, and life circumstances, termed "personomics", into treatment decisions. They highlight the importance of non-pharmacological care, monitoring comorbidities, and using patient-reported outcome measures (PROMs) and home monitoring to better reflect disease burden and guide individualized care strategies.[7] An international committee reviewed

Table 2. Common misdiagnoses and diagnostic delay in rare ILDs.

Disease	Common Misdiagnoses	Average Diagnostic Delay	Sample size	Reference
LAM	Asthma, COPD, pneumothorax	~4.8 years	n=505 (U.S. LAM Registry)	Gupta, McCormack et al.[16]
PLCH	Asthma, sarcoidosis, emphysema	2-5 years estimated		-
HPS	IPF, sarcoidosis	3-7 years estimated		-
BHDS	Emphysema, spontaneous pneumothorax	7.6 years	n=100 (East China cohort)	Hu et al.[18]
PAP	Pneumonia, alveolar hemorrhage	2-4 years estimated		Trapnell et al.[19]
PAM	Tuberculosis, miliary metastasis	Often incidental; up to decades		Uçan et al.[20] Wang et al.[21]
FIP	IPF, connective tissue disease ILD	Variable, often familial delay		-
PPFE	Advanced fibrosis, post-infectious ILD, sequela	2-6 years		Gamble et al.[22]
IgG4-ILD	Sarcoidosis, HP, lymphoma	Variable		-

Table preparation method: *Electronic search of PubMed using specific keywords (disease names given in table) were conducted. Clinical trials, randomised clinical trials, and case reports were also screened individually by using filters. The data included was limited to English publications.* ***BHDS:*** *Birt-Hogg-Dubé syndrome,* ***FIP:*** *Familial interstitial pneumonias,* ***HP:*** *Hypersensitivity pneumonitis,* ***HPS:*** *Hermansky-Pudlak syndrome,* ***IPF:*** *Idiopathic pulmonary fibrosis,* ***ILD:*** *Interstitial lung disease,* ***LAM:*** *Lymphangioleiomyomatosis,* ***PPFE:*** *Pleuroparenchymal fibroelastosis,* ***PAM:*** *Pulmonary alveolar microlithiasis,* ***PAP:*** *Pulmonary alveolar proteinosis,* ***PLCH:*** *Pulmonary Langerhans cell histiocytosis.*

the current state of patient-centered outcomes in ILD. The study emphasizes the importance of understanding how ILD affects patients' quality of life, symptoms, functional status, and psychological well-being.[23] PROMs and subdomains that we can use to measure patient perspectives in ILDs are summarized in Table 3.

HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH RARE ILDS

Health related quality of life (HRQoL) is often markedly impaired in rare ILD patients. Table 4 summarizes HRQoL studies for rare ILDs.[24-29] Validated generic instruments (SF-36, SGRQ, EQ-5D) and any

Table 3. Patient reported outcome measurements.

Patient-centered outcome	Subdomains	Measurements
Health-related quality of life	General	SF-36 EQ-5D-5L PROMIS-29
	Disease specific	SGRQ-I K-BILD ATAQ-IPF IPF-PROM
Symptoms	Dyspnea Cough Fatigue Treatment adverse events	mMRC, BDI-TDI, D-12 LCQ, CQLQ FAS, MFI, PESaM
Psychological and emotional well-being	Depression and/or Anxiety Grief Stress Emotional freedom Confidence Sleep disturbances	HADS, GAD-7 ESS, SA-SDQ
Functional status	Daily activities Capacity to function at home and at work Ability to leave home to participate in enjoyable activities and/or travel	
Supplemental oxygen need	Need for supplemental oxygen prescription and amount of oxygen prescribed Type and availability of oxygen delivery device Cost and navigating logistics	
Hospitalizations	Hospitalization-free days	
Acquisition of knowledge	Therapies and clinical trials available Risks and benefits of tests and procedures Prognosis and level of certainty for what the future holds Supportive care options	

ATAQ-IPF: *A tool to assess quality of life in IPF,* ***BDI-TDI:*** *Baseline dyspnea index-transition dyspnea index,* ***CQLQ:*** *Cough quality of life questionnaire,* ***D-12:*** *Dyspnea-12,* ***EQ-5D-5L:*** *EuroQol-5 dimension-5 level,* ***ESS:*** *Epworth sleepiness scale,* ***FAS:*** *Fatigue assessment scale,* ***GAD-7:*** *Generalized anxiety disorder-7.* ***HADS:*** *Hospital anxiety and depression scale.* ***IPF-PROM: IPF*** *Patient-reported outcome measure.* ***K-BILD:*** *King's brief interstitial lung disease health status questionnaire,* ***LCQ:*** *Leicester cough questionnaire,* ***MFI:*** *Multidimensional fatigue inventory,* ***mMRC:*** *modified medical research council dyspnea scale,* ***PESaM:*** *Patient experiences and satisfaction with medication,* ***PROMIS:*** *Patient-reported outcome measurement information system,* ***SA-SDQ:*** *sleep apnea scale of sleep disorders questionnaire,* ***SF-36:*** *Short form-36,* ***SGRQ-I:*** *IPF-specific version of the St, George's respiratory questionnaire.*

Table 4. Health related quality of life in rare interstitial lung diseases.

Disease	HRQoL measure and results	Comparative findings	Sample size and reference
LAM	SF-36 domains "General Health" and "Vitality" were lowest, indicating worst perceived health. ~35% had clinical anxiety and 17% depression. MILES trial: sirolimus improved EuroQoL and VAS QoL score but showed no significant change in SF-36 or SGRQ scores. The LAM-specific ATAQ-LAM showed strong internal consistency and its scores (e.g. dyspnea domain) correlated with FEV_1.	QoL in LAM is markedly impaired despite moderate lung function; psychological factors and exercise capacity correlate with SF-36 more than FEV_1. Sirolimus stabilized lung function and modestly improved QoL.	N=45, Queiroz et al.[24] N=89, McCormack et al. MILES Trial[25] N=69, Walker et al.[26]
PLCH	Baseline mean±SD SGRQ total score was 20.2 ± 18.8 indicating mild- moderate HRQoL impairment. Patients who later had lung function deterioration had a worse SGRQ at baseline (mean ~25.7) vs those without decline (~15.1)	SGRQ scores were substantially higher (worse QoL) in PLCH patients. A higher SGRQ (by ~10 points) at baseline was significantly associated with increased risk of FEV_1 and DLCO decline over time.	N=58, Tazi et al.[27]
PAP	In a randomized trial, SGRQ total scores significantly improved in the GM-CSF treatment group by 3 months (and maintained through 24 months) compared to no treatment	QoL improved with inhaled GM-CSF led to clinically meaningful SGRQ improvement vs placebo	N=36, Tian et al.[28]
PPFE	No quantitative HRQoL data		
HPS	No dedicated QoL scores		
BHDS	No quantitative HRQoL data		
PAM	No published QoL scores		
FIP	No specific data	HRQoL in familial fibrosis is similar to sporadic IPF.	
Pulmonary amyloidosis	No ILD-specific QoL study. In systemic amyloidosis, baseline SF-36 scores were dramatically low.		N=544, Seldin et al.[29]

ATAQ-LAM: *A tool to assess quality of life in LAM.* ***BHDS:*** *Birt-Hogg-Dubé syndrome.* ***FEV_1:*** *Forced expiratory volume at one second.* ***FIP:*** *Familial interstitial pneumonias.* ***GM-CSF:*** *Granulocyte macrophage colony stimulating factor.* ***HPS:*** *Hermansky-Pudlak syndrome.* ***HRQoL:*** *Health related quality of life.* ***IPF:*** *Idiopathic pulmonary fibrosis.* ***LAM:*** *Lymphangioleiomyomatosis.* ***PPFE:*** *Pleuroparenchymal fibroelastosis.* ***PAM:*** *Pulmonary alveolar microlithiasis.* ***PAP:*** *Pulmonary alveolar proteinosis.* ***PLCH:*** *Pulmonary Langerhans cell histiocytosis.* ***QoL:*** *Quality of Life.* ***SF-36:*** *Short Form-36.* ***SGRQ-I:*** *St. George's Respiratory Questionnaire.* ***VAS:*** *Visual Analog Scale.*
Higher SGRQ scores denote worse QoL (range 0-100). SF-36 is scaled 0-100 per domain (higher = better). Each disease's rarity limits sample sizes, and many findings are from registry or case series rather than large, controlled studies. QoL in these rare ILDs is generally significantly lower than age-matched healthy norms, underscoring the burden of disease. All references are provided for specific data points.

disease-specific QoL scales are noted, along with sample sizes (N), key QoL results (mean or median scores), and any comparative findings (e.g. vs. controls or general population).

PSYCHOLOGICAL WELL-BEING AND EMOTIONAL BURDEN

Patients with rare ILDs commonly experience significant psychosocial challenges including anxiety, depression, isolation and frustration. 46% of women with LAM have clinically significant anxiety and 55% report symptoms of depression.[30] Many patients worry about what the future holds as the disease progresses, especially since LAM often affects younger women and can lead to unpredictable lung function decline. Women with LAM often feel frustrated by their physical limitations and the way LAM "takes experiences" from their lives.[8] In focus groups, patients described feeling life had been "ripped out from under" them, reflecting high frustration and resentment toward the disease. Hope tends to remain high for most LAM patients; many women exhibit resilience and even find positivity or purpose despite LAM (e.g. adopting coping strategies and a "Flip" positive mindset).[31] In another rare ILD, 31% of adult PLCH patients have clinically significant anxiety measured by the Hospital Anxiety and Depression scale (HADS).[11] In a large U.S. claims-based cohort, ~29% of PAP patients had a diagnosed anxiety or depressive disorder.[32] Frustration is frequently voiced by PAP patients. They can be frustrated by symptoms (like breathlessness and fatigue) and the need for invasive treatments (e.g., repeated lung lavages), as well as the lack of a definitive cure.[12] No specific patient-survey data are available about the emotional status of other rare ILDs due to their extreme rarity.

The unpredictable course of rare ILDs (some patients stabilize, others progress) can cause frustration. Patients often feel distressed by the lack of knowledge about the disease and the limited treatment options, which adds to their frustration. Rarity of the diseases almost certainly leads to 'feeling isolated' and patients have difficulty finding others who share their diagnosis. However, social support in LAM is generally strong, and most patients report adequate support networks. The LAM community (e.g. the LAM Foundation's "Lammies") provides connection with fellow patients, which helps mitigate isolation.[33]

EXPERIENCE WITH HEALTH CARE SYSTEMS

The experiences of patients with rare ILDs within the healthcare system are shaped by the unique challenges and needs associated with living with a rare disease. Many patients may face a lack of specialist guidance during the diagnostic and treatment process and often have to exert significant effort to access accurate information and appropriate care due to the limited number of physicians with expertise. This situation places an additional burden on patients in terms of navigating the healthcare system and reaching the right center and specialist. Even if patients are able to reach the right physician and center and are followed up in such specialized facilities, these centers are often not located in the city where they live. As a result, they may face additional social and economic challenges such as difficulties with transportation, accommodation, and financial burden. Furthermore, in emergency situations like pneumothorax, there may not be enough time to access these specialized centers, leading patients to seek care in non-specialist hospitals or from non-expert physicians, which can present additional difficulties.

Patients emphasize the importance of a multidisciplinary approach: they prefer to be followed in centers where pulmonologists work in collaboration with thoracic surgeons (for pneumothorax management), radiologists, rheumatologists, nephrologists (for renal angiomyolipoma), dermatologists (skin manifestations), and, when necessary, transplant teams.[9,33] Since rare ILDs can involve extrapulmonary manifestations, coordination among different specialties ensures more comprehensive care.

One of the key challenges in the healthcare experience is the lack of access to information and appropriate guidance.[34] Many patients report having to conduct their own research to obtain comprehensive information about the disease after receiving a diagnosis. In this regard, rare disease databases such as Orphanet serve as valuable resources.[35] Living with a rare ILD may present a challenge for patients also due to the gaps in patient education, which can impact patient health and quality of life. Patients with rare ILDs feel they lack knowledge, such as disease progression, symptom management, and coping strategies. The results of a study conducted by asking open-ended questions to patients with systemic sclerosis-associated

ILD underscores the importance of tailored educational interventions to empower patients.[36]

PATIENT SUPPORT GROUPS AND ASSOCIATIONS

Patient support groups have become a positive component of the healthcare experience for individuals with rare ILDs. For example, The LAM Foundation (USA) and LAM patient organizations across Europe (LAM Action, LAM Italia) provide patients with reliable information and opportunities to connect with others living with the disease. The message, "You are not alone; many others have walked this path before you," forms the foundation of these support groups. Through these platforms, patients can share their experiences, access lists of expert physicians, and stay informed about emerging treatment or research opportunities.[33]

TREATMENT EXPECTATIONS

Patients expect that the treatments they receive will help control the progression of their disease and preserve their quality of life. Patients primarily expect treatment to alleviate symptoms such as dyspnea and fatigue and to enable them to maintain their daily activities.[23] Similarly, patients whose exertional dyspnea has improved through medical treatment or pulmonary rehabilitation report being able to participate more actively in social life.[37] In the long term, patients hope not only for the stabilization of disease progression but also, if possible, for regression or the discovery of curative therapies. For example, patients with LAM closely follow new drug development research; in one survey, 75% of individuals with LAM identified the opportunity to participate in clinical trials as a significant unmet need.[9]

Another key expectation from treatment is that side effects remain manageable. Patients expect their physicians to proactively manage these adverse effects and to preserve quality of life through dose adjustments or supportive therapies. The Patient Experiences and Satisfaction with Medications (PESaM) questionnaire was developed and validated to assess patient-reported experiences, satisfaction, and expectations regarding medication use in IPF. It has shown good content and construct validity and could been effectively used in studies to support shared decision-making by capturing patients' views on treatment effectiveness, side effects, and ease of use.[38] PESAM is a measurement tool to use both daily practice and research purposes.

For those with advanced disease, expectations also extend to lung transplantation: patients anticipate being promptly listed when appropriate and receiving timely support throughout the transplant process. In summary, the ideal treatment approach for patients with rare ILDs is one that halts disease progression, controls symptoms, minimizes side effects, and enables patients to maintain as normal a life as possible. While current therapies partially meet these goals and are met with patient gratitude, the absence of a definitive cure continues to shape their hopes for future therapeutic advancements.

CONCLUSION

The experiences of patients with a rare ILD not only reveal the pathophysiology of the disease but also highlight its human dimension. Patients living with these rare diseases face the daily struggle of breathlessness and fatigue, while also coping with uncertainty, anxiety, and social isolation. Understanding the perspective of patients is key to providing better care through an empathetic approach. Pulmonologists should be aware of the quality-of-life concerns of these patients, the impact of diagnostic delays, the barriers they face in accessing treatment, and the psychosocial burden of the disease. Patients want to be heard, understood, and treated through a holistic approach. Improving care for patients with rare ILDs requires a multidisciplinary and patient-centered approach that goes beyond medical treatment to address emotional and social needs. Physicians must listen not only to what patients say but also to what they may not be able to express, recognizing that only then can the challenges of living with a rare disease be truly alleviated. This empathetic and comprehensive perspective can make a meaningful difference in the lives of patients and lead to a more effective treatment journey for all involved.

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CHAPTER 16

THE LAM STORY: FROM GRASS ROOTS PATIENT ADVOCACY TO AN EFFECTIVE TREATMENT

LAM HİKAYESİ: HASTA SAVUNUCULUĞUNDAN ETKİN TEDAVİYE

Dr. Sue Byrnes
Prof. Dr. Francis X. McCormack

THE LAM STORY: FROM GRASS ROOTS PATIENT ADVOCACY TO AN EFFECTIVE TREATMENT

LAM HİKAYESİ: HASTA SAVUNUCULUĞUNDAN ETKİN TEDAVİYE

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ABSTRACT

Although this book chapter is framed under the title The LAM Story, its broader aim is to illuminate how physicians, scientists, patients, and their families can come together around a rare disease, uniting with the shared purpose of developing effective treatments and ultimately better survival. By tracing this journey, from the intimate beginnings of a unique personal story that sowed the first seed, to the collective endeavor of thousands joining hands, it seeks to inspire the emergence of similar narratives across other fields of medicine and beyond.

The opening of the chapter recounts the testimony of Sue Byrnes, who, beyond being the founder of the LAM Foundation, speaks as a mother and a caregiver who refused to surrender to despair. Her account portrays a figure who, while navigating paths previously unknown to her, had the courage to open doors, guide companions, and become a beacon of resilience. In doing so, her story reminds physicians, medical fellows, and scientists alike that their true domain is the human being. It brings science down from its above clouds abstraction to the lived realities of patients and their families, urging those engaged in research to recall for whom and toward what promises they dedicate their work.

The founding story of the LAM Foundation begins with a determination to draw attention of relevant institutions to the challenges faced by patients with rare diseases, particularly the consequences of lacking access to scientifically supported information on diagnosis, treatment, and prognosis. It conveys the psychological and social dimensions experienced by a patient, and her family, who suddenly find themselves confronted with a disease of difficult clinical course at a moment when they felt at their strongest. At the same time, the obstacles encountered on the path to diagnosis reflect circumstances that remain relevant for many rare diseases even today.

Rather than withdrawing from the struggle, the story demonstrates how taking the necessary steps one after another can yield consequences on the individual, patient-group, and societal levels. The establishment of a foundation where patients, their families, and physicians working in the field could come together, the support of research aimed at enabling effective treatments through the resources it generated, and the creation of opportunities for all members of the team to engage in scientific and social settings while learning from each other's perspectives together offer a methodological model. This model, rooted in lived experience, presents an approach adaptable to diverse fields.

The second part of the chapter presents the reflections of Professor Francis X. McCormack, whose extensive contributions have shaped the field of rare interstitial lung diseases. Professor McCormack offers a historical overview of the scientific research that has carried this journey to the present day. The concluding epilogue resonates not only with physicians and scientists but also with decision-makers in the pharmaceutical industry, the third essential pillar in the search for therapies in rare diseases. In doing so, he underscores the shared responsibility of all stakeholders in healthcare systems, highlighting the profound significance of each step. Recent advances and future directions are also cited in relation to treatment options and organizational purposes.

Finally, by considering the human being, especially the patient and their loved ones, as a biopsychosocial whole, this part of the book brings together diverse perspectives. It invites readers to reflect upon their own stories and, in doing so, encourages them to take action.

Keywords: *Rare interstitial lung diseases; Orphan diseases; Orphan drugs; Holistic approach; Lymphangioleiomyomatosis; Narrative medicine; Advocacy*

ÖZET

Öksüz hastalıkları kapsayan bu kitapta LAM Hikayesi adı verilse de bir nadir hastalık için nasıl hekimlerin, bilim insanlarının, hastaların ve hasta yakınlarının bir araya geldiğini, etkili tedavi ve sonuçta da yaşam süresini artırmayı hedefleyip nasıl başarılara imza attığını anlatarak gelecekte benzer hikayelerin diğer alanlarda da hayata geçmesine aracı olmak amaçlanmıştır. Süreci ilk tohumun atılmasına yol açan öznel ve özel bir hikâyeden alıp binlerce kişinin bir amaç uğruna el ele vermesinin hikayesi anlatılmaktadır. Sue Byrnes, LAM Vakfının kurucusu olması sıfatının ötesinde bir anne, yenilgiyi kabul etmeyen bir hasta yakını, hakkında hiçbir fikri olmayan yolları cesaretle kat ederken kapıları açan, yol arkadaşlarına rehberlik eden bir insan olarak ilk bölümde yaşadıklarını anlatmaktadır. Bu anlatılanlar aynı zamanda, hekimlere, hekim adaylarına, bilim insanlarına uğraş alanlarının insan olduğunu yeniden anımsatacak, bilimin bulutlar üzerindeki yerinden yer yüzüne, hasta ve hasta yakınlarının yanına indirerek kime, ne vaat ederek çalışmaları gerektiğini bir kez daha fark ettirecektir.

LAM Vakfının kuruluş öyküsü nadir hastalıkların yaşadıkları zorluklara, özellikle de bilimsel verilerle desteklenen tanı, tedavi ve prognoz bilgilerine ulaşamamanın neden olduğu durumlara ilgili kurumların dikkatini çekme kararlılığı ile başlamaktadır. En güçlü olduğunu düşündüğü zamanda, birdenbire zor bir klinik seyri olan bir hastalıkla yüzleşen hastanın ve onun yakınlarının hissettikleri konunun hem psikolojik hem sosyal yönünü gözler önüne seriyor. Öte yandan tanıya ulaşırken yaşanan sorunlar da çok zaman nadir hastalıklar için günümüzde de geçerli olan durumları içeriyor. Mücadeleden kaçmak yerine atılması gereken adımları birbiri ardına atmanın hem bireysel hem hasta grupları hem de toplumsal sonuçlarını fark edebilmek bu hikâyenin devamında mümkün oluyor. Hastaların ve yakınlarının aynı zamanda konuyla ilgili çalışan hekimlerin bir araya geldiği bir vakfın kurulması, onun elde ettiği gelir ile etkili tedavinin bulunmasına olanak tanıyacak araştırmaların desteklenmesi, ekibin bütün üyelerinin bilimsel ve sosyal ortamlarda bir araya gelerek birbirinin bakış açılarını öğrenmesi bir yöntem bilgisi olarak da çeşitli alanlara uyarlanabilecek bir model sunuyor.

İkinci bölüm, nadir interstisyel akciğer hastalıkları alanına sayısız bilimsel katkılar yapmış olan Profesör Francis X. McCormack'ın süreçte bilimsel araştırmaların tarihçesini ve bugüne uzanan yolun özetini paylaştığı kısımdır. Özellikle bölüm sonuna eklediği epilog ile hekimlere ve bilim insanlarına, hatta nadir hastalıklarda tedavi arayışına destek olması beklenen, sac ayağının üçüncü parçası olarak ilaç endüstrisinin karar alıcılarına, hepsinin birleşmesinde genel olarak sağlık sistemlerinin paydaşlarına atılacak her adımın anlamını fark ettirmektedir. Ayrıca, bu bölümde tedavideki yeni gelişmeler ve organizasyon açısından yeni yapılanmalar gibi konulardan da söz edilmektedir.

Biyopsikososyal bir varlık olarak değerlendirdiğimiz insan (özelde hasta ve hasta yakınları), kitabın bu bölümünde bütün bakış açılarını bir arada görmeye ve okurları kendi hikayeleri için düşünmeye, sonra da harekete geçmeye yüreklendiriyor.

Anahtar Kelimeler: *Nadir interstisyel akciğer hastalıkları; Öksüz hastalık; Bütüncül yaklaşım; Lenfanjiyoleyomiyomatozis; Anlattı tıbbı; Hak savunuculuğu*

LAM FOUNDATION: GRASS ROOTS PATIENT ADVOCACY

Seeking for the Diagnosis of Lymphangioleiomyomatosis (LAM)

As founder of the LAM Foundation, I would like to begin my contribution to the Lymphangioleiomyomatosis (LAM) story by expressing my gratitude to the editors of this book for their interest, and to the readers, whose engagement may help our story grow in their minds, hearts, and practices. I will briefly share my personal journey, "Devastation to Destination", from the very beginning in the hope that our experiences will illuminate a path for others facing the unthinkable, a devastating diagnosis of an orphan condition in a loved one. I will then pause to give the floor to Dr. McCormack, who will provide the scientific perspective.

My daughter Andrea was a tremendous soccer player. Soccer was Andrea's passion, her identity, and the motivation that kept her going, until she could go no more. In 1991, during her freshman year at Mount Union College, she severely injured her knee, and her life was changed forever. Andrea suffered through numerous reconstructive surgeries and three years of rehab- all to no avail. She was left with an incredibly weak knee and a 12" scar. My daughter never played another game of soccer. She returned to college but giving up soccer caused anxiety attacks that would continue to haunt her.

Andrea and I have always been very close. We often sat together on her bed before she turned in for the night. It was in 1992 when we were talking in bed and she asked, "If I tell you something, will you not think I'm crazy?" "Of course not," I replied. Andrea said, "I know this sounds strange, but I feel like I have a terrible disease". I, of course, was stunned because there was nothing to indicate that that could be the case. She had no explanation-it was simply a feeling she had had inside for some time and had just picked up the nerve to tell me. Andrea had always been intuitive, and she often sensed things before they happened, but this was just too eerie for words.

In 1993, Andrea began to experience severe abdominal pain that wouldn't go away. I'll never forget the heartbreak and helplessness I felt seeing her lying on the floor of our family room writhing in pain. On

six different occasions, we rushed her to the emergency room but received no definitive diagnosis. During their examinations, doctors saw the long scar on her leg, listened to her story, and concluded that her pain was emotional. She was often sent home with a diagnosis of spastic colon or irritable bowel syndrome, "most likely due to anxiety or stress". The lack of a definitive diagnosis was frustrating, but to hear doctors imply that it could be in her head was maddening. How can you judge the extent of someone else's pain? It was clear that the pain was real. My daughter was tough; she was not one to exaggerate. Through her long-time involvement in sports, she had proven her high tolerance for pain, but I had no idea about what tests should be done to dig deeper, and I certainly wasn't qualified to battle with the experts. I felt helpless and didn't know where to turn.

Later that year, the family went to visit Andrea at Bethany College in West Virginia where she was coaching women's soccer. As we watched her soccer game and cheered the team on, Andrea's abdominal pain began to resurface more severely than ever. Paramedics were called and I will never forget watching Andrea being carried up the long steep hill from the soccer field to the ambulance waiting to take her to the emergency room – yes, one more time. When we arrived at the hospital and explained to the doctor that she had previously been diagnosed with spastic colon and irritable bowel syndrome, he immediately rejected the diagnosis, explaining, "Her pain is much too severe for either of those. We need to do a CT scan." Finally! Someone was going to pursue this further! I was grateful for the doctor's diligence but not pleased with what he discovered. A CT scan of the abdominal area revealed that Andrea had a massive 21-centimeter tumor on her kidney, and it had been hemorrhaging. The doctor explained that the tumor had to be removed right away and that she would undoubtedly lose her kidney. The results revealed that it was a benign tumor called an angiomyolipoma. The news was much better than we expected, and Andrea would soon be released from the hospital!

The following year we planned a vacation to Denver, Colorado. The day before we left, Andrea's shortness of breath was coupled with relentless chest pain, so we postponed our trip. We made an appointment with the doctor who listened to her chest and said her breathing sounded fine. He did not see the need for an x-ray, surmising that her chest pain and shortness of breath were most likely signs of anxiety. Andrea was feeling much better the next morning and thought she could make the trip. During the flight to the mile-high city, Andrea's symptoms returned and grew rapidly worse. Her breathing was extremely difficult and the intense pressure in both her back and chest became unbearable. I alerted the flight attendant who called ahead to have paramedics waiting when we touched down. Andrea was whisked off the plane to the emergency vehicle. The paramedics were immediately alarmed because they couldn't hear her lungs or pick up a heartbeat. We soon learned that she had had a tension pneumothorax. The doctors explained that she would have died if she had arrived two hours later.

Andrea's first appointment was with a well-respected pulmonologist at the hospital who was considered the best in the city. He ordered a CT scan which revealed small cysts throughout her lungs, but no one, including the pulmonologist or the radiologist who read the CT scan, had ever seen anything like it. They couldn't give us a potential diagnosis. Since this disorder was such a mystery, we knew we had to be thorough in our investigation. I contacted the National Institutes of Health (NIH) and asked for recommendations from doctors at four major institutions to look at Andrea's CT scans. The waiting game was torturous since the diagnosis reports came to us via snail mail. All four institutions agreed that Andrea had LAM, formally known as Lymphangioleiomyomatosis. That word was terrifying enough, but not nearly as scary as the content in the only article we could find. Much of it was over my head, but it was clear that there was no effective treatment. Panicked, my eyes frantically searched the report for prognosis. I found it in the last section of the article called Survival. In the very first sentence I read that in 1973, "death from respiratory insufficiency usually occurred within four years of the onset of lung disease." Then the authors of the 1990 publication referred to more "encouraging news" from their study, showing that 78% of their patients were still living 8.5 years after the onset of disease. They call this encouraging news?!

There were no adequate words to describe this horror. My mind was filled with a million agonizing thoughts. How long would my daughter be with me? What would I ever do without her? But Andrea was my major concern as she waited unknowingly in the outer room. How would she handle this? How do we break the news to her? Parents are supposed to protect

their children, but we couldn't protect her from this. Childrearing manuals don't instruct you how to tell your 22-year-old daughter that she has a disease that could take her life.

Living with the Diagnosis of LAM

It was time. The next day we faced the delicate task of sharing the news with Andrea. She was stunned. Oddly enough, even though it was a lung disease, the first thing she asked was if she could have children. We had read in the article that pregnancy is thought to accelerate the disease, so learning that was difficult for all of us, but especially for her. She was so good with children and had always wanted "tons of them", which is why she chose to be an elementary teacher. Andrea was sobbing as she threw her arms around us and said, "I am so scared!" We held her tightly as all of us wept.

I immediately wrote to Dr. Francis X. McCormack, a doctor who was moving from Denver to Cincinnati. When he entered his new office at the University of Cincinnati, he saw an empty desk . . . except for a letter . . . from me. He called to schedule an appointment with Andrea as his very first patient in Cincinnati. During our visit, he explained that LAM is an aggressive lung disease that strikes women, usually during their childbearing years. Dr. McCormack remained as positive as he could and described Andrea's particular case as mild, which was music to our ears. He said that it would most likely be years before she might experience any symptoms. While she was encouraged by his words, he also made it clear that she had a slowly progressive disease with no effective treatment.

We were both trying to be brave during our trip home. It became apparent that Andrea was contemplating the severity of her situation. In an effort to comfort her, I impulsively blurted out, "I'm going to do something about this, Andrea. I promise you, I will change all of this." I don't know who put those words in my mouth, because I didn't have a clue what I was going to do!! My outburst took on a life of its own, reverberating in the silence that fell over the car. Then Andrea reached over to touch me and said, "Mom, you're my best hope." I'll never forget those words and the impact they had on me. They were instantly engraved in my heart. She was right. LAM had been identified for more than 60 years before it became part of our lives, yet there had been no research. Could that be altered? Could I change anything? I didn't know for sure, but it was clear that I needed to get busy. I was forced to accept Andrea's diagnosis, but I refused to accept that LAM would take her life (Figure 1).

Dedicating My Life to LAM

The publication we received that fateful day was the only one of any significance that we could find. Reading through the article again, I noticed something at



Figure 1. Sue Byrnes and her daughter Andrea; during the Breath for Hope Gala in the LAMposium.

the end that I had failed to see in the midst of my devastation. Doctors were recommending a national registry of LAM patients. A national registry - that didn't sound too complicated! Perhaps I could support my daughter by helping doctors become more knowledgeable about LAM. The first thing I needed to do was to find out how a national registry functioned. What I learned rather quickly was that a national registry was no small feat. I would need the support of Congress to make it happen. I contacted the National Organization of Rare Disease (NORD) to request the names of anyone in their database who was affected by LAM. There were only ten! I immediately picked up the phone to enlist their help with a letter-writing campaign. The goal: to convince Congress to push the NIH to form a national registry of LAM patients.

Isolated and alone for many years, most of these women with LAM had never communicated with anyone else affected by the disease. They imagined dying without anyone caring enough to gather their names or organize any kind of effort to fight this rare disease on their behalf. Many were too sick to do it themselves. Eventually, every single one of them agreed to help with a letter writing campaign dubbed the Labor of Love. These ten women put me in touch with a few other women with LAM and soon the word got out. One-by-one, they called with their personal journeys. Hungry for someone to listen, many of them talked for hours! It was therapy for them, but they couldn't possibly know how frightening it was for me to hear their heartbreaking words- to listen to their breathlessness. But these were special women and their courage and strength amazed and inspired me. I knew I was doing the right thing and I was determined to work even harder.

After making the decision to spearhead a letter-writing campaign for a National LAM Registry, I realized I had a minor problem. I didn't own a computer! My portable typewriter was with Andrea at school, so my only alternative was to drag out my father's antique Remington 16 typewriter (Figure 2). The letter-writing campaign began. Dr. McCormack suggested that I write to the pulmonary community as well, asking them to write to the National Heart, Lung, and Blood Institute (NHLBI) in support of a national LAM registry. He had supported my efforts and told



Figure 2. The antique Remington 16 typewriter used by Sue Byrnes's father. The letter which Sue Byrnes wrote to the NIH and to Professor Francis McCormack is appearing on the paper in the carriage.

me that what I was doing was important. He wanted to help, had shown heart, compassion, and commitment. He agreed to help with the medical database of physicians. Together, we wrote to over 1,000 pulmonary doctors. LAM patients were charged with writing letters and encouraging others to do the same, and it was clear they felt empowered that they were doing something about their plight. They became even more determined, and the letters kept coming. They sent copies of their congressperson's responses, and I filed them away as mementos. Keeping busy was therapeutic and the support offered by so many was rewarding, but were we making a difference? Oh, yes! In response to the thousands of letters they received, the NHLBI commissioned a Working Group Committee of expert physicians. I was continually questioned about how I could expect the NIH to put so much effort into a disease that affects only one in a million women. People often don't understand that if you're that one in a million, it doesn't matter how many people are affected! I was not going to give up. Besides…I knew that there had to be many others who had LAM without knowing it.

In July 1995, Dr. Claude Lenfant, National Heart Lung and Blood Institute (NHLBI) Director, invited my husband and me to meet with him. At that meeting, Dr. Lenfant not only agreed to a national registry, but also committed to sponsoring a LAM workshop and issued a program announcement advertising their receptiveness to LAM grant proposals. I was thrilled! These were major steps toward stimulating LAM research. We had more than accomplished our goal. Needless to say, the women with LAM and their families were ecstatic. It was a most gratifying experience.

Dr. McCormack began to see how determined I was to save my daughter and offered continual encouragement. One day he said, "Sue, if you are really serious about funding research, you need to start a foundation". I was definitely serious but start a foundation?! The accomplishments we'd made in such a short time were encouraging but establishing an organization by myself was daunting. It would dramatically change my life. I could no longer be a music teacher. Every relationship in my life would probably be affected. However, my newly acquired understanding of just how precious life is and the thought of losing my daughter were deciding factors in moving forward. I began to put the idea into motion, and before I got out of bed each morning, I said to myself, "Every spare moment of today counts toward my daughter's life." That's what drove my motivation to find a cure and I knew a foundation was my best hope.

1995 - The LAM Foundation Begins

In August 1995, I resigned from my position as an elementary music teacher. My husband and I took the necessary steps to establish The LAM Foundation as a 501(c)(3) nonprofit organization, with research as its central mission. Dr. McCormack agreed to become the Founding Scientific Director. The dining room became my office and the search for a cure began. "A journey of a thousand miles begins with a single step" by Chinese philosopher Lao-tzu was chosen to represent our efforts to find a cure.

As LAM patients were referred to the Foundation, my list of ten women grew to 88 in the first year. One-by-one, they learned of the Foundation's existence and called with their personal stories. They described LAM as the "lonely disease", expressing that it was like being stranded on an island with no one caring enough to even gather their names. One patient told me that, as she passed people on the street she thought, "Not one of them will ever know or care about what I'm going through." Most women with LAM had never talked to anyone else who was affected by the disease, so relating their past history was therapeutic. Most of them had gone misdiagnosed and undiagnosed for years, some having as many as fifteen lung collapses before learning they had LAM. Women with LAM were told that their shortness of breath was "in their heads" or they were "out of shape" and often advised to see a psychiatrist.

Listening to their personal journeys and hardships became especially painful for me. I envisioned my daughter as they related their stories, realizing that she, too, could face the same fate. It was important for me to listen to every word, because I would want someone to do the same for my daughter. After grappling with this disease for years, I still wake up in the night in disbelief that my daughter has LAM. As time went on, I felt an indescribable bond with these women. They were my inspiration and my strength, making me more and more determined to find a cure.

But in my effort to help these women, I found myself overwhelmed by a world completely foreign to me; I functioned daily outside my realm of expertise. I knew very little about scientific research and I was

forced to become knowledgeable about the endless parade of obligations that running a Foundation entailed. However, we had accomplished our first goal to form a National LAM Registry, so it gave me the courage to move forward and the hope that we could actually find a cure. We were on our way to funding the first-ever LAM research!

FOR THE EFFECTIVE TREATMENT

Dr. Francis X. McCormack

Formation of the LAM Foundation in 1995 was the pivotal step in all progress that followed for LAM. Patients registered at the rate of about 100 per year in the early years of the organization, and before long numbered in the thousands. Sue Byrnes did a fantastic job of gaining their trust and convincing them of the importance of supporting research, and together we developed a model for an innovative, highly interactive annual conference called the LAMposium that convened scientists and patients to discuss progress and chart new research directions. The donations in the first few years of the Foundation's existence were sufficient to fund a few pilot projects. I assembled a volunteer scientific advisory board of physician scientists who I had come to respect through my training and early faculty years, and we established a mechanism for peer review. Three amazing scientific developments occurred in the decade from 1993-2003 that greatly accelerated progress in LAM: 1) the genes responsible for tuberous sclerosis complex were discovered and linked to LAM, 2) LAM was found to recur in transplanted lungs, and genetic studies demonstrated that the pathogenic cells that destroyed the lung arose from the recipient, consistent with a metastatic mechanism, 3) the tuberous sclerosis genes were shown to regulate the mTOR pathway, which controls cellular metabolism and growth, and mutations that interfere with their function constitutively activate mTOR in the LAM lung.[1-3]

LAM Foundation funding, which had grown to be much more substantial over time, played a key role in each of these advances, and set the stage for trials. A highly specific inhibitor of the mTOR pathway called sirolimus (rapamycin) had recently been FDA approved for the prevention of renal transplant rejection and was available for testing. An open label trial of sirolimus in 25 patients with TSC or LAM was conducted in Cincinnati to determine if the drug reduced the volume of angiomyolipomas (AML), the benign kidney tumor that occurs in these patients, as a proof of principle study.[4] The results were compelling. Over the 1 yr treatment period, not only did the AMLs shrink by about 50%, but lung function in a number of patients with LAM improved substantially. On the basis of this result, we approached industry (Merck) about conducting a pivotal trial in LAM with their mTOR inhibitor, rapamune (i.e.-sirolimus), but the disease was considered to be too rare for the level of investment that would be required, and they declined. So, a group of physician investigators in the North America and Asia banded together and applied for and received more than $8M in funding from a dozen sources including the National Institutes of Health (NIH), the Tuberous Sclerosis Alliance, Wyeth and the Japanese and Canadian governments. The LAM Foundation committed about $500,000, which was a substantial fraction of their net worth, and pledged their assistance with recruitment and logistics. The trial was conducted through the Cincinnati-based NIH Rare Lung Disease Consortium (RLDC); a network of 10 domestic sites and 3 international sites in Canada and Japan. The double blind, investigator initiated Multicenter International LAM Efficacy of Sirolimus (MILES) trial (NCT00414648) was designed to test the hypothesis that sirolimus stabilizes lung function (FEV1) in patients with LAM.[5] Of 111 patients consented, 89 were randomized to receive dose-adjusted sirolimus or sham dose-adjusted placebo for 1 year, followed by a 1 yr observation period off therapy. The primary endpoint was difference between groups in the rate of change in the slope of forced expiratory volume in 1 second (FEV1). During the MILES study, VEGF-D was developed as a diagnostic biomarker that could obviate the need for biopsy.[6] That advance broadened the eligibility criteria for in MILES to include subjects who had no other diagnostic features (i.e.-concomitant TSC or AML) and who had not had a biopsy, boosting enrollment to the point that the study was adequately powered to answer the question of efficacy. The conclusion of the five year long trial, reported on April 28, 2011 in the New England Journal of Medicine, was that sirolimus stabilizes lung function, reduces serum VEGF-D levels, and results in improvement in some measures of functional performance and quality of life.[5] In the second year of the trial when the study article was held, lung function decline resumed, demonstrating that this therapy

is suppressive rather than remission inducing. With this result in hand, we approached Pfizer (which had acquired Merck) about changing the rapamune label to include LAM as an indication, and they initially declined due to the limited patent life and other considerations. We decided to approach with the FDA about our intent to file a Citizen's Petition to compel Pfizer to change the label. It turns out, the FDA is not very fond of that approach because the pathway to approval is not as well defined as more conventional routes, and after reviewing the MILES data, they invited Pfizer to submit an application for the label change. Pfizer was interested, and we transferred the Orphan Drug Designation that had been obtained on our IND to Pfizer. The FDA also advised us to apply for Breakthrough Designation, and that was also successful. Unfortunately, since we had not planned the trial with a LAM indication in mind, we had not assembled a Clinical Study Report (CSR) along the way that the FDA requires as part of the application. Volunteers on the trial team at the University of Cincinnati spent two years working with Pfizer to assemble that 2,500 page document on their weekends and evenings. The application was finally submitted to the FDA on Christmas eve in 2014, and was approved in June of 2015. FDA approval has been followed by approval by governmental agencies in over 40 other countries, including members of the European Union, Japan and many countries in South America, all on the basis of the MILES trial.

The NIH MIDAS Registry was established in 2015 to track the real world safety and efficacy of sirolimus in LAM through time (NCT02432560). These data which demonstrate the durable efficacy and long term safety of sirolimus use in LAM are currently being prepared for presentation at the 30th anniversary LAM Foundation Conference in September 2025. In addition, the NIH MILED (Multicenter Intervential LAM Early Disease Trial) is a randomized controlled trial that was launched in 2017 to determine if early, low dose sirolimus can prevent progression to more advanced stages while lung disease is still mild (NCT03150914). The last patient from that study completed their final visit in June 2025, and the data is currently being analyzed for presentation at the annual LAM meeting as well. If positive, the hope is that LAM clinicians start disease stabilizing therapy earlier, in a prophylactic mode, instead of waiting for the inevitable decline in lung function to an arbitrary level defined by the Guidelines, such as an FEV1 of 70% predicted.[7-9]

Several resources that were developed during MILES have proven to have lasting value. VEGF-D remains a clinically useful diagnostic and prognostic biomarker for LAM that limits the need for invasive measures and helps to stratify patients for trials.[10] The Rare Lung Disease Network that was formed (in part) for the MILES trial and other early studies continues to conduct studies together, to review difficult cases, and to hold international conferences.

The American Thoracic Society/Japanese Respiratory Society (ATS/JRS) LAM Guidelines were published in 2016 and 2017 to encourage clinicians in the community and in LAM clinics to treat patients with sirolimus, make use of VEGF-D as a diagnostic test, to not rely on CT alone for the diagnosis of LAM, to avoid the use of hormonal therapies or doxycycline pending definitive trials, to perform pleurodesis after the first pneumothorax, to consider patients with prior pleurodesis as viable candidates for transplantation, and when biopsy is necessary, to consider less invasive (including bronchoscopic) approaches before committing to thoracoscopic lung biopsy.[8,9]

Epilogue-There are a number of factors that have aligned to make rapid progress in LAM possible. LAM affects young women who are our granddaughters, daughters, mothers and wives, so there are frequently three generations of family members on both sides who are motivated to join the fight against the injustice of a non-self inflicted disease that mimics emphysema and strikes in the prime of life. Patient advocacy efforts by the LAM Foundation raised the profile of the disease in the medical and scientific communities by orders of magnitude. The LAM field has been exceedingly fortunate for the very high level of scientific interest that has been focused on the cellular pathways that become deranged in TSC and LAM for more than three decades because of its central role in cellular metabolism. The annual LAM Foundation conference has been a primary motivating force, by putting a human face on the disease and revealing the urgency and importance of the work to all who study LAM. The research funding that was generated through that meeting and other efforts produced preliminary data that formed the basis for larger federal grants, pivotal clinical trials and breakthrough discoveries. The expertise, flexibility and resources of academic health centers came through for patients with

this rare disease seeking a treatment based on a repurposed drug, which is not practical for pharma support, but proved to be the fastest route to new therapies. The altruism of physician scientists and coordinators who donated large amounts of time and effort to conduct trials, compile reports and other initiatives was exceeded only by the courage of patients who stepped forward to commit to two years on study with a 50% chance of assignment to placebo, while the promising drug being tested was freely available by prescription from any physician. In essence, MILES subjects donated 10-20% of their lung function to get an answer for all LAM patients and for all time. There is no question who the heroes are in this story.

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CHAPTER 17

END-OF-LIFE CARE IN RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSİYEL AKCİĞER HASTALIKLARINDA YAŞAM SONU BAKIMI

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END-OF-LIFE CARE IN RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSİYEL AKCİĞER HASTALIKLARINDA YAŞAM SONU BAKIMI

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ABSTRACT

Rare interstitial lung diseases (ILD) represent a heterogeneous group of respiratory diseases characterized by inflammation and fibrosis in the lung interstitium. Despite being perceived as rare diseases, ILD is the 40th most common cause of death globally, with a 52% increase in mortality over the last 10 years. The majority of these diseases progress over time, leading to respiratory failure and the need for comprehensive palliative care.

Increased dyspnea at rest, refractory hypoxemia, increased hospitalizations, decreased functional capacity are the most frequently observed signs of clinical deterioration. These signs indicate that it is time for end-of-life planning for the patients and families. Patients with advanced ILD experience a high burden of symptoms, especially at the end of life. Early integration of palliative care can significantly improve quality of life.

A comprehensive needs assessment in individuals with interstitial lung disease (ILD) is defined as a key component of the palliative care process. This assessment should address the physical, psychosocial and practical needs of not only patients but also informal caregivers and family members, including the timing and coordination of support services.

A multidisciplinary and individualized needs assessment approach rather than prognosis-based approaches is recommended in patients with ILD. It is important that this approach is carried out during stable phases of the disease rather than during acute exacerbations.

Advance Care Planning (ACP) is essential in ILD and should define patient values, preferences, and goals in advance and has been identified as an essential component of the palliative care process. Patients' choices for end-of-life management (e.g., mechanical ventilation, resuscitation) are shaped by prognostic understanding, disease burden, spiritual and existential concerns.

End-of-life care in rare ILDs requires a multidisciplinary and individualized approach centered on the needs of the patient and their family. The experience and collaboration of healthcare professionals is important in key areas such as symptom management, communication and advanced care planning. Early integration of palliative care not only improves symptom control and quality of life but also enhances active participation of patients and families in the care process.

In this context, incorporating current clinical guidelines and new pharmacological/psychosocial support approaches will improve the effectiveness of care. Furthermore, additional studies on the roles of multidisciplinary teams and the experiences of patients and their families will contribute to the development of patient-centered care models in the future.

Keywords: *Palliative care; End-of-life care; Interstitial lung diseases; Rare interstitial lung diseases; Patient centered care*

ÖZET

Nadir interstisyel akciğer hastalıkları (İAH), akciğer interstisyumunda inflamasyon ve fibrozis ile karakterize, heterojen bir hastalık grubunu temsil eder. Nadir görülen hastalıklar olarak algılansa da İAH küresel ölçekte 40. en sık ölüm nedenidir ve son 10 yılda mortalitede %52'lik bir artış gözlenmiştir. Bu hastalıkların büyük çoğunluğu zamanla ilerleyerek solunum yetmezliğine ve ileri evre palyatif bakım ihtiyacına neden olmaktadır.

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İstirahatte artan dispne, refrakter hipoksemi, artan hastane yatışları, fonksiyonel kapasitenin azalması en sık gözlenen klinik kötüleşme belirtileridir. Bu belirtiler, hastaya ve ailesine yaşam sonu planlamasının zamanının geldiğini ifade etmek için bir fırsat sunmaktadır. Erken entegre edilen palyatif bakım, yaşam kalitesini belirgin ölçüde artırabilmektedir.

İnterstisyel akciğer hastalığı (İAH) olan bireylerde bütüncül ihtiyaç değerlendirmesi, palyatif bakım sürecinin temel bileşenlerinden biri olarak tanımlanmaktadır. Bu değerlendirme, yalnızca hastaların değil, informal bakım verenlerin ve aile bireylerinin de fiziksel, psikososyal ve pratik gereksinimlerini kapsamlı bir biçimde ele almalı; ayrıca destek hizmetlerinin zamanlaması ve koordinasyonunu da içermelidir.

İAH hastalarında prognoza dayalı yaklaşımlardan ziyade, multidisipliner ve bireyselleştirilmiş bir ihtiyaç değerlendirme yaklaşımı önerilmektedir. Bu yaklaşımın, hastalığın akut alevlenme dönemlerinden ziyade, stabil evrelerde gerçekleştirilmesi önemlidir.

İleri bakım planlaması hasta değerlerinin ve bakım hedeflerinin önceden tanımlanmasını sağlamaktadır. Bu planlama, hastanın karar verme kapasitesi varken başlatılmalıdır. İAH hastalarında yaşam sonu yönetimine ilişkin tercihler (örneğin mekanik ventilasyon, resüsitasyon) bireyin prognoza ilişkin farkındalığı, hastalık yükü ve varoluşsal kaygılarından etkilenmektedir.

Nadir interstisyel akciğer hastalıklarında yaşam sonu bakımı, hasta ve ailesinin ihtiyaçlarını merkeze alan multidisipliner ve bireyselleştirilmiş bir yaklaşımı gerektirir. Semptom yönetimi, iletişim ve ileri bakım planlaması gibi temel başlıklarda sağlık profesyonellerinin deneyimi ve iş birliği önemlidir. Erken dönemde palyatif bakım entegrasyonu, semptom kontrolünü ve yaşam kalitesini artırırken, hastaların ve ailelerin bakım sürecine aktif katılımını da güçlendirir. Bu bağlamda, güncel klinik kılavuzlar ve yeni farmakolojik/psikososyal destek yaklaşımlarının da dikkate alınması, bakımın etkinliğini artıracaktır. Ayrıca, multidisipliner ekiplerin rolü ve hasta/hasta yakınlarının deneyimleriyle ilgili daha fazla çalışma yapılması, gelecekte hasta merkezli bakım modellerinin geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: *Palyatif bakım; Yaşam sonu bakım; İnterstisyel akciğer hastalıkları; Nadir interstisyel akciğer hastalıkları; Hasta merkezli bakım*

INTRODUCTION

Rare interstitial lung diseases (ILDs) represent a heterogeneous group of respiratory diseases characterized by inflammation and fibrosis in the lung interstitium. While some rare ILDs, such as lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH) and idiopathic pleuroparenchymal fibroelastosis (PPFE), may have a slow course, others may progress rapidly, leading to severe morbidity and mortality. Despite being perceived as rare diseases, ILD is the 40th most common cause of death globally, with a 52% increase in mortality over the last 10 years.[1] The majority of these diseases progress over time, leading to respiratory failure and the need for comprehensive palliative care.

This chapter aims to discuss the basic principles of end-of-life care in rare ILDs, including symptom control, communication strategies, psychosocial support, and ethical approaches. Since data specific to rare ILDs are scarce, the topic is approached using information from ILDs in general. When a chronic lung disease progresses to the end-of-life stage, the specific diagnosis may become less relevant. However, living with a rare or ultra-rare disease, with its unique uncertainties and concerns, can increase the overall burden, not only at the end, but throughout the entire course of the illness. These recommendations are provided to support healthcare providers until disease-specific data on rare ILDs become available.

DETERMINATION OF DISEASE COURSE AND PROGNOSIS

Prognosis is difficult to determine in rare ILDs. These diseases often present with a heterogeneous course; some progress slowly while others deteriorate rapidly. Unlike more common ILD such as Idiopathic Pulmonary Fibrosis (IPF), prognostic and predictive indicators for rare ILD are limited.

The need for urgent palliative care in symptomatic ILD patients is inevitable. An even greater challenge for clinics is to identify patients with ILD whose progression, while not yet severe, is unlikely to be reversible. For IPF, disease progression is typical, making early palliative care appropriate. On the other hand, patients with fibrotic sarcoidosis often have minimal symptoms and may achieve long-term stabilization, thus requiring less intensive palliative interventions. The most difficult group to determine the need for future palliative care is patients with non-IPF progressive fibrotic ILD with irreversible fibrosis as they may either stabilize or progress despite treatment.[2,3]

Factors Complicating Prognosis in Patients with ILD

Although there are limited data and small patient populations in the literature, the factors complicating prognosis in ILD patients are listed as below:

- Heterogeneous clinical course

- Underlying connective tissue diseases
- **Associated complications:** infection, pulmonary hypertension, pneumothorax

ILD is associated with a high disease burden and prominent symptoms, severely reduced quality of life and shortened life expectancy. Regardless of the cause or histological type, chronic ILD is characterized by cough, dyspnea, fatigue and diminished emotional well-being, which severely impact quality of life.[4,5] As the disease progresses, patients experience an increasing symptom burden, particularly dyspnea, which may be even more severe than that observed in end-stage lung cancer.[6,7]

The Most Common Indicators of Clinical Deterioration in Patients with ILD

Alveolar hypoventilation and hypercapnia are not common in the early phase of acute respiratory failure in ILDs. The respiratory muscles might be adapting to the increase in the loads of breathing due to lung pathology. In the more advanced stages of the disease, fatigue develops in the respiratory muscles, leading to carbon dioxide retention.[8] Acute respiratory failure often involves gas exchange abnormalities, with severe hypoxemia and pH shift to acidosis due to carbon dioxide retention, particularly in advanced stages where respiratory muscle fatigue sets in.[9]

Increased dyspnea at rest, refractory hypoxemia, increased hospitalizations, decreased functional capacity are the most frequently observed signs of clinical deterioration. These signs indicate that it is time for end-of-life planning for the patients and families. Patients and their families are often open to discussing current needs, but they may avoid conversations about future care. They want conversations about treatment to be "now and here"; however, they expect future care issues to be initiated by healthcare providers.[10]

Physical, psychological, social, or existential needs, whether explicitly stated or implied through clinical deterioration, should trigger consideration of a palliative approach. In addition, indirect indicators reflecting severity of disease or health care (e.g., frequent hospitalizations, respiratory failure, progressive loss of function) can be helpful in identifying individuals with such needs.[11]

SYMPTOM BURDEN AND PALLIATIVE APPROACHES

Patients with advanced ILD experience a high burden of symptoms, especially at the end of life. Dyspnea, cough, fatigue and anxiety are the most common symptoms. Early integration of palliative care can significantly improve quality of life.

Management of Dyspnea

Dyspnea is one of the most distressing symptoms in ILD and contributes to a negative cycle of inactivity, muscle loss, and physical deconditioning.[12] Data on the efficacy of opioid therapy in fibrotic ILDs are limited and the available evidence is heterogeneous. The existing evidence does not support the concern that low-dose opioids cause respiratory depression such as oxygen desaturation. Clinical experience suggests that these doses are effective for symptom relief in dyspnea management.[13] When the cause of dyspnea is irreversible or unresponsive to treatment, opioids are the first-line pharmacological agents for the palliative management of dyspnea, regardless of etiology. Systematic reviews show that oral and parenteral opioids significantly relieve the symptoms of dyspnea, while nebulized opioids are not proven effective, and thus not recommended. While symptomatic improvement can be achieved with oral morphine at doses as low as 10 mg per day, a ceiling effect in efficacy is observed at doses above 30 mg. Symptom relief can begin at 10 mg/day of oral morphine, but the maximum beneficial effect is achieved above 30 mg/day. Adverse effects such as sedation (drowsiness), nausea and constipation observed at these dose ranges are generally manageable and there is no increased risk of serious adverse effects (e.g., respiratory depression).[14]

When initiating opioid treatment for dyspnea, it is recommended to start with a short-acting formulation at a regular dose (e.g., 2.5-5 mg oral morphine or equivalent every 4-6 hours) to assess efficacy and tolerability. Once a stable and appropriate dose is reached, conversion to slow-release morphine may be considered for patient compliance and symptom control.[14] Although opioids are frequently used to relieve dyspnea, some patients may resist opioids due to fear of side effects or dependence. Similarly, physicians may under-prescribe opioids due to theoretical concerns about respiratory suppression.[13] The opioid ther-

apy for refractory dyspnea is summarized as diagram in Figure 1.[15]

Oxygen Therapy

Oxygen supplementation is considered the standard treatment for ILD patients with hypoxemia and dyspnea. It is recommended during exercise or at rest to alleviate symptoms. In randomized controlled trials with patients with fibrotic ILDs, oxygen therapy during daily activities has been shown to improve quality of life. However, in clinical practice, factors limiting the effective use of oxygen therapy include the inability to meet the high dose requirements of advanced patients and concerns about oxidative stress may lead to hypercapnia or progressive fibrosis. There is no scientific basis for these concerns, so the priority should be dyspnea relief when life extension is no longer possible, especially in advanced or end-stage diseases.[16,17]

Non-Invasive Ventilation

Non-invasive ventilation may provide temporary relief in selected patients but should be used with caution in the end-of-life period. Non-pharmacological options like non-invasive mechanical ventilation (NIMV) and pulmonary rehabilitation have demonstrated benefits in selected dyspnea patients.[18] Holistic and patient-centered approaches to dyspnea, especially in advanced ILD, are presented in Table 1.[1]

Cough Management

Persistent cough is a bothersome symptom that significantly reduces quality of life in patients with ILDs. Though treatment outcomes with pharmaceutical agents vary, certain neuromodulators, such as opioids, low-dose prednisolone, and gabapentin, may relieve symptoms in some patients, and thus may be tried empirically.[19]

Thalidomide has been reported to have benefit for cough in IPF in a small study but is not widely used. Pirfenidone has been observed to reduce cough frequency and improve quality of life; however, these results need confirmation in randomized controlled

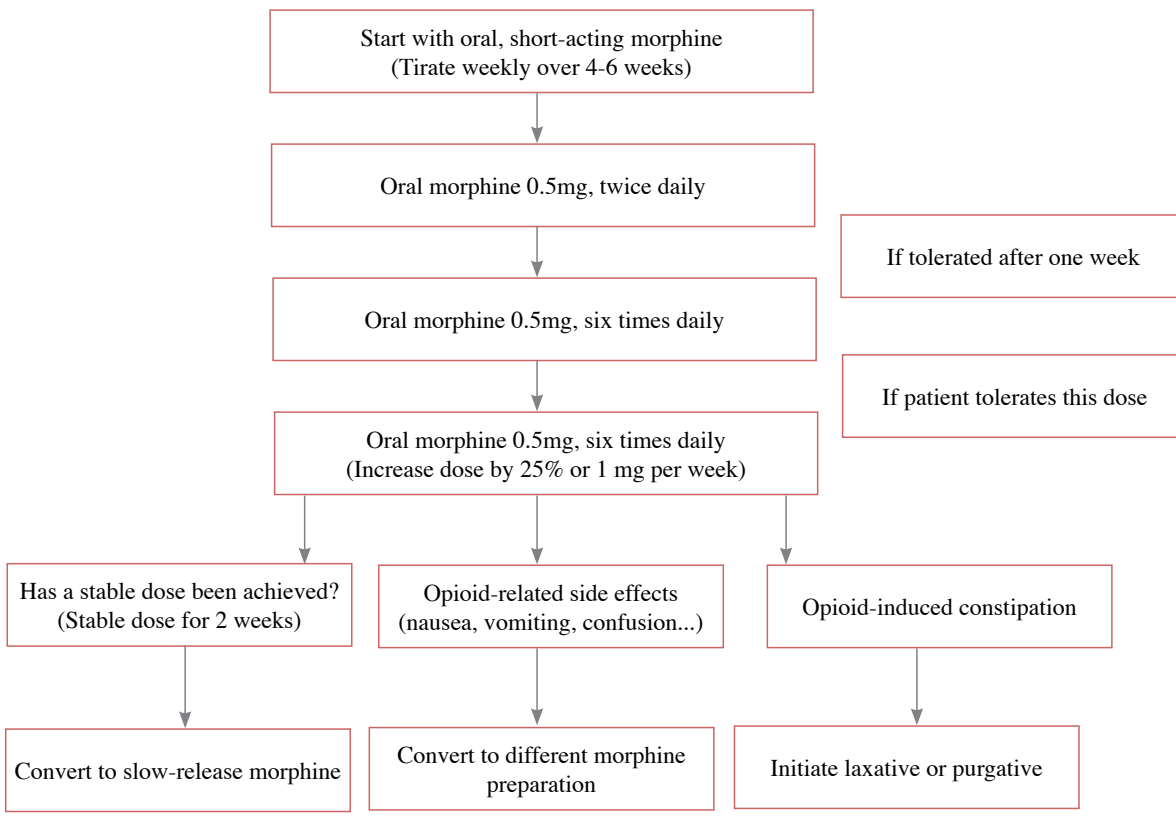


Figure 1. For a relief in refractory dyspnea, opioid therapy can be scheduled according to an approach in stepwise.[15]
Adapted from the article by Marciniuk DD, et al..

Table 1. Holistic and patient-centered approaches to dyspnea.[1]

Method	Description/Use
Pharmacological Approaches	
Treatment of reversible causes	Management of underlying causes such as infection, pulmonary hypertension
Low-dose opioids	Can be used to relieve symptoms of dyspnea
Benzodiazepines	Recommended if anxiety is a major factor
Supplemental oxygen therapy	In the presence of hypoxemia
Bronchodilators	Preferred if airflow obstruction is present
Non-pharmacological Approaches	
Cool air/fans	Reduce respiratory effort
Relaxation and breathing techniques	Control of respiration and anxiety management
Pulmonary rehabilitation	Improves physical endurance, supports symptom management
Positioning	Optimize respiratory muscle function
Reassurance/psychological support	Reduces anxiety and fear
Cognitive Behavioral Therapy (CBT)	For psychogenic dyspnea
Energy conservation strategies	Manage dyspnea during daily activity
Comfortable clothing	Prevent restriction of chest movement
Oral care	Prevents dry mouth and discomfort
Dyspnea Intervention Service	Multidisciplinary support

Adapted from the article by Kreuter M, et al..

trials. A new formulation of sodium cromoglycate has been shown to significantly reduce chronic cough in patients with IPF.[20]

Medications used in the treatment of persistent Cough in ILD are shown in Table 2.[21]

In addition to pharmacologic treatments, non-pharmacological measures such as managing gastroesophageal reflux disease, angiotensin-converting-enzyme inhibitors, or postnasal drip should also be addressed in ILD patients with persistent cough.[22]

Psychological Symptoms

Fibrotic ILD is characterized by cough and shortness of breath. Anxiety and depression are common, especially as symptoms worsen. The psychosocial burden affects both patients and caregivers, and the need for support often increases as the disease progresses.

Antidepressants and anxiolytics are recommended for the management of depression and anxiety. Antipsychotics may be necessary for managing delirium. In order to provide effective palliative care, comprehensive psychosocial assessment is crucial, including communication quality with family and caregivers. Establishing communication between family members is important to increase the support the patient receives from his/her social environment. Interventions like short-term psychotherapy, problem-solving therapy, and counseling can improve the patient's psychological well-being.[23]

Common psychological stressors causing anxiety

Table 2. Medications for persistent cough in ILD.[21]

	Medication	Dose	Remarks
Cough suppressants (antitussives)	Codeine	10-30 mg orally, 3-4x/day (max 120 mg/day)	Addictive potential
	Dextromethorphan	10-30 mg orally, 3-4x/day (max 120 mg/day)	Non-opioid, alternative to codeine
	Morphine Severe cough, in the terminal period	2.5-5 mg orally, every 4 hours	Used in palliative care
Local anesthetics (neu-ropathic cough)	Lidocaine (nebulize/spray)	2-5 mL of 2% every 6-8 hours	Temporary effect, risk of aspiration
Neuropathic cough treatment	Gabapentin	100-300 mg/day, Up to 600-1800 mg/day	For neuropathic cough
	Pregabalin	Start 25-75mg/day, Up to 150-300 mg/day	
Bronchodilators	Theophylline	100-200 mg orally, every 12 hours	Use if bronchospasm is present
Steroids	Prednisolone	10-40 mg/day orally, taper as needed	For inflammation
	Dexamethasone	4-8 mg/day orally/ intravenously	Useful if edema or compression is present
Other agents	Benzonatate Peripheral cough Receptor blocker	100-200 mg orally, every 8 hours, max 600 mg/day	Do not chew or swallow or open the capsule
	Thalidomide In palliative care	100 mg orally at bedtime	Sedative, teratogenic
Mucolytic	Acetylcysteine	600 mg orally 1-2x/day Nebulized 3-5 mL of 20% solution	

Adapted from the article by Morice AH, et al.

and depression in most patients include uncertainty about illness trajectory and treatment, fear of death and existential distress, loss of identity and roles, guilt or worry about family and regret about unfinished goals. Recent meta-analyses confirm the effectiveness of non-pharmacological interventions on anxiety and depression such as mindfulness-based cognitive therapy, meaning-centered psychotherapy, spiritual support, dignity therapy, social support, patient-centered communication and complementary medicine (e.g., aromatherapy, massage, reflexology, acupuncture, hypnotherapy, music therapy, reiki).[24]

All patients with advanced ILD should be offered evidence-based psychological interventions, regarding their current or foreseeable difficulties and risk of psychiatric morbidity. These not only reduce emotional distress but also help patients adjust and maintain quality of life.[24]

Delirium is frequently observed in late-stage ILD, especially during the end-of-life stage. It may be triggered by hypoxia, hypercapnia, medication side effects (opioids, corticosteroids), or systemic inflammation. Pharmacological treatment may be required in addition to patient comfort, management of pain and dyspnea, regulation of nutrition, and reduction of distress. Medications used in the treatment of delirium are summarized in Table 3.[25,26]

It is often difficult to distinguish symptoms such as depression, anxiety and delirium from the terminal stages of the disease. Therefore, palliative care providers should be in contact with psychiatrists for

Table 3. Medications for Delirium in ILD.[25,26]

	Medication	Dose	Remarks
Antipsychotics (in hyperactive delir-ium)	Haloperidol	0.5-2 mg oral/IV/IM, repeat every 30-60 minutes	Monitor ECG (QT prolongation risk)
Atypical antipsy-chotics	Risperidone Olanzapine Quetiapine	0.25-1 mg orally 2.5-5 mg orally/IM 12.5-50 mg orally	Preferred in haloperidol-intolerant patients Risk of sedation in hypoactive delirium
Benzodiazepines (terminal agitation)	Lorazepam Midazolam	0.5-1mg oral/SC/IV 1-2.5 mg SC/IV infusion; 0.5-2 mg/hour	Use with antipsychotics to prevent worsening delirium alone
Palliative Sedation	Midazolam Propofol	SC/IV infusion In intensive care conditions	Refractory delirium and uncontrolled symptoms

IV: *intravenous,* ***IM:*** *intramuscular,* ***SC:*** *subcutaneous,* ***ECG:*** *electrocardiogram.*
Adapted from the article by Agusti A, et al. and Cherny NI, et al..

comorbidities that require psychopharmacological and psychotherapeutic interventions and affect the patient's quality and length of life.

Palliative Sedation

Palliative sedation is administered to terminally ill patients when they experience severe pain and unbearable suffering. Sedation refers to the use of soothing/sedative medications aimed at alleviating or eliminating pain, discomfort, and anxiety, based on established procedures and guidelines.

Palliative sedation (PS) is used at the end of life to alleviate unacceptable pain that is refractory to other therapies, or when other therapies are not expected to help in a given timeframe. PS is employed when traditional opioid-based treatments fail to adequately control pain or cause severe complications. It is also preferred for alleviating physical symptoms such as delirium, pain, dyspnea, nausea, and others. PS is often associated with agitation in the last days and hours of the patient's life.[27]

Midazolam is the preferred first-line sedative and is administered by intravenous (IV) or subcutaneous infusion. Midazolam should be started with 0.5-1 mg IV every 3-4 minutes until the desired sedation depth is achieved. Dose adjustments are necessary for elderly or patients with liver/kidney impairment.[28]

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist used for sedation in mechanical ventilated perioperative patients. Clinical case studies show that it has provided benefit in intractable pain and management of delirium and can be safely used in palliative care units. In addition, dexmedetomidine offers "wakeful sedation" and is useful for agitation without suppressing respiration. Unlike benzodiazepines and opioids, it allows patients to remain oriented and communicative.[28]

As for propofol, there is limited data on its use in palliative sedation. These studies suggest that IV propofol is safe and effective in experienced hands, particularly in intensive care.[28]

ADVANCE CARE PLANNING AND COMMUNICATION

Advance Care Planning (ACP) is essential in ILD and should define patient values, preferences, and goals in advance and has been identified as an essential component of the palliative care process.[29] Patients' choices for end-of-life care (e.g., mechanical ventilation, resuscitation) are shaped by prognostic understanding, disease burden, spiritual and existential concerns. ACP improves patient engagement, preference documentation, and perceived control over illness. Importantly, preferences may evolve over time and should be revisited regularly.[30,31] Effective ACP requires skilled, trusted healthcare professionals, involvement of caregivers (with patient's consent), discussions tailored to patient readiness and condition. Talks should

be conducted at the patient's convenience and with the participation of caregivers.[32,33]

Early planning and proactive communication about disease progression and end-of-life care needs improve adaptation and reduce uncertainty in patients and families.[34]

Identifying Goals of Care

A comprehensive needs assessment in individuals with ILD is defined as a key component of the palliative care process. This assessment should address the physical, psychosocial and practical needs of not only patients but also informal caregivers and family members, including the timing and coordination of support services. The literature emphasizes that this process should be comprehensive, accessible (e.g., including home visits), interdisciplinary and organized to avoid redundancy.[35,36]

A multidisciplinary and individualized needs assessment approach rather than prognosis-based approaches is recommended in patients with ILD. It is important that this approach is carried out during stable phases of the disease rather than during acute exacerbations. In the literature, there are three systematic models described for ILD patients: NAT-ILD (a validated needs assessment tool), ILD-palliative care package (a multidisciplinary and clinician-focused decision support tool) and IPOS (Integrated Palliative Care Outcome Scale to assess physical and emotional symptoms and communication/practical issues). These structured assessment approaches support a more effective identification and management of the needs of both patients and caregivers.[36]

Legal and Ethical Documentation

Although all discussions are relevant to the broad spectrum of severity, the needs of patients with advanced or end-stage ILD are highly variable. Dignified end-of-life care and death mean avoiding futile interventions such as invasive ventilation, extracorporeal membrane oxygenation and resuscitation in dying patients. However, the judgments and expectations of patients with end-stage disease and their caregivers should be recognized and taken into account.[37]

Mechanical ventilation, especially when applied invasively, is associated with extremely high mortality in patients with IPF. Therefore, invasive mechanical ventilation should be avoided in the majority of patients with IPF-related respiratory failure. In such patients, NIMV should be prioritized. The decision for intubation should be carefully evaluated considering the patient's clinical condition, high mortality risk and prognosis. In this process, open and transparent communication should be established with the patient and their family, and a patient-centered approach should be adopted in shared decision-making.[38]

Due to the lack of sufficient evidence regarding single or bilateral lung transplantation, the IPF guideline refrains from providing recommendations and states that further evaluation should be based on results from future randomized controlled trials. However, all patients with moderate to advanced IPF who do not have significant comorbidities, or absolute contraindications should be presented with lung transplantation as a potential treatment option. Considering the long waiting lists, timely referral to a suitable transplant center is of utmost importance.[39]

Issues related to the beginning and end of life are among the most controversial topics in bio-ethics and bio-law. The question of who the primary decision-maker should be in end-of-life care, as well as concepts such as quality of life, futile or ineffective treatments, fair allocation of limited resources, life-sustaining treatments (withholding, withdrawing, patient refusal), advance directives, and the right to a dignified death frequently come to the forefront.

Within the framework of the "right to die with dignity," which is among the patient rights, it is a fundamental human right that patients in the final stages of life receive care in conditions that respect human dignity, benefit from all rights they are entitled to as individuals and are provided with high-quality care and treatment in line with autonomy and privacy rights.

Although euthanasia is not legal under Turkish law, it is acknowledged that patients in the terminal phase of an incurable disease should receive care that ensures their autonomy, comfort, and dignity. The Patient Rights Regulation clearly states that even if it is not possible to save the patient's life or preserve their health, there remains an obligation to alleviate or eliminate suffering.[40,41]

MULTIDISCIPLINARY APPROACH

The multidimensional goals of palliative care require interdisciplinary collaboration and a wide range of competencies. Any member of the clinical team ex-

perienced in compassionate and holistic patient care can lead the palliative care process in interstitial lung disease (ILD). However, most pulmonologists may not have received specific training in this area or may struggle to dedicate time to such needs, leading to delayed recognition of the need for palliative care. Similarly, palliative care specialists may lack sufficient knowledge of the clinical course and management strategies specific to ILD.

Therefore, an integrated and multidisciplinary team approach is recommended to effectively address the needs of patients and caregivers. In this context, ILD nurses working in appropriate healthcare systems can play a key role in the palliative care process. The involvement of both ILD-specialized nurses and palliative care nurses has been shown to improve the quality of patient care. Access to a specialized ILD nurse can contribute to significant improvements in quality of life for both patients and caregivers by increasing the effectiveness of care services.[42,43]

The disciplines required in the multidisciplinary team for palliative care in ILD and their core responsibilities are given in Table 4.

Due to the unpredictable course of ILD, especially idiopathic pulmonary fibrosis (IPF), with some patients experiencing relative stability and others suffering faster decline in lung function and/or acute exacerbations, early evaluation of end-of-life care preferences and initiation of palliative care are recommended.[39] It has been reported that end-of-life decisions in IPF patients are mostly made in the advanced stages of the disease and only 14% of patients are referred to palliative care services. Even in ILD patients with severe oxygen dependency, end-of-life care discussions were held in only 41% of cases.[7]

ETHICAL AND CULTURAL APPROACHES

End-of-life decisions should be addressed within the framework of ethical principles, focusing on patient autonomy and the principle of non-maleficence. The feasibility and effectiveness of palliative care are influenced not only by the clinical characteristics of the primary disease but also by multidimensional factors such as socioeconomic conditions, cultural and religious values, and the organization of healthcare services. Particularly in respiratory diseases such as pulmonary conditions, the inability to adequately control tobacco use and environmental air pollution, along with demographic variables like an aging population, significantly increases the disease burden in low- and middle-income countries.[44]

Religious, cultural and other belief systems are especially important in a patient-centered palliative care approach. The religious and cultural values, judgments and expectations of patients with end-stage diseases and their caregivers should be recognized and considered when making decisions about the withdrawal of mechanical ventilation or intensive care support. Spiritual needs are complex and often overlap with social or psychological needs. While a patient's religious belief may be recorded for administrative purposes, this may not necessarily be addressed in clinical discussions. For shared decision-making regarding the involvement of spiritual leaders in palliative care, physicians should discuss their patients' religious identities.[37,45]

Table 4. Members in the multidisciplinary team and the core responsibilities of each member.[42]

Team Member	Core responsibilities
Pulmonologist	Disease management, prognosis determination
Palliative care specialist	Symptom control, patient and family support
Nurse and respiratory therapist	Day care support, education, reassurance
Psychologist/Social worker	Psychosocial support, bereavement support
Spiritual counselor	Providing religious, cultural and spiritual support

Adapted from the article by Sinclair C, et al..

THE GRIEVING PROCESS AND SUPPORT

Following the death of a beloved one, almost 15% of family members and caregivers experience complicated grief reactions manifesting as significant psychological issues. There are no known risk factors to reliably predict this response. Therefore, healthcare teams should establish a relationship with caregivers prior to the patient's death. As seen in other terminal illnesses, this enables more effective monitoring and support of the grieving process.[7]

CONCLUSION

End-of-life care in rare ILDs requires a multidisciplinary and individualized approach centered on the needs of the patient and their family. The experience and collaboration of healthcare professionals is important in key areas such as symptom management, communication and advanced care planning. Early integration of palliative care not only improves symptom control and quality of life but also enhances active participation of patients and families in the care process. In this context, incorporating current clinical guidelines and new pharmacological/psychosocial support approaches will improve the effectiveness of care. Furthermore, additional studies on the roles of multidisciplinary teams and the experiences of patients and their families will contribute to the development of patient-centered care models in the future.

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CHAPTER 18

TELEMEDICINE OPPORTUNITIES FOR RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARI İÇİN TELE-TIBBIN SAĞLADIĞI FIRSATLAR

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TELEMEDICINE OPPORTUNITIES FOR RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARI İÇİN TELE-TIBBIN SAĞLADIĞI FIRSATLAR

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ABSTRACT

Telemedicine leverages information and communication technologies (ICT) to provide remote consultation, monitoring, and personalized care, thereby overcoming barriers to healthcare access, particularly for patients living in geographically isolated areas. By eliminating the need for travel, it enables earlier diagnosis, timely treatment, and regular follow-up, while simultaneously reducing patient burden and lowering healthcare costs.

Telemedicine systems are generally divided into two main categories: synchronous (real-time) and asynchronous (store-and-forward). Synchronous interactions allow immediate patient-physician communication, whereas asynchronous systems enable data sharing and expert consultation across different timeframes, offering flexibility and efficiency. Integration with electronic health records (EHR) facilitates longitudinal tracking of patient data, contributing significantly to clinical practice.

In the context of rare interstitial lung diseases (ILDs), where expertise is often concentrated in a limited number of referral centers, telemedicine gains particular importance. It can bridge primary and secondary care providers with referral centers, allowing patients to access expert opinions without the need for long-distance travel. Virtual multidisciplinary team meetings may support shared decision-making and enhance knowledge exchange, ultimately improving both patient outcomes and physician education. Furthermore, teleconsultations may help patients feel more secure and reduce the sense of isolation commonly associated with rare diseases.

Despite these advantages, telemedicine faces challenges such as technological inequities, concerns over data security, and the need for robust legal and ethical frameworks. Addressing these barriers is critical for sustainable integration of telemedicine into routine clinical practice. Meanwhile, advances in digital health tools and artificial intelligence hold the potential to strengthen remote monitoring, enable earlier recognition of disease progression, and optimize personalized care strategies.

In conclusion, telemedicine represents a promising and increasingly indispensable tool in the management of rare ILDs. Through remote consultation, digital data sharing, and virtual multidisciplinary collaboration, it may not only improve access to specialized healthcare but also reinforce a more patient-centered healthcare system.

Keywords: *Telemedicine; Interstitial lung disease; Rare interstitial lung disease; Remote monitoring; Digital health technologies; Digital health*

ÖZET

Tele-tıp, bilgi ve iletişim teknolojilerinden (ICT) yararlanarak uzaktan danışmanlık, izleme ve kişiselleştirilmiş bakım sunmakta ve özellikle coğrafi olarak izole bölgelerde yaşayan ya da uzman merkezlere ulaşımı kısıtlı olan hastalar için sağlık hizmetlerine erişimdeki engelleri aşmaktadır. Seyahat gerekliliğini ortadan kaldırarak daha erken tanı, zamanında tedavi ve düzenli takip imkânı sağlarken, aynı zamanda sağlık kuruluşlarının üzerindeki hasta yükünü azaltmakta ve sağlık hizmeti maliyetlerini düşürerek sistemin sürdürülebilirliğine katkıda bulunmaktadır.

Tele-tıp sistemleri genel olarak senkron (gerçek zamanlı) ve asenkron (veri aktarımına dayalı) olmak üzere iki ana gruba ayrılmaktadır. Senkron etkileşimler hasta-hekim arasında anında görüşme imkânı sunarken, asenkron sistemler farklı zaman dilimlerinde veri paylaşımını ve uzman görüşü alınmasını mümkün kılarak esneklik ve verimlilik sağlar. Elektronik sağlık kayıtları (EHR) ile entegrasyon, hasta

verilerinin uzunlamasına takibini kolaylaştırmakta, klinik karar destek sistemleriyle birlikte kullanıldığında ise bakımın kalitesini artırma potansiyeli taşımaktadır.

Nadir interstisyel akciğer hastalıkları (İAH) bağlamında, uzmanlık bilgisinin genellikle sınırlı sayıdaki referans merkezinde toplanmış olması tele-tıbbın önemini daha da artırmaktadır. Tele-tıp, birinci ve ikinci basamak hekimleri ile referans merkezler arasında köprü kurabilir ve hastaların uzun mesafeler katetmeden uzman görüşüne ulaşabilmesine imkân sağlayabilir. Ayrıca sanal multidisipliner kurul toplantıları, ortak karar alma süreçlerini destekleyebilir, bilgi paylaşımını kolaylaştırarak hem hasta sonuçlarını hem de hekimlerin sürekli mesleki gelişimini destekleyebilir. Tele-konsültasyonlar aynı zamanda hastaların kendilerini daha güvende hissetmelerine ve nadir hastalıklarla ilişkili yalnızlık duygusunun azalmasına katkıda bulunabilir.

Bununla birlikte, tele-tıp uygulamaları teknolojik eşitsizlikler, veri güvenliği kaygıları ve güçlü hukuki/etik çerçeve gereksinimleri gibi engellerle karşı karşıyadır. Bu sorunların çözülmesi, tele-tıbbın klinik uygulamalara sürdürülebilir bir şekilde entegre edilebilmesi açısından kritik önemdedir. Öte yandan, dijital sağlık araçları ve yapay zekâdaki gelişmeler, uzaktan izlemeyi güçlendirme, hastalık progresyonunu daha erken tanıma ve kişiselleştirilmiş bakım stratejilerini optimize etme potansiyeli taşımaktadır.

Sonuç olarak, tele-tıp, nadir İAH'ların yönetiminde umut verici ve giderek daha vazgeçilmez bir araç haline gelmektedir. Uzaktan danışmanlık, dijital veri paylaşımı ve sanal multidisipliner işbirliği yoluyla hem uzman sağlık hizmetlerine erişim iyileştirilebilir hem de hasta merkezli bir sağlık sistemi güçlendirilebilir.

Anahtar Kelimeler: *Tele-tıp; İnterstisyel akciğer hastalıkları; Nadir interstisyel akciğer hastalıkları; Uzaktan hasta izlemi; Dijital sağlık teknolojileri; Dijital sağlık*

CASE PRESENTATION

A 31-year-old female, a non-smoker with no significant exposure history, works as an office employee. She had been experiencing dyspnea for the past 10 years, which had progressively worsened. Recently, her shortness of breath and hypoxemia increased, leading to admission to the intensive care unit last month.

The patient sought a second opinion regarding her diagnosis. Living far from the recommended tertiary center and being dependent on continuous oxygen support, she was on the verge of giving up. Fortunately, during her search for alternatives, she discovered that the pulmonologist offered a telemedicine option via video consultation. This method was used for both the initial evaluation and subsequent follow-ups.

Her medical history revealed that at 1.5 years of age, she had been evaluated for delayed motor development, specifically, an inability to hold her head up, although no respiratory symptoms were noted at the time. A familial predisposition to disease was later recognized, as her aunt, uncle, and sister had all been diagnosed with pulmonary alveolar microlithiasis (PAM).

Chest X-rays from the last 10 years were reviewed remotely through the patient's personal account on the national digital health platform (e-Nabız). Radiological images revealed diffuse hyperdense opacities in both lungs. Spirometry and DLCO, last performed 8 years ago, showed a restrictive pattern (FEV_1/FVC: 84%, FVC:1.46 L [39% predicted], DLco:19%, DLco/VA:45%). Thoracic computed tomography (CT) demonstrated widespread calcifications and consolidations. Although she was previously evaluated as a candidate for lung transplantation, she had declined due to concerns about procedural risks.

During the second-opinion consultation, the pulmonologist conducted a real-time video consultation with the patient, obtained a detailed history, and reviewed her available investigations. Given the diagnosis of this rare and currently untreatable condition, the physician chose to use teleconsultation to facilitate access to an international PAM specialist center.

With the patient's informed consent, the consultation was recorded and later reviewed asynchronously by Prof. Francis McCormack (University of Cincinnati) in a physician-to-physician remote consultation (effectively, a third opinion). This allowed the patient to be assessed as though she had physically visited the reference center. The real-time anamnesis was translated by the primary physician, and prior investigations were reviewed via screen sharing of the patient's e-Nabız profile, all conducted with full consent (Figure 1).

The distance between the patient's home and the primary physician's hospital was 750 km, while the distance between the two consulting physicians' institutions was 9,102 km.

INTRODUCTION

Telemedicine refers to the delivery of healthcare services remotely through information and communication technologies (ICT). While telehealth encompass-



Figure 1. Teleconsultation for a patient with pulmonary alveolar microlithiasis (PAM). A real-time video consultation was conducted with Prof. Francis X. McCormack (University of Cincinnati) using video conferencing and save-and-share methods. After a detailed history, the patient's examinations were jointly reviewed. The distance between the patient's home and the primary physician's hospital was 750 km, while the distance between the two consulting physicians' institutions was 9,102 km.

es a broader scope, including public health practices such as prevention, health promotion, and health education, telemedicine specifically focuses on clinical applications, particularly diagnosis, treatment, and follow-up care.[1] It serves as an alternative to in-person medical evaluation and includes services such as patient education, chronic disease management, medical consultations, image sharing, electronic prescription issuance, and clinical decision support.

The World Health Organization (WHO) defines telemedicine as "the delivery of healthcare services by all healthcare professionals where distance is a critical factor, using ICT for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers, all in the interest of advancing the health of individuals and communities."[2] Accordingly, telemedicine has the potential to play a key role in reducing disparities in healthcare access, especially in rural and underserved regions. It enables patients to consult specialists without the need for travel, reduces the strain on healthcare systems, and provides a cost-effective alternative under certain conditions, making it a widely implemented and increasingly accepted approach.

Although the concept of telemedicine is not new, rapid advancements in ICT have brought remote healthcare delivery to the forefront, particularly in areas with physician shortages or in efforts to promote equity in healthcare access. Telemedicine has been both a consequence and a catalyst for a long-standing socio-technical transformation in medical practice.[3] This transformation accelerated dramatically during the COVID-19 pandemic, when face-to-face healthcare was restricted due to infection risks. Telemedicine thus emerged as a necessity rather than a convenience. Throughout the pandemic, it became a vital tool for patient monitoring, limiting virus transmission, enabling early diagnosis and treatment of infected individuals, and, most importantly, ensuring uninterrupted care for patients with multiple chronic conditions.[4-7]

In the post-pandemic period, telemedicine services have become permanent in many countries, particularly in the United States, where they have been formally integrated into national healthcare policies.[8] Despite these positive developments, challenges remain as regulatory inconsistencies, technological inequality, and lack of provider training continue to hinder widespread adoption in some regions.[3]

MODELS OF TELEMEDICINE

Telemedicine applications can be categorized into two primary models based on the timing of data exchange: synchronous (real-time) and asynchronous (store-

and-forward) systems. This classification reflects the timing of interaction between the patient and physician and has critical implications for both the required technological infrastructure and the clinical use case.[9]

Synchronous Systems (Real-Time Communication)

In synchronous systems, healthcare services are delivered through real-time communication between the patient and the healthcare provider. This interaction typically occurs via video conferencing, telephone calls, or live chat platforms.[10]

The main advantages of synchronous telemedicine systems include:

- Immediate feedback between physician and patient,
- Rapid response for emergencies or complex clinical decisions,
- An interactive structure that enhances patient satisfaction.

These systems are commonly used in virtual consultations, psychiatric evaluations, video-based chronic disease management, and remote rehabilitation programs.[11] However, both the patient and healthcare provider must be online at the same time, which may lead to accessibility challenges or scheduling limitations.

Asynchronous Systems

In asynchronous systems, the exchange of medical data and information occurs with a time delay. Patients upload their information, such as symptom logs, digital images (e.g., CT scans, MRI, X-rays), laboratory results, or messages, to electronic platforms, which healthcare providers then review at a later time.[12]

This approach is often referred to as the "store-and-forward" method. The benefits of asynchronous systems include:

- Elimination of time and location constraints,
- More flexible workload management for healthcare professionals,
- Suitability for data archiving, comparative evaluation, and AI-assisted analysis.

Asynchronous telemedicine is particularly effective in specialties that rely heavily on imaging and data analysis, such as dermatology, radiology, pathology, and sleep medicine.

INTEGRATION WITH DIGITAL HEALTH RECORD SYSTEMS

The effectiveness and sustainability of telemedicine applications are not limited to the availability of communication technologies such as video conferencing or text-based messaging. For truly effective digital healthcare service delivery, it is crucial that these systems work in integration with electronic health record (EHR) systems.[13] In today's modern healthcare systems, a digital health profile is created for each individual; these profiles contain multidimensional data such as diagnostic information, prescriptions, laboratory and imaging results, hospital visits, and treatment plans. Telemedicine platforms' real-time and uninterrupted access to these digital health records enable healthcare professionals to conduct more comprehensive, personalized, and secure patient assessments.

Sweden is one of the earliest adopters of telemedicine and eHealth technologies. Remote electrocardiogram (ECG) transmission was first tested in 1915, and by the 1960s, services like EEG and teleradiology were being developed.[14] The use of digital health records together with telemedicine started to grow with Sweden's national health portal, *1177 Vårdguiden*, which was launched in 2003. Through this system, patients can easily book appointments, check lab results, message their doctors, and get medical advice remotely using digital tools. Sweden showed early on that a centralized and connected digital health system can work successfully.[15]

Telemedicine initiatives in Australia began gaining attention in the early 1990s, primarily aimed at improving access to healthcare services in rural and remote areas. In 1996, the Australian House of Representatives Standing Committee on Family and Community Affairs launched a national inquiry titled "Health Information Management and Telemedicine", marking a significant step in national-level engagement. During this period, several pilot projects were implemented across different states.[16] Subsequently, Australia launched its national digital health system, *My Health Record*, in 2012 based on an opt-in (voluntary participation) model. However, due to low enrollment rates, the system transitioned to an opt-out model in 2019, meaning all citizens were automatically enrolled unless they actively chose to withdraw. The system includes prescriptions, pathology and imaging reports, and is designed to function in harmony with telemedicine applications.[17] The

COVID-19 pandemic brought a major transformation in Australia's primary healthcare system by accelerating the integration of digital technologies. Telehealth and virtual care models were rapidly adopted and incorporated into conventional face-to-face healthcare services.[18] Finally, in 2023, a mobile application called "My Health App" was introduced to further improve user access to health records and services.[19]

In the United States, although there is no centralized national digital health system, healthcare services have significantly benefited from private-sector innovations. One notable example is the MyChart platform, which allows patients to easily schedule virtual appointments, view their medical results, request prescription refills, and communicate directly with their doctors, all from a single digital interface.[20] The widespread use of MyChart after the COVID-19 pandemic has helped improve patient engagement, reduce unnecessary clinic visits, and streamline access to care, particularly for those with chronic conditions or mobility challenges.[21]

In Germany, the implementation of the *Elektronische Patientenakte (ePA)* in 2021 marked a major step toward a more transparent and accessible healthcare system. Initially based on voluntary participation, the program has switched to an automatic registration model in order to increase usage. Through the ePA, citizens can now view their medical history, receive follow-up care more efficiently, and avoid redundant testing which is facilitated by the digital sharing of information among healthcare providers. By connecting patients, family doctors, and specialists on a unified platform, the ePA supports more coordinated and personalized care throughout the healthcare journey.[22]

In Turkey, the e-Nabız system was introduced by the Ministry of Health in 2015 and rapidly expanded during the COVID-19 pandemic. The system enables the digital sharing of laboratory results, prescriptions, radiological images, and clinical notes. In the study conducted by Çetin et al., who assessed patients through video conference-based telemedicine in the pulmonary diseases' clinic, more than half of the patients had previous diagnostic tests available, which were successfully reviewed.[5]

Telemedicine is not merely a communication tool, but a vital component of a broader digital health ecosystem that must be integrated with data management systems, patient monitoring technologies, and AI-driven decision support tools. However, this integration is not solely technical, it also involves legal and ethical considerations. Safeguarding personal health data and ensuring compliance with national regulations are essential for maintaining the security, trustworthiness, and long-term sustainability of these systems.

In parallel with the adoption of AI-driven technologies, a humanistic approach must remain central to every stage of the process, treating the individual not merely as a patient, but as a person. Equipping physicians with strong communication skills and training in the patient–physician relationship is just as important as using digital tools for achieving diagnostic precision.

TELEMEDICINE IN RARE ILDS

As mentioned throughout this book, rare ILDs represent a heterogeneous group of disorders, some affecting fewer than one in a million people, and may exhibit diverse clinical characteristics even within the same disease entity. Due to their rarity, these conditions are often associated with limited medical expertise, insufficient research and data, and a lack of specialized care centers and services. Diagnosing and managing this often-neglected group of diseases is challenging for both patients and healthcare providers. Few studies focusing on patient perspective and disease burden are presented in detail in the relevant section of the current book.

Numerous studies have been published regarding the successful use of telemedicine for clinical purposes in lung diseases.[23] Teleconsultation, defined as consultation via video and/or audio using information and communication technologies, includes remote symptom monitoring, tracking vital signs and functional parameters through digital technologies, remote education, referral, and tele-rehabilitation, all of which are commonly used in pulmonary practice.[24] While most of these studies have focused on asthma, COPD, and sleep-related respiratory disorders, telemedicine is also used for ILDs.[25-31] While phone or video-based applications are available, the advantages of video consultations have emerged due to increased contact between patients and healthcare professionals.[32-34]

The majority of studies focus on telemonitoring and home spirometry. It has been noted that telemonitoring contributes to maintaining biopsychosocial health in patients with significant respiratory complaints, those on oxygen therapy, and those with a high dis-

ease burden. A randomized controlled trial in patients with idiopathic pulmonary fibrosis (IPF) demonstrated positive results regarding home monitoring programs, improving psychological health, enabling personalized treatment decisions, and achieving high patient satisfaction.[27] In a survey investigating healthcare services during the COVID-19 pandemic in ILD patients, it was found that in-person consultations were largely replaced by phone-based telemedicine applications. Most patients reported positive experiences, including the elimination of travel time and the ability to receive care in a safe environment.[29]

Home care for ILD patients has the potential to reduce inequality in access to specialist centers, lighten the burden on healthcare systems, improve quality of life, and help prevent adverse outcomes by facilitating the early detection of acute exacerbations.[35] However, there is limited research on tele-rehabilitation in ILDs, though positive results regarding functional and clinical parameters have been shared.[30,31] The Portuguese Pulmonology Society's recommendations for the use of telemedicine in lung diseases, including ILDs, list several suggestions for teleconsultation, emphasizing appropriate patient selection, evaluation of symptoms and disease using valid questionnaires, monitoring treatment adherence and side effects, tracking vital and functional parameters, evaluating comorbidities, and using telemedicine for smoking cessation support.[36]

A recent review discusses the use of telemedicine in ILDs from three perspectives: remote patient monitoring, enabling self-monitoring, and facilitating communication among healthcare providers. In this article, the term "Internet of Medical Things (IoMT)" refers to teleconsultations, virtual multidisciplinary team meetings (MDTs), digital health information exchange, online peer support, home monitoring, and telerehabilitation. While these tools were found to be both feasible and reliable, their widespread implementation in clinical practice is still considered insufficient. This underscores the need for further research in larger, real-world cohorts to confirm and clinically validate the promising results of pilot studies and facilitate their integration into routine.[37]

Although there have been no specific studies on telemedicine applications for rare ILDs, these data can be considered relevant to rare ILDs due to the similar rationale and disease process management. Moreover, rare ILDs often require patients to be followed up in specialized centers located at a considerable distance from them. The absence of effective treatment may also lead patients to avoid clinical visits. In summary, the difficulty and burden of traveling to a specialist center highlight the significant advantages telemedicine may offer in the management of rare ILDs.

Both patients and healthcare providers may face challenges during follow-ups on rare ILDs. Telemedicine can be a crucial alternative for supporting local experts in terms of information and experience, allowing them to receive training about the disease and patient perspectives. A recent study based on video consultations with rare ILD patients, where recorded sessions were shared during a congress session and discussed among healthcare providers, emphasized that telemedicine could be a key tool in post-graduate medical education, particularly in sharing knowledge and experience about diseases that are less frequently encountered in medical practice.[38]

CHALLENGES AND ETHICAL ISSUES IN TELEMEDICINE

Telemedicine has significantly improved healthcare delivery by enhancing access, reducing delays caused by travel, and minimizing the need for face-to-face interactions, particularly during the COVID-19 pandemic. However, its rapid expansion has revealed several technical and ethical challenges that must be addressed to ensure its safe, effective, and equitable use in routine clinical practice.

A key technical barrier is unequal access to technology. Individuals living in rural areas or with limited socioeconomic resources may lack adequate internet connectivity or the digital literacy required to participate in remote consultations. This digital divide risks exacerbating existing inequalities in healthcare access and outcomes.[39]

Remote consultations also present clinical limitations. The absence of physical examination in virtual settings may impair diagnostic accuracy, particularly for conditions requiring lung auscultation, chest palpation, or detailed neurological assessments. For instance, early signs of interstitial lung disease, such as inspiratory crackles, or subtle neurological deficits might be missed without in-person evaluation.

Data privacy and cybersecurity represent additional

critical concerns. Without robust encryption and authentication protocols, telemedicine systems remain vulnerable to unauthorized access and data breaches. Protecting patient confidentiality is essential for maintaining trust in digital healthcare.[37]

Obtaining informed consent is a crucial component for patient data management, and this practice is rooted in the ethical principle of non-maleficence, which focuses on minimizing harm.[40] From an ethical standpoint, informed consent becomes more complex in virtual care environments. Patients must clearly understand the potential limitations and risks of remote consultations. This necessitates the development of standardized digital consent procedures that ensure transparency and patient autonomy. In the study of Thamula et al., immediate electronic capture of the consents given by participants found useful to facilitate accurate and efficient onward sharing of data and samples according to participant preferences that can be easily electronically queried.[41]

Legal and professional responsibilities are also evolving. Determining liability in cases of medical error, particularly in cross-border or inter-jurisdictional settings, remains unclear in many regions. Furthermore, establishing consistent standards of care in virtual practice continues to challenge healthcare regulators. The review by Nittari et al. highlights the major ethical and legal challenges in the practice of telemedicine. These include informed consent, data protection, malpractice liability, and the absence of standardized international legislation. The study emphasizes that the lack of regulatory clarity and the variability in national laws can hinder the safe and consistent use of telemedicine, especially across borders.[42]

While telemedicine holds considerable promise, its integration into healthcare systems must be supported by robust investments in digital infrastructure, well-defined ethical and legal frameworks, and strategies aimed at reducing inequities in access. Ongoing research should focus on evaluating its long-term impact on care quality, patient safety, and overall health system efficiency. Moreover, telemedicine may reshape the traditional patient-physician relationship. Although virtual care enhances accessibility and convenience, it may compromise the depth of interpersonal communication, particularly in fields such as psychiatry, palliative care, and chronic disease management.

FUTURE PERSPECTIVES: ARTIFICIAL INTELLIGENCE, REMOTE DEVICES, AND DIGITAL CLINICS

Rapid advancements in telemedicine and digital health technologies are driving fundamental changes in the delivery of healthcare. Telemedicine has evolved far beyond simple video consultations and has become central to diagnosis, monitoring, treatment planning, and clinical decision-making. The integration of portable medical devices, mobile health applications, and artificial intelligence (AI) systems improves the quality and accessibility of care, particularly for chronic disease management and for patients in hard-to-reach areas.

One of the most notable examples of this technological progress is the smart stethoscope. These digital versions of traditional stethoscopes record heart and lung sounds with high sensitivity and transmit the data in real time to clinicians via cloud-based platforms. The audio signals are filtered and analyzed by AI algorithms, which can automatically detect pathological findings such as wheezing, crackles, or murmurs and present these as suggestions to physicians. This technology enables remote physical examination, allowing clinicians to assess patients without being physically present. It is particularly valuable for chronic obstructive pulmonary disease (COPD), asthma, heart failure, and other respiratory conditions because it enhances patient comfort and reduces the burden on the healthcare system.[43,44]

Mobile health (mHealth) applications are another critical component supporting patient self-management in their home environment. These apps allow patients to record daily symptoms such as dyspnea, cough, or sleep disturbances, track medication adherence, and improve treatment compliance. Data collected through these platforms can be shared in real time with healthcare providers and used to guide clinical decisions. Such digital symptom monitoring is especially useful for diseases like interstitial lung disease and sleep apnea, serving as early warning systems and optimizing disease control.

Artificial intelligence (AI) is profoundly transforming diagnostic and therapeutic processes into respiratory medicine. One of the most prominent applications lies in medical imaging, particularly in the interpretation of high-resolution computed tomogra-

phy (HRCT) scans. AI algorithms can identify disease-specific radiological patterns with remarkable sensitivity, often detecting subtle changes that may not be easily recognized by the human eye. This is especially valuable in diseases such as IPF, where early detection is crucial for timely intervention and improved outcomes. AI-driven tools can assist clinicians by highlighting fibrotic changes, honeycombing, or ground-glass opacities, which are often nuanced and distributed heterogeneously across the lung parenchyma.[45] Together, these innovations exemplify the potential of AI to reshape pulmonary care by augmenting clinical judgment, reducing diagnostic delays, and enabling more proactive and individualized disease management strategies.[46]

A recent narrative review addresses rare diseases as a distinct entity, exploring public health strategies, digital health opportunities, and ethical considerations. It illustrates the challenges involved by comparing manually selected data points with outputs from advanced artificial intelligence systems. The authors reference philosopher Immanuel Kant's notion of noumena to emphasize that "only individuals with rare disabling conditions can genuinely convey the reality of living with those conditions."[40] Increasing awareness and fostering empathy are essential steps toward understanding what it truly means to live with such conditions. In this context, the digital era should be viewed as an opportunity to amplify patient voices and promote equity in rare disease care.

Considering these developments, the future of telemedicine can be envisioned as a comprehensive ecosystem integrating AI-driven clinical decision support, remote monitoring technologies, and continuous digital communication between patients and healthcare professionals. This integrated system not only enhances the effectiveness of care but also allows for personalized treatment approaches that improve patient safety and quality of life. Widespread adoption of these technologies, particularly in regions with geographic or socioeconomic barriers, holds the potential to reduce health disparities significantly.

Digital platforms to be used for national or international collaboration among multiple disciplines can be possible and widely applicable. Tele-MDD (Remote Multidisciplinary Discussion) meetings may be one of the future goals to be formed and extended. Besides many advantages, this may help to address the diversity, complexity, and specificity of data sequences of rare diseases.[40] Since AI and digital health technologies within telemedicine are becoming indispensable tools that make clinical practice more precise, accessible, and sustainable, their broader implementation in the coming years is expected to bring groundbreaking improvements in early diagnosis, effective monitoring, and optimal disease management.

CASE ANALYSIS

A young patient with pulmonary alveolar microlithiasis (PAM), struggling to remain engaged in life despite respiratory failure and continuing to work with liquid oxygen, was assessed via teleconsultation. After the consultation, the patient's video consultation recording was shared with an international reference center, allowing for a discussion of the experiences with other patients. While no definitive treatment recommendation could be made in medical practice, the impact on the patient included improved accessibility to specialist care, increased trust in the physician, and a sense of not being alone. For the attending physician, the experience reinforced the feeling of having done everything possible to benefit the patient.

The recorded video consultation, which was initially taken to obtain a third opinion, was later considered for use in medical education. Following this idea, the patient perspective in rare diseases was discussed during a national chest diseases congress session, and the educational impact on physicians was published.[38] The patient, who shared the burden of fighting the disease and waiting, summarized this process. *"It is a privilege for me to help raise awareness among doctors about the rare disease with which I have been diagnosed. Thank you for carrying our voice to the place where it most needs to be heard."*

CONCLUSION

Telemedicine offers significant advantages in the management of chronic diseases, including the ability to provide care in patients' home environments without the fear of transmission, reducing the difficulty of travel, minimizing healthcare facility visits, enabling telemonitoring, and facilitating the early recognition of changes related to the disease and tracking treatment outcomes through continued care by the same physician. In addition to these benefits, considering the complexity and potential severity of rare ILDs, telemedicine can also facilitate communication between

patients and local physicians with reference centers. This approach can help bridge gaps in care, improving both patient management and the continuity of follow-up. Moreover, telemedicine can be an effective tool in the education of healthcare providers, enhancing their expertise in managing rare diseases. The implementation of telemedicine, as a transformative modality in modern medicine, requires a comprehensive and balanced approach, one that is evidence-informed, ethically grounded, and contextually adapted.

With the integration of digital health technologies and AI-powered applications, more precise, accessible, and sustainable healthcare can be achieved. For example, AI may be a good candidate to be an essential member of structured the MDD team, particularly in the management of rare ILDs.

Given these significant potentials, it is crucial to develop strategies to address legal and ethical challenges while ensuring that the essence of patient-physician communication is preserved. It is essential to expand the use of telemedicine applications based on the principles of good medical practice.

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CHAPTER 19

LUNG TRANSPLANTATION IN RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSYEL AKCİĞER HASTALIKLARINDA AKCİĞER NAKLİ

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LUNG TRANSPLANTATION IN RARE INTERSTITIAL LUNG DISEASES

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ABSTRACT

In rare interstitial lung diseases (ILDs), diagnostic uncertainty, limited access to effective pharmacologic therapies, and difficulties in reaching experienced centers complicate patient management. These challenges often persist in the lung transplantation process when the disease progresses to end-stage respiratory failure. Lung transplantation can significantly improve both survival and quality of life in selected subtypes of rare ILDs. However, standardized, disease-specific criteria for referral to transplant centers and listing remain undefined.

Given the heterogeneous clinical course of these diseases, the success of transplantation largely depends on appropriate patient selection. All available medical treatment options should be exhausted prior to listing, and surgical feasibility must be carefully assessed. Certain ILD subtypes present with technical challenges during surgery, for example, recurrent pneumothorax and pleural adhesions in cystic ILDs, extensive mediastinal calcifications in silicosis, or pleural thickening and chest wall rigidity in pleuroparenchymal fibroelastosis.

In diseases associated with a risk of extrapulmonary involvement, such as Langerhans cell histiocytosis and lymphangioleiomyomatosis (LAM), early referral to a transplant center is critical for excluding systemic spread, thoroughly evaluating comorbidities, and treating any existing infections. Early referral also allows sufficient time to address potentially preventable or correctable contraindications. Otherwise, patients presenting in a severely debilitated state may be unsuitable for rehabilitation or may not have adequate time on the waiting list to receive a suitable donor.

The choice between single and double lung transplantation is determined by factors including the underlying disease, patient age, comorbidities, and the presence of pulmonary hypertension. While double lung transplantation provides a greater volume of healthy parenchyma and may offer long-term functional benefits, it is associated with longer operative times and an increased risk of perioperative complications. Consequently, single lung transplantation is generally preferred in patients with idiopathic pulmonary fibrosis and elderly individuals with ILD, whereas double lung transplantation is recommended for patients with cystic fibrosis, bronchiectasis, LAM, and severe pulmonary hypertension.

For patients with rare ILDs who experience progressive disease despite medical therapy or who lack effective treatment options and develop end-stage lung failure, lung transplantation remains the only curative option that can prolong survival and improve quality of life. There is a continued need to develop standardized, disease-specific clinical criteria to guide transplant decision-making in this population.

Keywords: *Rare interstitial lung diseases; Lung transplantation; Curative treatment; Patient selection; Waiting list*

ÖZET

Nadir görülen interstisyel akciğer hastalıklarında (İAH), tanı sürecindeki belirsizlikler, uygun ilaç tedavisine erişimde yaşanan güçlükler ve deneyimli merkezlere ulaşmadaki zorluklar hasta yönetimini zorlaştırmaktadır. Bu belirsizlikler, hastalık son dönem akciğer yetmezliğine ilerlediğinde gündeme gelen akciğer nakli sürecinde de devam etmektedir. Akciğer nakli, bazı nadir İAH alt tiplerinde yaşam süresi ve kalitesini anlamlı şekilde artırabilmektedir. Ancak, hangi hastaların ne zaman nakil merkezine yönlendirilmesi gerektiğine dair hastalığa özgü, standardize edilmiş kriterler hâlâ oluşturulmamıştır.

Bu hastalık grubu heterojen bir klinik seyir gösterdiğinden, nakil başarısı büyük ölçüde doğru hasta

seçimine bağlıdır. Tüm medikal tedavi seçeneklerinin tüketildiğinden emin olunmalı ve cerrahi uygunluk dikkatle değerlendirilmelidir. Örneğin, kistik İAH'larda tekrarlayan pnömotorakslar ve plevral yapışıklıklar, silikoziste mediastinal kalsifikasyonlar, plöroparankimal fibroelastoziste kalınlaşmış plevra gibi anatomik faktörler cerrahi zorluklara neden olabilir.

Ekstrapulmoner tutulum riski taşıyan Langerhans hücreli histiyositoz ve Lenfanjiyoleyomiyomatozis (LAM) gibi hastalıklarda, sistemik yayılımın dışlanması, komorbiditelerin detaylı değerlendirilmesi ve mevcut enfeksiyonların tedavisi amacıyla hastaların erken dönemde nakil merkezine yönlendirilmesi kritik öneme sahiptir. Bu erken yönlendirme, aynı zamanda önlenebilir veya düzeltilebilir kontrendikasyonların giderilmesi için gerekli zamanı sağlamaktadır. Aksi takdirde, ileri derecede düşkün başvuran hastalar rehabilitasyona uygun olmayabilir veya bekleme listesinde uygun donör bulunması için yeterli süreye sahip olamayabilir.

Akciğer naklinde tek veya çift akciğer seçimi; altta yatan hastalık, hasta yaşı, komorbiditeler ve pulmoner hipertansiyon varlığı gibi faktörlere bağlı olarak belirlenmektedir. Çift akciğer nakli, daha geniş sağlıklı parankim sağlayarak uzun dönem fonksiyonel avantaj sunabilmekle birlikte, operasyon süresinin uzaması ve perioperatif komplikasyon riskinde artış gibi ek morbiditelerle ilişkilidir. Bu nedenle, idiopatik pulmoner fibrozis ve ileri yaş İAH hastalarında genellikle tek akciğer nakli tercih edilirken; kistik fibrozis, bronşektazi, LAM ve ağır pulmoner hipertansiyon olgularında çift akciğer nakli önerilmektedir

Nadir görülen interstisyel akciğer hastalıklarında, mevcut medikal tedavilere rağmen hastalığı ilerleyen ya da etkin tedavi seçeneği bulunmayan ve son dönem akciğer yetmezliği gelişen olgular için akciğer nakli, yaşam süresini uzatan ve yaşam kalitesini artıran tek küratif tedavi seçeneğidir. Bu hasta grubunda nakil kararı açısından hastalığa özgü, standartlaştırılmış klinik kriterlerin geliştirilmesine duyulan ihtiyaç devam etmektedir.

Anahtar Kelimeler: *Nadir interstisyel akciğer hastalıkları; Akciğer nakli; Küratif tedavi; Hasta seçimi; Bekleme listesi*

CASE PRESENTATION

A 28-year-old male patient was referred to our outpatient clinic from another province for evaluation for lung transplantation due to pulmonary Langerhans cell histiocytosis (PLCH). The patient's anthropometric measurements were as follows: height 168 cm, weight 49 kg, and body mass index (BMI) 17.4 kg/m^2. His blood type was A Rh-positive. The patient had a 17 pack-years history of smoking, which he had discontinued six months prior to presentation. He was employed as a biomedical technician. Physical examination revealed surgical scars consistent with previous thoracotomies located beneath both scapulae on the posterior thoracic wall.

The patient's clinical history began at the age of 15 with an episode of right-sided spontaneous pneumothorax. This initial event was managed with tube thoracostomy and underwater seal drainage, after which the patient was discharged. One year later, he experienced a recurrence of pneumothorax on the same side, necessitating surgical intervention. The procedure was initially attempted via video-assisted thoracoscopic surgery (VATS); however, due to extensive pleural adhesions, conversion to an open thoracotomy was required, and a bullectomy was subsequently performed. Three years postoperatively, the patient re-presented with dyspnea, and a left-sided pneumothorax was detected. Tube thoracostomy with underwater seal drainage was performed again, but the pneumothorax recurred after chest tube removal, requiring surgical intervention. During the subsequent left thoracotomy, a bullectomy and pleural abrasion were performed. In the same surgical session, a wedge biopsy was obtained.

Histopathological examination initially revealed findings consistent with eosinophilic granuloma/PLCH. However, consultation with a tertiary pathology center and further immunohistochemical analysis, including CD1a staining, were recommended for definitive diagnosis. Immunohistochemical analysis subsequently demonstrated strong CD1a and S100 positivity, confirming the diagnosis of PLCH.

Oral methylprednisolone therapy was initiated at a dose of 48 mg and gradually tapered over one year before discontinuation. The patient remained clinically stable for the subsequent two years, after which he developed another right-sided pneumothorax. This episode was managed with tube thoracostomy, and the patient was discharged. However, approximately twenty days later, a recurrent pneumothorax occurred on the same side, which was again treated with tube thoracostomy and underwater seal drainage. Notably, the patient continued smoking throughout this period. The patient, who developed dyspnea six months ago, quit smoking and was referred to our clinic for lung transplantation evaluation. Four months prior, long-term home oxygen therapy was initiated.

At the time of initial evaluation at our clinic, the patient was not receiving any pharmacologic therapy. Pulmonary function testing demonstrated a forced vital capacity (FVC) of 2.82 liters (61% of the predicted value), a forced expiratory volume in one second

(FEV_1) of 2.15 liters (55% of predicted), and an FEV_1/FVC ratio of 76%. The patient was unable to complete the diffusing capacity of the lungs for carbon monoxide (DLco) assessment. During the six-minute walk test, he ambulated a total distance of 369 meters, with oxygen saturation decreasing from a baseline of 91% to 76% at the conclusion of the test. The patient required two rest periods to complete the test. High-resolution computed tomography (HRCT) of the chest is shown in Figure 1. Perfusion scintigraphy demonstrated that the left lung contributed 61% and the right lung 39% to total pulmonary perfusion. Transthoracic echocardiography revealed a pulmonary artery systolic pressure of 40 mmHg. Right heart catheterization confirmed the presence of pulmonary hypertension, with a measured mean pulmonary artery pressure of 31 mmHg and a pulmonary vascular resistance of 5.5 Wood units.

Systemic evaluations, including coronary angiography; arterial and venous Doppler ultrasonography of the extremities; Doppler studies of the carotid and vertebral arteries; abdominal and thyroid ultrasonography; and CT scans of the brain, paranasal sinuses, and abdomen revealed no pathological findings. Bone densitometry revealed osteopenia. Extensive laboratory investigations were conducted, with vitamin D deficiency identified as the only notable abnormality; supplementation was subsequently initiated. Positron emission tomography (PET) imaging was performed to evaluate for extrapulmonary involvement of LCH, but no evidence of extrapulmonary disease was found. Microbiological cultures remained sterile. Panel reactive antibody (PRA) testing detected no antibodies against HLA class I or class II antigens. Chest computed tomography (CT) revealed end-stage cystic lung disease.

INTRODUCTION

Lung transplantation is a life-prolonging and quality-enhancing treatment option for patients who develop progressive respiratory failure and end-stage lung disease despite all other available therapies. The first successful lung transplantation was performed in 1983 at the University of Toronto in Canada on a patient with interstitial fibrosis. Since then, the proportion of interstitial lung diseases (ILDs) among lung transplant recipients worldwide has steadily increased, and after 2007, ILD surpassed chronic obstructive pulmonary disease (COPD) as the leading indication for lung transplantation.[1] According to the most recent registry report of the International Society for Heart and Lung Transplantation (ISHLT), covering the 32-year period from 1992 to 2024, idiopathic pulmonary fibrosis (IPF) accounted for 27% of adult lung transplants globally, while COPD accounted for 24%, cystic fibrosis for

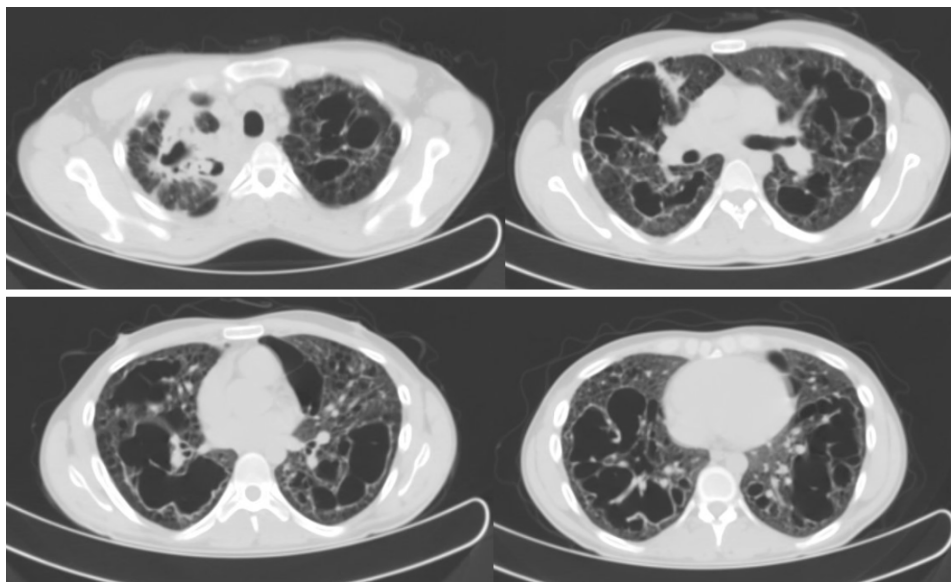


Figure 1. Pre-transplant thoracic computed tomography of a patient diagnosed with Langerhans cell histiocytosis, demonstrating an aspergilloma within a cavitary lesion.

10%, and the remaining 35% were categorized under "other diseases".[1,2] The rare ILDs, which are the subject of this book, may individually represent a small proportion; however, collectively, they form a significant part of this "other" category, which accounts for approximately one-third of all lung transplants (Figure 2). In this chapter, the focus will be on "orphan interstitial lung diseases" within lung transplantation, conditions that are not only rare but are also treated with a therapy that is, by its nature, considered an orphan intervention.

INDICATIONS AND CONTRAINDICATIONS FOR LUNG TRANSPLANTATION

The limited awareness, diagnostic challenges, and therapeutic uncertainties associated with orphan interstitial lung diseases also persist in the context of lung transplantation indications. Except for lymphangioleiomyomatosis (LAM), there are no disease-specific criteria for most of these conditions. Patients are typically referred to lung transplant centers and listed for transplantation based on the general criteria established for "interstitial lung diseases."[3]

The success of lung transplantation is highly dependent on appropriate patient selection. Since graft dysfunction, organ rejection, lifelong immunosuppressive therapy, medication-related adverse effects, and opportunistic infections may occur in both the early and late post-transplant periods, determining which patients are suitable candidates for transplantation remains a critical step in the process.

According to the ISHLT consensus document, lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria.[3]

- High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed.
- High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function.[3]

Since rare ILDs can affect multiple organ systems, it is essential to conduct a comprehensive pre-transplant evaluation and to refer patients to lung transplant centers early. Early referral allows time for the optimization of modifiable risk factors and the management of potentially adverse conditions.[3]

Risk factors that may negatively impact lung transplantation outcomes, increase perioperative risks, or be considered contraindications are summarized in Table 1. Each transplant center assesses these criteria based on its own clinical experience. A factor that may be considered a contraindication at one center may not necessarily be regarded as such at another. Therefore, before concluding that a patient is not a suitable candidate for lung transplantation, it is recommended that the patient be evaluated by at least two different transplant centers.

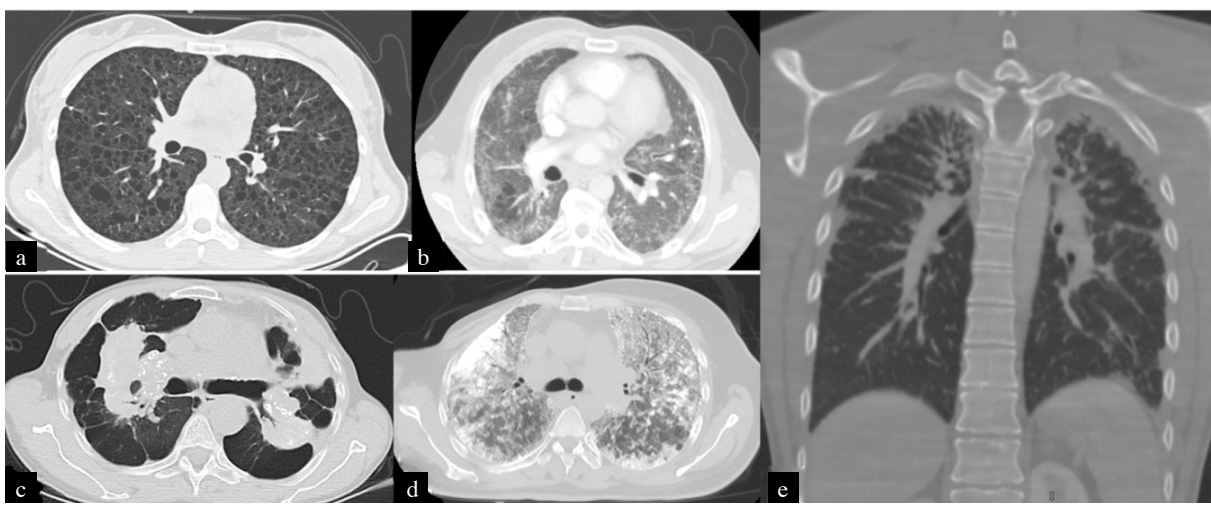


Figure 2. Thoracic computerized tomography images of some of the rare interstitial lung diseases: **a)** Lymphangioleiomyomatosis; **b)** Pulmonary alveolar proteinosis; **c)** Silicosis; **d)** Pulmonary alveolar microlithiasis; **e)** Pleuroparenchymal fibroelastosis.

Table 1. Risk factors for poor post-transplant outcomes.

Contraindications/risks	Features
Absolute Contraindications	• Patient unwillingness or refusal to undergo transplanta-tion • Active malignancy with a high probability of recurrence or mortality • Estimated glomerular filtration rate (eGFR) below 40 mL/min/1.73 m², unless a combined organ transplant is be-ing considered • Recent acute coronary event or myocardial infarction (within the past 30 days) • Recent cerebrovascular accident (stroke) within the previous month • Presence of liver cirrhosis with signs of portal hypertension or impaired synthetic function, unless part of a planned mul-ti-organ transplant • Acute liver failure • Ongoing acute kidney injury with rising creatinine levels or dialysis dependence, and low likelihood of renal recovery • Septic shock • Active systemic or extrapulmonary infections • Current or inadequately treated tuberculosis • HIV infection with an uncontrolled (detectable) viral load • Severely impaired functional status with limited capacity or rehabilitation after transplantation • Ongoing decline in cognitive function • Persistent non-compliance with medical recommendations despite interventions • Current substance abuse or dependence, including tobacco, vaping products, cannabis (inhaled), or intravenous drugs • Any serious, uncontrolled comorbid condition likely to compromise survival after transplantation
Risk Factors with High or Substantially Increased Risk Candidates with these conditions may be considered in centers with expertise specific to the condition. When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing the risk of adverse outcomes.	• Advanced age (>70 years) • Advanced coronary artery disease necessitating coronary artery bypass surgery at the time of transplantation • Left ventricular ejection fraction below 40% • Clinically significant cerebrovascular pathology • Marked esophageal motility disorders • Hematologic abnormalities that are not amenable to treatment (e.g., bleeding diathesis, thrombotic disorders, or profound bone marrow suppression) • Body mass index (BMI) exceeding 35 kg/m² • Severe underweight (BMI <16 kg/m²): • Markedly reduced functional capacity with uncertain post-transplant rehabilitation potential • Presence of psychiatric or neurocognitive disorders likely to affect adherence, in the absence of adequate psychosocial sup-port • Lack of a stable or dependable caregiving network • Persistent lack of comprehension regarding disease severity or transplant implications despite thorough education • Chronic infection with Mycobacterium abscessus: • Colonization or active infection with Lomentospora prolifi-cans: • History of infection with Burkholderia cenocepacia or Burkholderia gladioli • Chronic hepatitis B or C infection with detectable viral load and evidence of hepatic fibrosis • Significant chest wall or spinal abnormalities anticipated to impair pulmonary mechanics after transplantation • Requirement for extracorporeal life support (ECLS) at the time of evaluation • Retransplantation within one year of the initial lung transplant

Table 1. Risk factors for poor post-transplant outcomes. Continues

Risk Factors Risk factors with unfavorable implications for short and /or long-term outcomes after lung transplant. While acceptable for lung transplant to consider patients with these risk factors, multiple risk factors together may increase risk for adverse post-transplant outcomes.	• Age between 65 and 70 years • Glomerular filtration rate ranging from 40 to 60 mL/min/1.73 m^2 • Mild to moderate coronary artery disease • Severe coronary artery disease amenable to revascularization via percutaneous coronary intervention before transplantation • History of coronary artery bypass graft surgery • Left ventricular ejection fraction decreased to 40-50% • Presence of peripheral vascular disease • Connective tissue disorders such as scleroderma, lupus, or inflammatory myopathies • Severe gastroesophageal reflux disease • Esophageal motility disorders • Thrombocytopenia, leukopenia, or anemia likely to persist after transplantation • Diagnosis of osteoporosis • Body mass index between 30 and 34.9 kg/m^2 • Body mass index between 16 and 17 kg/m^2 • Physical frailty • Hypoalbuminemia (low serum albumin levels) • Poorly controlled diabetes mellitus • Use of consumable marijuana • Infection with Scedosporium apiospermum • HIV infection with an undetectable viral load • Previous thoracic surgeries • History of pleurodesis • Requirement for mechanical ventilation • Retransplantation needed more than one year after for obstructive chronic lung allograft dysfunction (CLAD)

Risk factors for poor post-transplant outcomes summarized in a Table format.[3]

According to the ISHLT consensus document, referral and listing criteria for lung transplantation in interstitial lung diseases are summarized in Table 2.[3]

LUNG TRANSPLANTATION ON THE BASIS OF RARE ILDS

Depending on the type of rare ILD, different aspects of lung transplantation need to be considered throughout the entire process. Pulmonary Langerhans cell histiocytosis (PLCH), lymphangioleiomyomatosis (LAM), Pulmonary alveolar proteinosis (PAP), Pulmonary alveolar microlithiasis (PAM), silicosis, and pleuropulmonary fibroelastosis (PPFE) are the main rare ILDs for which lung transplantation-related considerations warrant discussion. All these rare ILDs are comprehensively addressed in the relevant chapters of this book.

Pulmonary Langerhans Cell Histiocytosis (PLCH)

Globally, approximately 0.4% of lung transplants have been performed in patients with PLCH.[4] The absence of clearly defined guidelines for referral to lung transplant centers in this population is largely attributable to several factors, including the typically prolonged survival, often exceeding 10 years post-diagnosis, the potential for pulmonary involvement to improve following smoking cessation, and the unpredictable response to medical therapies. In patients with PLCH who progress to end-stage lung disease, pulmonary hypertension is frequently observed and is recognized as a significant factor associated with reduced survival.

In the United States, approximately 0.25% of lung transplants have been performed in patients with PLCH. Reported post-transplant survival rates at 1, 3, 5, and 10 years are 85%, 65%, 49%, and 22%, respectively. Notably, post-transplant survival has been significantly higher in female recipients compared to males, with a mean survival of 9.3 years versus 3.9 years. Interestingly, the presence of preoperative pulmonary hypertension has not been shown to negatively impact post-transplant survival. Although disease-specific lung transplant criteria for PLCH are

Table 2. ISHLT Lung Transplant Candidate Recommendations in ILD.[3]

Timing of Referral	Timing of Listing

• Referral should occur at diagnosis, even if treatment has already begun, when histopathology confirms UIP or imaging shows a probable or definite UIP pattern.
• Any pulmonary fibrosis case with forced vital capacity (FVC) below 80% of predicted or diffusing capacity for carbon monoxide (DLCO) under 40% of predicted.
• Pulmonary fibrosis patients exhibiting any of the following within the last two years:
  • A relative decline of 10% or more in FVC
  • A relative decline of 15% or more in DLCO
  • A relative 5% decline in FVC combined with worsening respiratory symptoms or radiological progression
• Need for supplemental oxygen at rest or during physical activity.
• In inflammatory interstitial lung diseases, evidence of disease progression on imaging or lung function tests despite ongoing therapy.
• Early referral is advised for patients with connective tissue disease-related or familial pulmonary fibrosis, given the possibility of extrapulmonary symptoms requiring specialized management.
	• Any type of pulmonary fibrosis showing one or more of the following within the last 6 months despite adequate treatment:
	  • An absolute reduction in FVC greater than 10%
	  • An absolute decrease in DLCO exceeding 10%
	  • An absolute decline in FVC over 5% accompanied by worsening imaging findings
	• Oxygen saturation dropping below 88% during a 6-minute walk test, or a decrease of more than 50 meters in walk distance over the past 6 months
	• Evidence of pulmonary hypertension detected by right heart catheterization or 2D echocardiography, provided diastolic dysfunction is not present
	• Hospital admission due to respiratory deterioration, pneumothorax, or acute exacerbation of disease

lacking, referral to a transplant center is recommended when pulmonary hypertension develops.[5]

Recurrence rates of approximately 20% have been reported in patients who continued smoking after lung transplantation or who had extrapulmonary involvement prior to transplantation.[6] Therefore, it is essential that patients with PLCH undergo thorough pre-transplant evaluations, including comprehensive whole-body imaging to assess for extrapulmonary disease. Additionally, confirmed smoking cessation is a critical prerequisite for transplantation in this population.

Additionally, a history of prior thoracic surgeries for recurrent pneumothoraces and the presence of hypophyseal involvement, such as diabetes insipidus, necessitate special consideration, as these patients differ from other lung transplant candidates in several important respects.

In the management of pneumothorax, lung surgery, such as pleural procedures aimed at preventing pneumothorax recurrence, should be performed as the initial approach in appropriate patients. Following surgical control of pneumothorax, cladribine should be considered as the first-line systemic therapy. Particularly in patients with pulmonary involvement at the nodular or nodulo-cystic stage, cladribine therapy is recommended as a priority.[7] In cases where there is no response to cladribine or in patients with advanced cystic disease and significantly impaired pulmonary function, lung transplantation should be considered as an appropriate treatment option.

Lymphangioleiomyomatosis (LAM)

With the widespread global use of mTOR inhibitor therapies, the need for lung transplantation in patients with LAM has decreased.[8] According to the International Society for Heart and Lung Transplantation (ISHLT), referral for lung transplantation evaluation should be considered for individuals with LAM who exhibit any of the following despite mTOR inhibitor therapy:

- Severely impaired lung function (e.g., FEV_1 < 30% predicted)
- Exertional dyspnea (New York Heart Association Class III or IV)

- Resting hypoxemia
- Pulmonary hypertension
- Refractory pneumothorax

Since pneumothorax is frequently seen even in mild forms of LAM, unlike other interstitial lung diseases, lung transplantation is generally not considered unless the pneumothorax is refractory to treatment. Recurrent pneumothoraces and prior pleural surgeries, which may result in pleural adhesions, should be carefully assessed by transplant teams due to the increased risk of perioperative bleeding. Single lung transplantation is generally discouraged in patients with LAM owing to the risk of pneumothorax in the native lung and the possibility of native lung hyperinflation syndrome. Whenever feasible, bilateral lung transplantation is the preferred approach.[8]

Lung transplantation listing is recommended for LAM patients who meet these referral criteria and show evidence of disease progression despite mTOR inhibitor therapy.[3] The discontinuation of mTOR inhibitors after placement on the transplant waiting list remains a controversial issue due to their potential adverse effects on bronchial anastomotic healing and the associated risk of bronchial dehiscence. A careful risk-benefit assessment is essential. In certain cases, switching from sirolimus to everolimus, which has a shorter half-life, and maintaining the drug at the lower end of the therapeutic range may enable continued therapy during the waiting period for transplantation.[9]

Renal angiomyolipomas warrant thorough evaluation before transplantation because of their high bleeding potential. Prophylactic embolization via catheter-based techniques is particularly recommended for lesions exceeding 6 cm in size.[8]

In lymphangioleiomyomatosis (LAM), the reported mean survival following lung transplantation is approximately 12 years. The 1-year, 5-year, and 10-year post-transplant survival rates are 94%, 73%, and 56%, respectively, significantly higher than those observed in most other lung diseases.[10]

Pulmonary Alveolar Proteinosis (PAP)

In PAP cases with progressive disease despite whole lung lavage (WLL) and/or pharmacological treatment, lung transplantation is considered for patients who meet the International Society for Heart and Lung Transplantation (ISHLT) lung transplant criteria for interstitial lung diseases.[11] PAP, a rare disease, has limited data on lung transplantation derived primarily from case series. In an international multicenter study evaluating a total of 44 patients, lung transplantation was performed on average 11.6 years after the diagnosis of PAP. Recurrence after transplantation was observed in 8 of these patients (18%), but this did not significantly affect overall survival. Reported survival rates at 1-, 3-, and 5-years post-transplant were 90.8%, 85.1%, and 69.9%, respectively.[12]

Pulmonary Alveolar Microlithiasis (PAM)

Currently, no proven effective medical therapies exist for PAM. Although the disease typically progresses slowly, lung transplantation remains the sole definitive treatment option once patients reach end-stage lung disease. Due to the absence of PAM-specific lung transplant referral criteria, the International Society for Heart and Lung Transplantation (ISHLT) guidelines for ILDs are utilized for transplant evaluation in this population. Despite the challenges posed by extensive calcification of the lung parenchyma, which complicates lung deflation during surgery, and the increased risk of perioperative bleeding due to pleural adhesions, successful outcomes have been reported following single or bilateral lung transplantation in patients with PAM.[13] Pulmonary hypertension secondary to PAM has been observed in nearly all transplanted patients. Referral for lung transplantation is recommended when pulmonary hypertension is present alongside the requirement for long-term oxygen therapy.[14,15]

Post-transplant survival in PAM patients is comparable to that of other lung transplant recipients, and to date, disease recurrence following transplantation has not been reported.

Silicosis

Silicosis is a rare ILD with no effective medical treatment, and lung transplantation is the only option once it progresses to end-stage. Calcified mediastinal and hilar lymph nodes complicate dissection of hilar structures during surgery, while pleural thickening increases the risk of bleeding, making pneumonectomy technically challenging in these patients. Since bilateral lung transplantation has not demonstrated superiority over single lung transplantation in silicosis, single lung transplantation may be preferred to minimize surgical risks.[16]

Long-term post-transplant mortality in silicosis patients is comparable to that observed in other lung diseases.[17] Reported survival rates after transplantation are 81% at 1 year and 68% at 3 years.[18] Given the surgical complexity, careful patient selection remains essential.

Pleuroparanchimal Fibroelastosis (PPFE)

The natural progression of PPFE, characterized by flattening and stiffening of the chest wall, may lead to persistent restrictive ventilatory impairment even after transplantation. Recipients with low body mass index (BMI) and a flattened chest wall often have a severely reduced thoracic cavity volume, resulting in size mismatch with the donor lungs. This may necessitate reducing the donor lung volume or opting for lobar transplantation. Bleeding due to pleural adhesions is common and may require reoperation.[19] These factors contribute to increased early postoperative mortality and adversely affect long-term survival in patients with PPFE.

In a French national cohort, early postoperative mortality was reported at 32%, with a mean survival of 21 months. The 1-, 2-, and 5-year post-transplant survival rates were 57.9%, 42.6%, and 38%, respectively.[19] In contrast, two studies from Japan reported a mean survival of 8.4 years and a 5-year post-transplant survival rate of 68.6%.[20,21] The poorer outcomes observed in the French cohort were attributed to transplantation being performed in patients with more advanced disease, greater restrictive physiology, flatter chest walls, and established pulmonary hypertension compared to those in the Japanese series.

Data on lung transplantation for PPFE remain limited to case series. Based on these findings, careful selection of both recipients and donors, early referral to transplant centers prior to severe chest wall flattening and stiffening, and optimal timing of transplantation are essential for achieving favorable outcomes.[22]

TYPE OF TRANPLANT SURGERY

The decision to perform either single or bilateral lung transplantation is primarily guided by the underlying disease, patient-specific factors, and center-specific protocols. Single lung transplantation is often preferred in patients with idiopathic pulmonary fibrosis (IPF) and selected cases of ILD, particularly in older individuals or those with significant comorbidities, as it involves a shorter operative time and potentially faster postoperative recovery. In contrast, bilateral lung transplantation is generally indicated for diseases characterized by bilateral lung involvement, chronic infection, or severe pulmonary vascular disease. Conditions such as cystic fibrosis, bronchiectasis, severe chronic obstructive pulmonary disease (COPD) in younger patients, pulmonary hypertension, and LAM typically necessitate bilateral lung transplantation due to better long-term outcomes and improved survival.[23] In cystic ILDs, bilateral lung transplantation is generally favored due to the increased risk of pneumothorax in the native cystic lung, as well as the potential for the development of aspergilloma and opportunistic bacterial infections, particularly under immunosuppressive therapy following transplantation.[24,25]

The severity of pulmonary hypertension is a key factor in determining whether to perform single or double lung transplantation. In patients with moderate pulmonary hypertension, defined by a mean pulmonary artery pressure (mPAP) between 25 and 40 mmHg, single lung transplantation is considered a safe and effective option. Although double lung transplantation is traditionally recommended for patients with severe pulmonary hypertension (mPAP >40 mmHg), recent studies have demonstrated that single lung transplantation can also yield favorable outcomes, particularly in elderly patients with significant comorbidities, provided that appropriate intraoperative mechanical circulatory support is used. These findings suggest that even in the presence of severe pulmonary hypertension, single lung transplantation should not be dismissed, especially when careful patient selection and optimal intraoperative management are ensured.[26]

CASE ANALYSIS

Based on these clinical findings, the patient was listed for lung transplantation in March 2020. During follow-up, the patient developed an aspergilloma within a cavitary lesion in the right lung, for which antifungal therapy with voriconazole was initiated. Owing to prolonged transplant wait times during the COVID-19 pandemic, the patient remained on the lung transplant waiting list for two years and eight months. On December 22, 2022, a suitable donor became available, and the patient subsequently underwent bilateral lung transplantation. Intraoperatively, central veno-arterial extracorporeal membrane oxygenation (ECMO)

support was employed due to underlying pulmonary hypertension. ECMO was successfully weaned and discontinued at the conclusion of the procedure. The patient was then transferred to the intensive care unit for postoperative management.

For immunosuppression, basiliximab was administered for induction, while maintenance therapy included tacrolimus, mycophenolate mofetil, and prednisolone. The perioperative and postoperative courses were uneventful. The patient was extubated on postoperative day two, transferred to the ward on day four, and discharged on postoperative day nineteen. Six months after transplantation, the patient successfully resumed his active professional life as a biomedical technician.

He has now been followed for 36 months post-transplant and continues to remain well without any complications.

CONCLUSION

While referral and listing criteria for lung transplantation in IPF are well-defined, it remains unclear which patient groups are suitable candidates for transplantation in rare ILDs. In this group of diseases, the lack of comprehensively defined patient profiles and the difficulty in determining disease progression can lead to significant challenges in the lung transplant referral and listing processes. The heterogeneous clinical presentations of these diseases complicate accurate assessment of individual patient needs and prognoses, making the management and decision-making processes more complex.[27] In rare ILDs with distinct features, such as cystic diseases with pleural adhesions following prior pleural surgery due to recurrent pneumothoraces, silicosis with extensive mediastinal calcifications that complicate dissection, or PPFE characterized by pleural thickening and chest wall stiffening, selecting appropriate transplant candidates remains particularly challenging for transplant centers.

However, when the right patient is selected, lung transplantation becomes a life-saving intervention for patients with orphan ILDs, and ultimately, brings an end to their orphanhood.

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CHAPTER 20

PULMONER REHABILITATION IN RARE INTERSTITIAL LUNG DISEASES

NADİR İNTERSTİSİYEL AKCİĞER HASTALIKLARINDA PULMONER REHABİLİTASYON

Assist. Prof. Dr. Ayşenur Yılmaz

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NADİR İNTERSTİSİYEL AKCİĞER HASTALIKLARINDA PULMONER REHABİLİTASYON

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ABSTRACT

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders characterized by inflammation and/or fibrosis of the lung parenchyma, leading to impaired gas exchange and progressive respiratory dysfunction. A common feature of these conditions is their chronic course, which significantly reduces patients' quality of life. Pulmonary alveolar proteinosis (PAP) is a rare subtype of ILD characterized by the abnormal accumulation of surfactant within the alveoli. This accumulation disrupts normal gas exchange and results in respiratory symptoms such as hypoxemia, dyspnea, and ineffective cough. Whole lung lavage (WLL) is currently considered the gold standard treatment for PAP, offering temporary relief of symptoms. However, WLL is invasive, carries the risk of procedure-related complications, and often requires repeated applications. Therefore, the development of safer, non-invasive, and supportive treatment approaches has become an important necessity for both patient comfort and long-term disease management. Pulmonary rehabilitation (PR), particularly when structured in an individualized and disease-specific manner, has emerged as a promising complementary strategy in the comprehensive management of rare ILDs, including PAP. Among the core components of PR, inspiratory muscle training (IMT) and expiratory muscle training (EMT) have shown evidence-based effectiveness in chronic lung diseases by enhancing respiratory muscle strength, improving cough efficiency, increasing exercise tolerance, and elevating quality of life. PAP, although supported by limited clinical data, has gained more attention in the literature in recent years due to the growing number of reported cases, making it a suitable model for evaluating the clinical outcomes of these interventions. This chapter presents the outcomes of a patient with PAP who underwent a tailored physiotherapy program. The structured rehabilitation led not only to improvements in physiological parameters but also to significant gains in functional capacity and psychosocial well-being. These findings underscore the crucial role of physiotherapy within multidisciplinary, patient-centered care models. In the management of rare and complex ILDs, PR can be considered an effective non-pharmacological therapeutic option. Expanding the implementation of such programs and sharing their results in scientific platforms may provide valuable contributions not only for PAP but also for the management of other rare ILDs.

Keywords: *Pulmonary alveolar proteinosis, interstitial lung disease; Rare interstitial lung disease; Pulmonary rehabilitation; Inspiratory muscle training*

ÖZET

İnterstisyel akciğer hastalıkları (İAH), akciğer parankiminde inflamasyon ve/veya fibrozis ile seyreden, gaz değişimini bozan ve ilerleyici solunum disfonksiyonuna yol açan heterojen bir hastalık grubudur. Bu hastalıkların ortak özelliği, kronik seyirli olmaları ve yaşam kalitesini belirgin şekilde azaltmalarıdır. Pulmoner alveoler proteinozis (PAP), alveoller içinde yüzey aktif madde (surfaktan) birikimi ile karakterize, nadir görülen bir İAH türüdür. Bu anormal birikim, alveollerin normal gaz değişimini bozarak hipoksemi, dispne ve etkisiz öksürük gibi solunumsal semptomlara yol açar. Günümüzde altın standart tedavi yöntemi olan total akciğer lavajı (TAL), semptomlarda geçici iyileşme sağlayabilse de invaziv bir girişim olması, işlem kaynaklı komplikasyon riski taşıması ve tekrarlayan uygulama gerekliliği nedeniyle sınırlılıklar barındırır. Bu nedenle, daha güvenli, non-invaziv ve destekleyici tedavi yaklaşımlarının geliştirilmesi hem hasta konforu hem de uzun vadeli hastalık yönetimi açısından büyük önem taşımaktadır. Pulmoner rehabilitasyon (PR), özellikle bireyselleştirilmiş ve hastalığa özgü biçimde yapılandırıldığında, PAP dahil olmak üzere nadir İAH'ların bütüncül yönetiminde

tamamlayıcı bir strateji olarak dikkat çekmektedir. PR kapsamında kullanılan inspiratuvar kas eğitimi (IMT) ve ekspiratuvar kas eğitimi (EMT) gibi yöntemler, kronik akciğer hastalarında solunum kas gücünü artırmada, öksürük etkinliğini iyileştirmede, egzersiz toleransını geliştirmede ve yaşam kalitesini yükseltmede kanıta dayalı etkinlik göstermiştir. PAP, sınırlı klinik veri bulunan ancak son yıllarda artan sayıda vaka bildirimiyle literatürde daha çok yer bulmaya başlayan bir hastalık olduğundan, bu tür müdahalelerin sonuçlarını değerlendirmek için uygun bir örnek oluşturmaktadır. Bu bölümde, PAP tanısı almış bir hastanın bireyselleştirilmiş fizyoterapi programından elde edilen sonuçlar sunulmaktadır. Uygulanan yapılandırılmış rehabilitasyon programı sayesinde yalnızca fizyolojik parametrelerde değil, fonksiyonel kapasite ve psikososyal düzeyde de kayda değer iyileşmeler gözlenmiştir. Bu bulgular, fizyoterapinin multidisipliner ve hasta merkezli bakım modellerinde kritik bir rol üstlenebileceğini göstermektedir. Nadir ve karmaşık seyirli İAH'ların yönetiminde PR, farmakolojik olmayan etkili bir tamamlayıcı tedavi seçeneği olarak öne çıkmaktadır. Bu tür uygulamaların yaygınlaştırılması ve elde edilen sonuçların bilimsel platformlarda paylaşılması, yalnızca PAP değil, diğer nadir İAH formlarının yönetimine de değerli katkılar sağlayacaktır.

Anahtar Kelimeler: *İnterstisyel akciğer hastalıkları; İdyopatik interstisyel pnömoni; Plöroparankimal fibroelastoz; Kemik iliği nakli; Akciğer nakli*

CASE PRESENTATION

A 49-year-old female patient, retired nurse, with a height of 164 cm and weight of 49 kg, was diagnosed with PAP twelve years ago. The patient had undergone bronchoscopy to investigate bilateral ground-glass opacities detected on thoracic computed tomography (CT) (Figure 1), performed during her initial presentation due to chest pain and shortness of breath. The diagnosis of PAP was confirmed based on typical findings observed in bronchoalveolar lavage and transbronchial biopsy. The patient had a smoking history of 20 pack-years and quit smoking after the diagnosis.

During follow-up, the patient experienced dyspnea, cough, low oxygen saturation, and decreased diffusion exercise capacity, leading to a total of 14 repeated WLL procedures. The patient had clubbing of fingers and respiratory muscle weakness. In auscultation of the lung, crackles in the lower lobes were the main findings. Following some of the WLL procedures, she experienced prolonged hypoxia that required admission to the intensive care unit and mechanical ventilator support. The patient also received long-term oxygen therapy and was found to have high levels of GM-CSF autoantibodies, resulting in intermittent inhalation treatment of GM-CSF both off-label and subsequently as part of a clinical trial. Despite these interventions, WLLs and drug treatments, the patient continued to experience complaints such as persistent cough, excessive sputum production, exertional dyspnea, and hypoxia that significantly impacted daily activities. In 2022, the patient also had a confirmed case of COVID-19. The deterioration of symptoms resulted in enrollment into a physiotherapy program as an option worth trying.

The patient was treated between July 2022 and September 2022. During this period, no changes were made to the medical treatment. She continued to use a combination of inhaled corticosteroids and bronchodilators which was already prescribed to alleviate symptoms. An informed consent was obtained from patient prior to the beginning of the pulmonary rehabilitation training.

"At first, I ran away from physical therapy, thinking I wouldn't have enough breath for it. But when my doctor told me that this was the last resort for me, I realized how serious the situation was. By insisting on rehabilitation, even though it was hard, I started to feel better in every way, I got stronger and even recovered enough to be free from oxygen support. If the doctor is not determined in this process, the patient may choose the easy way out. This can result in missing out on the substantial benefits of treatment. Physicians should make it clear to their patients that unless they commit to the prescribed physical therapy, no other treatment will be provided." NY, 51, female, diagnosed PAP 14 years ago.

PHYSICAL THERAPY AND REHABILITATION IN ILDS

Pulmonary rehabilitation (PR) has been recommended in the guidelines for IPF for decades. In the first IPF guideline in 2000, PR has been mentioned among other management issues and recommended to encourage IPF patients even though the evidence was lacking. The benefits of combining exercise training, education, and psychosocial were listed as an improvement in exercise tolerance, together with decreased symptoms of breathlessness, improved quality of life, and less need for health care services, except the improvements in lung function unlikely to occur.[1] This guideline has been followed by others, mainly positioned PR among the non-pharmacological treatments such as oxygen support. In the IPF guideline published in 2011, statement has been made by mentioning the level of rec-

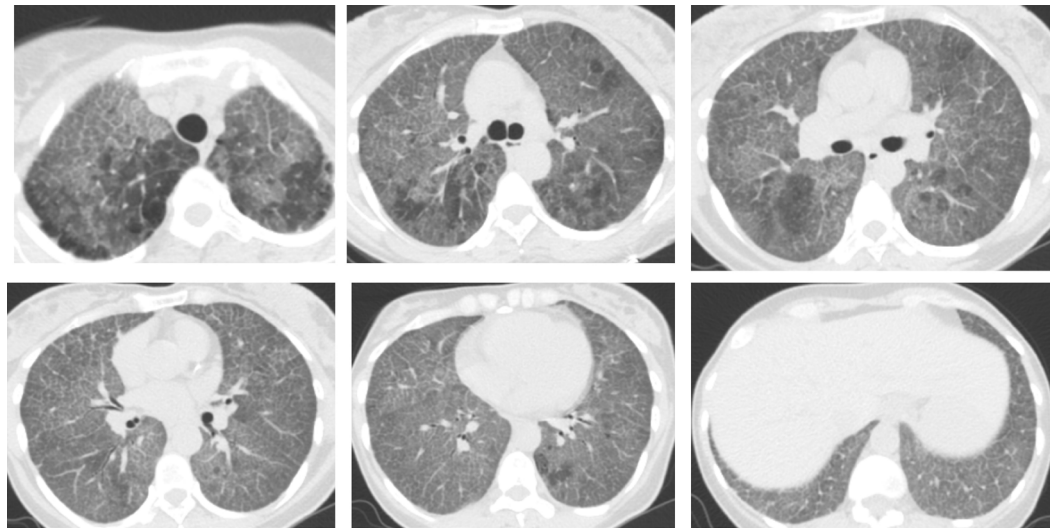


Figure 1. Thoracic CT: Diffuse ground glass appearance in both lungs, relevant to crazy paving pattern, accompanied by interlobular and intralobular septal thickening.

ommendation as weak, however by recommending PR in the majority of IPF patients.[2] In this guideline, the rationale for this recommendation has been based on two controlled trials of PR in IPF demonstrated an improvement in walk distance and symptoms or quality of life, and the positive impact has been more pronounced in patients with worse baseline functional status. An update on interstitial pneumonias has been focused on the classification not the treatment, therefore searching about PR is in vain.[3] A recent comprehensive guideline has an important task to discuss recent advances on IPF including a new term, Progressive Pulmonary Fibrosis (PPF), and PR has been mentioned only by name among the non-pharmacological treatment with oxygen support.[4]

After all, a recent practice guideline has stated that PR is underused despite its proven benefits for patients with chronic respiratory disease and aimed to lead to greater knowledge of the proven benefits of PR, highlight the role of PR in evidence-based health care, and in turn foster referrals to and more effective delivery of PR for people with chronic respiratory disease.[5] It emerged as a highly effective complementary treatment strategy aimed at alleviating respiratory symptoms, enhancing exercise capacity, and improving patients' overall quality of life in chronic lung diseases.

In the IPF Guideline, PR programs described briefly involving aerobic conditioning, strength and flexibility training, educational lectures, nutritional interventions, and psychosocial support.[2] In recent review for ILDs, PR can find a place only in one sentence as in: "Pulmonary rehabilitation can also improve exercise capacity and health-related quality of life, especially if started early." On the other hand, in the treatment algorithm from this overview on ILDs, rare ILDs (only PAP and LAM included) were out of the mainstream with scarce recommendation for treatment and PR was not among these treatments, as in IPF which has drug treatment with two options. However, PR placed in the other arm but at the bottom after all drug treatments by saying when the patient needs were not addressed: Symptom relief, pulmonary rehabilitation, psychological support.[6]

This approach is beneficial not only for common ILD subtypes such as idiopathic pulmonary fibrosis (IPF), but also for rare diseases like pulmonary alveolar proteinosis (PAP), lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and sarcoidosis, each of which presents unique pathophysiological characteristics requiring tailored rehabilitation strategies.[7]

Each subtype of ILD, particularly rare ILDs, must be considered based on the specific characteristics of the disease and through an individualized approach. In a review focusing on one of the rare ILDs, pleuroparenchymal fibroelastosis (PPFE), a highly progressive disease with no effective treatment, a retrospective analysis of nine patients with idiopathic PPFE who

completed a 10-week exercise training program was reported to be beneficial in terms of exercise capacity, dyspnea, anxiety, depression, and health-related quality of life.[8] However, the study also raised a cautionary note for physicians regarding the potential risk of complications such as pneumothorax and pneumomediastinum.[9]

Emerging evidence from a recent study suggests that engagement in pulmonary rehabilitation could contribute to longer-term survival, up to five years, in patients with ILD, including those with IPF. Beyond the well-established clinical benefits, this potential survival improvement highlights the critical need to integrate PR into routine ILD management.[10] An editorial highlights the study's added value by noting that "using individual patient data, this study also goes beyond study-level meta-analysis of a few small trials that were individually, and in meta-analysis, not able to show a significant survival benefit of PR," thereby emphasizing the strength of its methodology and findings.[11] The editorial concludes by stressing that achieving holistic care in ILD is only possible through promoting awareness of PR across all levels, including patients, healthcare providers, and funding stakeholders, while also ensuring both access and reimbursement are adequately addressed.

In summary, this modality is mostly neglected in ILD, even in IPF, the most common and progressive subtype of ILDs. Being a rare or ultra-rare ILD may not be the main obstacle to the lack of PR approaches and studies, especially when the role of PR, and rehabilitation in general, is not sufficiently recognized within the ILD group. On the contrary, physicians may seek such approaches in rare ILDs, since effective treatments are often unavailable and the disease course may be progressive. At the very least, pulmonary rehabilitation plays a key role in the preparation for and post-procedural period of lung transplantation.[12] This chapter aims to raise awareness on the topic and promote the implementation of these programs in patient management through a successful example.

COMPONENTS OF PULMONARY REHABILITATION

Standard pulmonary rehabilitation programs generally consist of four components. These are given below:

Aerobic Exercise Training

Aerobic exercise aims to improve cardiorespiratory endurance, enhance oxygen utilization, and increase overall exercise tolerance.

Implementation Details

- **Exercise types:** Treadmill walking, stationary cycling, brisk walking
- **Intensity:** Submaximal (60-80% of predicted maximum heart rate), moderate to somewhat hard on the Borg scale (3-5 for dyspnea/perceived exertion)
- **Duration & frequency:** 20-40 minutes per session, 3-5 times per week
- **Goals:** Reduce breathlessness, improve muscle oxygen efficiency, and increase tolerance to daily physical activities.[13,14]

Resistive Muscle Strengthening

Peripheral muscle weakness can significantly limit functional capacity in patients with pulmonary disease. Resistance training improves muscular strength, endurance, and mobility.

Implementation Details

- **Target muscle groups:** Quadriceps, hamstrings, calf muscles, shoulder and arm muscles
- **Equipment:** Dumbbells, weight machines, resistance bands
- **Sets/repetitions:** 2-3 sets of 8-12 repetitions at moderate resistance
- **Goals:** Enhance muscle mass and strength, reduce fatigue, and support functional independence.[13]

Respiratory Muscle Training (Inspiratory and Expiratory)

Respiratory muscle training aims to strengthen the muscles involved in breathing, which is particularly important in diseases like PAP, where cough effectiveness and ventilatory capacity are compromised.

Inspiratory Muscle Training (IMT)

- **Devices:** Threshold IMT, POWERbreathe, etc.
- **Intensity:** Starts at 30-50% of baseline Pimax, with progressive loading
- **Frequency:** 1-2 sessions daily, 15-30 minutes each
- **Goal:** Strengthen the diaphragm and accessory respiratory muscles.[15]

Expiratory Muscle Training (EMT):

- **Devices:** Threshold PEP, EMST150, or similar resistance-based devices
- **Intensity:** Initially set at 30-50% of the patient's maximal expiratory pressure (PEmax), gradually increased as tolerated
- **Goal:** Improve cough strength, facilitate airway clearance, and strengthen expiratory muscles.16
- **Frequency:** 1-2 sessions Daily, 5 to 7 days per week, 15-30 minutes each

Patient Education

Patient education empowers individuals to understand their disease, manage symptoms effectively, and actively participate in self-care. It covers disease-specific information such as the pathophysiology and symptoms of PAP, proper medication uses and inhaler techniques, energy conservation strategies and daily activity planning, breathing techniques like pursed-lip and controlled breathing, as well as guidance on nutrition, psychosocial support, and stress management.[13]

Exercise training, in particular, has been shown to reduce dyspnea and significantly improve functional capacity by enhancing ventilatory efficiency. In ILD patients with exercise-induced desaturation, supplemental oxygen during exercise can prevent hypoxemia and enable better tolerance to physical activity.[14] Additionally, training of the inspiratory and expiratory muscles is crucial for improving cough effectiveness and facilitating secretion clearance.[15,16]

EVIDENCE-BASED OUTCOMES

The effectiveness of pulmonary rehabilitation (PR) in patients with interstitial lung diseases (ILD) has been well established through numerous high-quality clinical studies. A comprehensive meta-analysis of 21 randomized controlled trials demonstrated that PR significantly improved functional exercise capacity, with an average increase of 40 meters in the 6-minute walk test (6MWT), along with clinically meaningful reductions in dyspnea (measured by the modified Medical Research Council (mMRC) scale) and improvements in health-related quality of life (HRQoL), without notable adverse effects.[14] In a 2024 randomized controlled trial, 30 patients with IPF underwent an 8-week home-based inspiratory muscle training (IMT) program via telerehabilitation, resulting in a 58-meter improvement in 6MWT, a reduction in mMRC scores from 2.2 to 1.4, and a significant increase in maximal inspiratory pressure (MIP), demonstrating the efficacy of remote IMT in enhancing respiratory and functional outcomes.[17] A 2022 systematic review found that center-based pulmonary rehabilitation in interstitial lung disease significantly improves functional exercise capacity (6-minute walk distance), reduces dyspnea, and enhances health-related quality of life.[18] A multicenter randomized study of a 6-month pulmonary rehabilitation program in IPF reported improvements in 6-minute walk distance, quadriceps strength, and SGRQ at program completion.[19] Furthermore, a systematic review of high-intensity interval training (HIIT) in ILD patients showed that HIIT is feasible and well-tolerated, providing improvements in endurance, ventilatory efficiency, and patient adherence despite the risk of oxygen desaturation.[20] The addition of IMT to conventional PR also proved beneficial in a randomized trial reporting increased PImax (+11 cmH_2O), 6MWT distance (+47.9 meters), and reductions in mMRC and SGRQ scores.[21] Notably, a five-year follow-up study of IPF patients found that participation in PR was associated with a 44% reduced risk of death or lung transplantation, highlighting not only symptom management benefits but also potential survival advantages.[10]

Clinical guidelines for pulmonary rehabilitation in patients with interstitial lung diseases (ILD) emphasize structured and individualized programs to optimize outcomes. A typical rehabilitation program should span 8 to 12 weeks, with sessions conducted two to three times per week. Both center-based and home-based models, including telerehabilitation approaches, have demonstrated comparable effectiveness in improving patient outcomes.[22] The core components of these programs include aerobic and resistance training, as well as adjunctive therapies such as inspiratory and expiratory muscle training (IMT/EMT), with supplemental oxygen administered when it was clinically indicated. Respiratory muscle training, in particular, has been shown to reduce dyspnea, enhance maximal inspiratory and expiratory pressures, and increase exercise capacity in ILD patients.[21] Furthermore, evidence suggests that the benefits of pulmonary rehabilitation may be sustained for up to 12 months following program completion, particularly when patients maintain physical activity and follow-up care is provided.[19]

A review on rare ILD, it has been pointed out that

the experience with pulmonary rehabilitation is still limited. Interestingly, this is the only part, for PPFE, in where rehabilitation was mentioned in a review dedicated to a selection of rare or ultrarare ILDs with a higher probability of being faced in clinical practice, pulmonary alveolar proteinosis (PAP), pulmonary alveolar microlithiasis (PAM), pleuroparenchymal fibroelastosis (PPFE), Hermansky–Pudlak syndrome (HPS), Lymphangioleiomyomatosis (LAM), and various multiple cystic lung diseases, Birt–Hogg–Dubé syndrome (BHDS), and Pulmonary Langerhans cell histiocytosis (PLCH).[23] It deserves to be thought about why the evidence is still limited.

A practice guideline on the efficacy of pulmonary rehabilitation (PR) in chronic lung diseases was recently published. This multidisciplinary panel issued a strong recommendation for PR in adults with interstitial lung disease and recommended offering the choice of center-based PR or telerehabilitation to patients with chronic respiratory disease, based on moderate-quality evidence.[5]

APPLICATION IN RARE ILD SUBTYPES: FOCUS ON PAP

Pulmonary alveolar proteinosis (PAP) is a rare ILD characterized by surfactant accumulation in the alveoli. While it shares clinical features with other ILDs, including dyspnea and oxygen dependence, it has a unique pathophysiology. The autoimmune form (aPAP) constitutes about 90% of cases and is associated with GM-CSF autoantibodies. Secondary forms often relate to smoking or occupational exposures.[24]

WLL (whole lung lavage) is the current gold standard for symptomatic PAP, but it presents challenges such as procedure variability, anesthesia risks, and repeated interventions. Inhaled GM-CSF offers promising results but is limited by cost and availability.[25]

PHYSIOTHERAPY AND PAP

Emerging evidence supports the integration of physical therapy as a valuable adjunct in the management of pulmonary alveolar proteinosis (PAP). Several studies have demonstrated the benefits of both manual and device-assisted physiotherapeutic interventions in improving secretion clearance and respiratory function. In one of the earliest reports, Bracci (1988) described meaningful improvements in pulmonary symptoms and function following chest physiotherapy in a patient with PAP, highlighting its potential therapeutic role.[26] More recently, Bahcaci and Uysal (2021) conducted a comparative case report demonstrating that the lung treated with adjunct manual physiotherapy, including postural drainage, tapotement, and vibration, exhibited greater secretion clearance and faster oxygenation recovery than the contralateral lung treated with WLL alone, underscoring the clinical utility of physiotherapy in PAP management.[27] In addition, device-based airway clearance has shown promise; Kumar and Schweiger (2012) reported that intraoperative use of high-frequency chest wall oscillation (HFCWO) via the Vest™ system during WLL facilitated secretion mobilization and reduced lavage duration.[28] Complementing these findings, a case study involving a 20-year-old female patient undergoing a 24-week pulmonary rehabilitation program, comprising aerobic exercise, inspiratory muscle training (IMT), and resistance training, demonstrated significant functional and symptomatic improvements, suggesting that comprehensive physiotherapy interventions can contribute meaningfully to the clinical management of PAP.[29]

Inspiratory muscle training (IMT) and expiratory muscle training (EMT) are essential, complementary components of respiratory rehabilitation and play a significant role in managing respiratory muscle weakness, particularly in conditions such as interstitial lung diseases (ILD) and pulmonary alveolar proteinosis (PAP). IMT targets inspiratory muscle dysfunction and ventilatory limitations by increasing maximal inspiratory pressure (PImax), leading to reductions in dyspnea, improvements in exercise tolerance, and enhanced oxygen utilization. This is particularly relevant in chronic hypoxemic conditions such as PAP, where inspiratory muscle strengthening contributes to better respiratory efficiency and reduced fatigue during exertion. IMT can be safely implemented in both clinical and home-based settings, with measurable benefits often observed within 5 to 8 weeks of consistent training.[15,21]

EMT, on the other hand, is especially valuable in addressing symptoms such as dyspnea and ineffective cough by improving maximal expiratory pressure (PEmax).[16] It also supports essential functions like speech, swallowing, and physical performance. In PAP, where alveolar filling and altered airway mechanics compromise cough effectiveness, EMT plays a critical role in enhancing secretion clearance, particularly after whole lung lavage (WLL), when the expectoration of residual

material is essential. EMT has also been shown to improve exercise capacity and quality of life in patients with chronic respiratory diseases and may serve as a non-invasive adjunct to WLL in PAP management.[16,30]

When combined, inspiratory muscle training (IMT) and expiratory muscle training (EMT) offer a comprehensive approach to respiratory rehabilitation by strengthening both inspiratory and expiratory muscle groups, optimizing ventilatory mechanics, and enhancing airway clearance. This integrative strategy may facilitate faster recovery following whole lung lavage (WLL), reduce the frequency of repeated procedures, and contribute to improved functional capacity and quality of life in patients with pulmonary alveolar proteinosis (PAP).

Pulmonary rehabilitation, encompassing both general and disease-specific interventions such as IMT and EMT, has been shown to yield significant functional, symptomatic, and psychosocial benefits in individuals with interstitial lung diseases (ILD). In rare ILD subtypes like PAP, the implementation of individualized rehabilitation programs may improve clinical outcomes and serve as an effective adjunct to standard medical therapies.

Considering the invasive nature and inherent limitations of WLL, there is growing rationale for integrating non-pharmacologic and non-invasive strategies, particularly targeted physiotherapy, into the multidisciplinary management of PAP. Further high-quality research is needed to establish standardized rehabilitation protocols tailored to this rare condition.

CASE ANALYSIS

The patient underwent treatment between July 2022 and September 2022. During this period, no modifications were made to the medical therapy. Pre- and post-treatment evaluations focused on dyspnea, respiratory muscle strength, and quality of life. Respiratory muscle strength and pulmonary function were assessed using the Cosmed Pony FX® device. The 6-Minute Walk Test (6MWT) was conducted in accordance with the guidelines established by the American Thoracic Society (ATS).[31] Heart rate, oxygen saturation (SpO_2), blood pressure, and respiratory rate were measured before and after the test. Leg fatigue and dyspnea were assessed using the Modified Borg Scale, and the distance covered during the test was recorded.

The St. George's Respiratory Questionnaire (SGRQ) was used to assess health-related quality of life (HRQoL) in respiratory patients, with higher scores indicating a greater impairment in quality of life.

At baseline, the patient was unable to complete the 6MWT and managed to walk only 360 meters. Resting oxygen saturation was 98% with supplemental oxygen and 95% without; however, it dropped to 80% during physical activity. The patient's maximal inspiratory pressure (MIP) was 52 cmH_2O and maximal expiratory pressure (MEP) was 58 cmH_2O. The modified Medical Research Council (mMRC) dyspnea score was 3.

Following completion of the home-based exercise program, the patient was re-evaluated and successfully completed the 6MWT, walking 432 meters. She improved sufficiently to attend rehabilitation sessions on an outpatient basis. Continuation of the rehabilitation program was conducted face-to-face at the hospital. During the sessions, the patient was able to perform all exercises without the need for supplemental oxygen.

In addition to inspiratory muscle training (IMT), the rehabilitation program included breathing control techniques, diaphragmatic breathing exercises, and other respiratory exercises. Relaxation techniques, postural correction exercises, and trunk muscle strengthening were also incorporated. A 30-minute walk every day is recommended.

IMT was administered over eight weeks using the Philips Respironics Threshold IMT® device with threshold loading. Training was conducted in a seated position using a nose clip. Each session included six loaded breathing cycles interspersed with 3-4 breathing control intervals. The patient was instructed to use the device twice daily for 30-minute sessions over 8 weeks. Inspiratory resistance was adjusted biweekly at the outpatient clinic to ensure that each resistive breath corresponded to 30-40% of the patient's maximal inspiratory pressure (PImax).[32]

The overall program was conducted three times per week, with one session at the clinic and two sessions at home. The first two weeks consisted of clinical treatment only. In the subsequent weeks, patients attended the clinic once per week and performed two home-based sessions. Home sessions were monitored weekly via phone calls. The full 8-week protocol included 12 supervised clinic sessions and 12 home-based sessions. Compliance, technique, and resistance levels were consistently monitored by the same physiotherapist throughout the study.

TREATMENT RESULTS

Upon completion of the intervention, improvements were noted in inspiratory (PImax) and expiratory (PEmax) muscle strength, exercise tolerance, and dyspnea levels. The 6MWT distance increased, reflecting enhanced exercise capacity. Notably, improvements were also observed in all domains of the SGRQ, indicating better quality of life.

Additionally, there was a detected increase in FEV1, FVC, and PEF presented as % of predicted. A general improvement in all measured outcomes was documented, with enhancement in SGRQ subdomains further supporting the clinical effectiveness of the intervention (Table 1).

The effectiveness of an 8-week program of inspiratory muscle training (IMT) combined with physiotherapy was evaluated in a patient with pulmonary alveolar proteinosis (PAP). A notable increase in exercise capacity, as well as improvements in both PIMAX and PEMAX, was observed. Additionally, a reduction in dyspnea and an improvement in quality of life were noted. Conversely, there was minimal change observed in pulmonary function tests. It is common for patients experiencing respiratory symptoms to avoid exercise due to a misconception that physical activity might exacerbate dyspnea. However, our patient benefited from respiratory physiotherapy, IMT, and exercise interventions.

Inspiratory muscle training has been shown to improve inspiratory muscle strength, reduce dyspnea, and enhance exercise capacity in patients with various chronic respiratory diseases, including COPD and interstitial lung diseases (ILDs).[15,21] Although evidence in PAP patients is limited, the physiological principles underlying IMT suggest it may be beneficial by improving the efficiency of respiratory mechanics and reducing the ventilatory demand during physical activity.

Table 1. Comparison of respiratory parameters, exercise capacity and quality of life before and after treatment.

Variables	Pre-treatment	Post-treatment	Δ
PIMAX (cmH2O)	52	103	**51**
PEMAX (cmH2O)	58	72	**14**
FEV1	1.37	1.38	**1**
FEV1%	47	51	**4**
FVC	158	162	**4**
FVC%	48	51	**3**
FEV1/FVC	85	85	**-**
PEF	156	165	**9**
PEF%	46	50	**4**
Exercise capacity (m)	360	432	**72**
SGRQ total point	75.61	55.35	**20.26**
SGRQ symptom	92.91	69.36	**23.55**
SGRQ activity	92.51	60.35	**32.16**
SGRQ effect	60.56	48.12	**12.44**
mMRC	3	1	**2**

Δ: *Change before and after treatment*

The improvement in the 6-minute walk distance and dyspnea scores in this case is consistent with previous studies indicating that pulmonary rehabilitation programs incorporating IMT can lead to clinically meaningful gains in exercise tolerance and symptom control.[14] While pulmonary function test parameters such as FEV1 and FVC often remain stable or change minimally after rehabilitation, functional outcomes and patient-reported measures (e.g., SGRQ) are more sensitive to improvement.[13]

In this case, the addition of trunk stabilization, breathing control, and postural exercises may have contributed to improved ventilatory pattern and thoracoabdominal coordination, further supporting overall respiratory efficiency. The fact that the patient was able to transition from home-based to outpatient sessions without requiring supplemental oxygen is a clinically meaningful outcome, suggesting improved activity tolerance and self-efficacy. The patient, who previously required more than 15 hours of oxygen therapy per day, progressed to using it only at night while sleeping.

This case supports the inclusion of tailored physiotherapy and IMT strategies within the multidisciplinary management of PAP. Future research with larger samples is needed to establish evidence-based rehabilitation protocols for this rare population.

In this patient, most of the process had to be carried out remotely, and the overall outcomes were satisfactory. A recent study involving eight patients with ILD evaluated their experiences with a telerehabilitation system for home-based PR. The findings showed that participants highly valued the intervention, reporting high levels of acceptance and usability, highlighting the potential of telerehabilitation to enhance access to PR for patients with ILD.[33]

CONCLUSION

Rare ILDs are challenging in terms of diagnosis and treatment; supportive therapies are critically important. PR can improve functional capacity and quality of life even in this patient population. Rehabilitation programs should be individualized for each patient.

Innovative approaches such as telerehabilitation may enhance accessibility, especially in rare disease populations. IMT can significantly improve respiratory muscle strength in PAP. Pulmonary rehabilitation provides functional and QOL benefits.

Individualized programs support promising approaches by being safe and effective in rare ILDs. Although clinical evidence is limited, experience gained from diseases such as IPF, and other chronic lung diseases serve as a guide for managing rare ILDs as well. In the era of technology, telerehabilitation offers many opportunities for PR in chronic lung diseases, including rare ILDs, to create a holistic approach which covers all components in an expert center.

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CHAPTER 21

FUTURE PERSPECTIVE ON RARE INTERSTITIAL LUNG DISEASES

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FUTURE PERSPECTIVE ON RARE INTERSTITIAL LUNG DISEASES

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ABSTRACT

Rare and ultra-rare interstitial lung diseases (ILDs) comprise a heterogeneous group of entities. The diagnostic journey for patients with rare ILD is frequently delayed and complex. Assessment of clinical, radiological, functional and histopathological features in the multidisciplinary expert committee may be challenging due to complex imaging patterns, non-specific clinical symptoms, or inconclusive biopsies. Furthermore, research advances in these rare diseases remain limited in most cases resulting in a poor understanding of pathogenesis, natural history and drug-regulation targeting. However, several emerging trends suggest an optimistic future for patient care and research in this group.

Digital platforms enabling data sharing across international networks can facilitate centralized expert review, which is essential for ultra-rare conditions. Advances in imaging analytics, including artificial intelligence (AI)-based interpretation of high-resolution computed tomography (HRCT), promise to reduce diagnostic delays and enhance accuracy in ultra-rare ILDs. The application of high-throughput omics technologies (genomics, transcriptomics, proteomics and metabolomics) can transform the diagnostic landscape of these rare ILDs. Proper molecular characterization will facilitate and optimize diagnosis even in early stages of disease, the identification of endotypes and phenotypes, and therapeutic decisions. Ultrarare-ILD therapeutic options are frequently off-label or supported by low-level research evidence. However, precision medicine is slowly transforming the landscape of these ILDs, targeting pathway-specific origins.

Ultra-rare ILDs are entering a new era of diagnostic and therapeutic precision. The merging of molecular insights, AI-driven tools, and collaborative networking is improving diagnostic awareness and certainty and accelerating the translation of science in clinical practice. Patient priorities and access to care and clinical research remain incompletely addressed.. However, the future holds promise for achieving these unmet needs and also conducting more individualized, precise and pathogenesis-driven patient care.

Keywords: *Interstitial lung diseases; Rare interstitial lung diseases; Future perspectives; Omic technologies; Molecular biology; Artificial intelligence driven tools*

ÖZET

Nadir ve ultra-nadir interstisyel akciğer hastalıkları (İAH), heterojen bir hastalık grubunu oluşturur. Nadir İAH tanısı alan hastaların tanısal süreci genellikle gecikmeler içermektedir ve karmaşıktır. Klinik, radyolojik, fonksiyonel ve histopatolojik bulguların multidisipliner uzmanların oluşturduğu konseyler tarafından değerlendirilmesi; örtüşen görüntüleme paternleri, özgül olmayan klinik semptomlar ya da sonuç vermeyen biyopsiler nedeniyle zorlayıcı olabilir. Ayrıca, bu İAH'larla ilgili araştırmalar çoğu durumda sınırlı kalmakta, bazı hastalıklar ise neredeyse hiç çalışılmamaktadır. Bu durum, patogenez, doğal seyir ve tedavi hedeflerine yönelik düzenlemeler gibi alanlarda bilgi eksikliğine neden olmaktadır. Ancak, hasta bakımı ve araştırma açısından yakın geleceğe dair iyimser beklentiler oluşturan bazı yeni girişimler ve eğilimler mevcuttur.

Uluslararası ağlar aracılığıyla veri paylaşımını mümkün kılan dijital platformlar, ultra-nadir hastalıklarda kritik öneme sahip uzman merkezlerde değerlendirilmeyi kolaylaştırabilir. Yüksek çözünürlüklü bilgisayarlı tomografi (YÇBT) görüntülerinin yapay zekâ tabanlı analizlerini içeren görüntüleme teknolojilerindeki ilerlemeler, tanıdaki gecikmeleri azaltma ve doğruluğu artırma potansiyeli taşımak-

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tadır. Genomik, transkriptomik, proteomik ve metabolomik gibi yüksek verimli "omik" teknolojilerin uygulanması, nadir İAH'ların tanısal yaklaşımında köklü dönüşümler yaratabilir. Uygun moleküler karakterizasyon; hastalığın erken evrelerinde bile tanının doğruluğunu artıracak, endotip ve fenotip belirlenmesini sağlayacak ve tedavi yanıtına göre şekillenen tedavi kararlarını optimize edecektir.

Ultra-nadir İAH'lardaki tedavi seçenekleri genellikle sınırlıdır, çoğunlukla endikasyon dışı kullanıma dayanır ve düşük düzeyde araştırma verileriyle desteklenmektedir. Bununla birlikte, kişiye özel tıp, bu hastalık grubunda tedavi yaklaşımlarını yavaş yavaş dönüştürmekte; özellikle yolak-spesifik kökeni hedefleyen vakalarda akciğer hasarını kısmen veya tamamen tersine çevirebilecek en ileri tedavi olanaklarını sunmaktadır.

Ultra-nadir İAH'ların tanı ve tedavide yeni bir hassasiyet çağına girmekte olduğunu söyleyebiliriz. Moleküler bilgiler, yapay zekâ destekli araçlar ve iş birliğine dayalı ağların birleşimi, tanısal farkındalık ve doğruluğu artırmakta ve bilimin klinik uygulamaya aktarımını hızlandırmaktadır. Bununla birlikte, özellikle adil sağlık hizmetine erişim ve klinik çalışmaların yapılabilmesi açısından önemli zorluklar ve hastaların karşılanmamış ihtiyaçları devam etmektedir. Ancak gelecek, bu eksiklerin giderilmesi ve daha bireyselleştirilmiş, hassas ve biyolojik temelli yaklaşımların sağlanması açısından umut vadetmektedir.

Anahtar Kelimeler: *İnterstisyel akciğer hastalıkları; Nadir interstisyel akciğer hastalıkları; Gelecek perspektifi; Omik teknolojiler; Moleküler biyoloji; Yapay zekâ destekli araçlar*

INTRODUCTON

Rare and ultra-rare interstitial lung diseases (ILDs) comprise a heterogeneous group of entities including cystic lung diseases, such as lymphangioleiomyomatosis (LAM) and Birt-Hogg-Dubé (BHD), and other well-defined ILDs, for instance pleuroparenchymal fibroelastosis (PPFE), inherited ILDs, pulmonary alveolar proteinosis (PAP), eosinophilic pneumonias and alveolar microlithiasis. These ILDs share challenges for early diagnosis, prognostic stratification, and treatment due to the ultra-low prevalence, clinical heterogeneity and limited therapeutic options.

Furthermore, research advances in these ILDs remain limited in most cases and as a group they are completely under-researched, which results in a poor understanding of pathogenesis, natural history and drug-regulation targeting. However, several emerging actions and trends suggest an optimistic near future for patient care and research in these entities. In this book, the future perspectives on each topic have been also discussed specifically to the relevant disease.

DIAGNOSTIC ADVANCES

The diagnostic journey for patients with rare ILD is frequently delayed and complex.[1] Assessment of clinical, radiological, functional and histopathological features on review by the multidisciplinary expert committee may be challenging due to overlapping imaging patterns, non-specific clinical symptoms, or inconclusive biopsies.[1,2] Furthermore, the rapid identification of some ultra-rare ILDs requires previous training and experience..[1,2] Digital platforms enabling data sharing across international networks can facilitate centralized expert review, which is essential for ultra-rare conditions.[2,3] Furthermore, emerging technologies are complementing classic diagnostic strategies.[3,4] Advances in imaging analytics, including artificial intelligence (AI)-based interpretation of high-resolution computed tomography (HRCT), promise to reduce diagnostic delays and enhance accuracy in ultra-rare ILDs.[3-6] Machine learning models trained on large imaging datasets are being developed to differentiate radiologic patterns and ILDs, which will be a great advance in countries or regions which lack an expert ILD radiologist.[3] Similarly, the integration of digital pathology and AI-assisted histological interpretation may further improve diagnostic precision, especially in centers lacking specialized expertise.[7] Furthermore, the extraction of high-dimensional features from medical images (radiomics) will help to reflect underlying tissue pathology, and assist in diagnosing disease in early stages and subclinical phenotypes.[4,5,8-11]

On the other hand, the application of high-throughput omics technologies (genomics, transcriptomics, proteomics and metabolomics) can transform the diagnostic landscape of these rare ILDs.[12,13] The proper molecular characterization with these sophisticated analyses will facilitate and optimize diagnosis even in early stages of disease, including the identification of endotypes and phenotypes, and therapeutic decision making based on predictive modeling.[14] Currently, only a few specific genetic fibrotic ILDs have been recognized, but surfactant protein genes and telomerase dysfunction has led to implications for both prognosis and family counseling.[15,16] Identification of SFTPC, ABCA3, NKX2-1, CSF2RA/B and some telomere related (TR) pathogenic gene variants provides both diagnostic and prognostic insights in children and young adults.[9,15-17] Advances in genomic diagnostics,

including whole-exome (WES) and whole genome sequencing (WGS), have facilitated earlier and more accurate detection of pathogenic variants, shifting the paradigm from phenotype-based diagnosis to genotype-driven classification and individualized disease monitoring and therapies.[15,18] Finally, liquid biopsy approaches, such as the analysis of cell-free DNA, exosomal RNA, or blood biomarkers, are being developed to create less invasive diagnostic tools and predictors of diseases progression.[19]

PATIENT STRATIFICATION AND MONITORING

The collaborative worldwide network on rare ILDs, including registries (eurILD, PAP Registry, LAM Foundation Registry), genetics (DNA worldwide consortium, Team Telomere, Genetic and Rare Diseases Information Center (GARD), Online Mendelian Inheritance In Man (OMIM)) and other multicenter translational studies provide a mechanism for patient differentiation, stratification and natural history modeling for prognostic prediction and optimization of therapeutic approaches.[20,21] However, only some advances in blood biomarkers have been clinically validated and translated in clinical practice such as the use of serum vascular endothelial growth factor-D (VEGF-D) as a diagnostic and prognostic biomarker.[22,23] and telomere length measurement (telomere shortening) for as a screening tool for genetic ILDs.[24,25] Currently there are several studies ongoing trying to validate other biomarkers for different ultra-rare ILDs to improve the precision monitoring and predicting the best therapeutic approach. These studies will support longitudinal tracking of pulmonary function decline, disease activity and treatment response, and understanding phenotypes at higher risk of rapid progression to guide early intervention.[26] Finally, advances in home monitoring devices and wearable technologies may also become useful for future monitoring strategies, especially in low-access or under-resourced populations, and reduce the burden of in-hospital complementary tests in working-active patients.[27]

FUTURE TREATMENT ADVANCES

Ultrarare-ILD therapeutic options are usually limited, frequently off-label or supported by low-level evidence. However, precision medicine is slowly transforming the landscape of these ILDs, especially in cases targeting pathway-specific origins, and exemplified by the remarkable advances in disease-modifying treatment provided below.[8,28]

1. Granulocyte-macrophage colony-stimulating factor (GM-CSF) replacement therapy (inhaled or subcutaneous) for autoimmune PAP represents an excellent example of precision targeting-therapy that reverses pulmonary changes and improves the clinical state of these patients.[29,30] The anti-GM-CSF antibody titration has become part of the diagnostic algorithm.[31-34] After the success of the phase-II IMPALA clinical trial, IMPALA-2 is a global, pivotal, phase 3, randomized, doble-blind, placebo-controlled clinical trial to compare the efficacy and safety of molgramostim 300 mcg self-administered once daily in patients with aPAP, which has been recently closed, and the preliminary results have been presented in the ATS Congress 2025.[35] Molgramostim reduced the ground-glass opacity scores at 24 weeks (p=0.0004) and showed statistically significant benefit on quality of life at week 24 (HRQoL, p=0.0084) and less breathing problems assessed by PGIS at both weeks 24 (p=0.035) and 48 (0.0049).[34] Furthermore, fewer patients required rescue whole lung lavages (WLL) in molgramostim group compared with placebo.[35] The complete results of this recent clinical trial (NCT04544293) will be published in the near future, and hopefully will support the approval of this therapy by government agencies..
2. Olipudase alfa is a recombinant human acid sphingomyelinase designed to replace the enzyme dysfunction in patients with acid sphingomyelinase deficiency (ASMD or previously known as Niemann-Pick disease).[36] It is the first therapy that replaces the underlying enzymatic defect in non-central nervous system ASMD, including the associated ILD.[36] Olipudase alfa is administered intravenously every two weeks through a gradual dose-escalation schedule up to 3mg/kg. The pivotal randomized phase 2/3 ASCEND trial included 36 adults with non-central nervous system ASMD showed an improvement of DLCO (+22% vs +3%, p=0.0004) with a favorable safety profile.[36]
3. Sirolimus, an mTOR inhibitor that reduces LAM cell proliferation, was approved as a first-line treatment for LAM patients with or without tuberous sclerosis after demonstrating its ability to stabilize pulmonary function and reduce angiomyolipoma size in the MILES clinical trial.[37] New clinical tri-

als are exploring combination regimens targeting other involved pathways looking for synergistic effects and induction of disease remission.[38-40]

Other therapeutic advances that are currently being explored include immunomodulation for monogenic autoinflammatory or autoimmune ILDs, such as JAK-STAT pathway therapies (ruxolitinib and baricitinib), statins, HDAC inhibitors, or anti-integrin therapies.[41] Gene-based strategies under investigation include antisense oligonucleotides (ASOs), RNA interference (RNAi), and CRISPR/Cas-mediated gene editing to correct or silence pathogenic mutations.[42,43] Preclinical studies employing gene editing (CRISPR-Cas9 correction of SFTPC pathogenic gene variants) and clinical trials with molecules that try to address the downstream consequences of telomere dysfunction are underway.[44] Telomerase activators, such as danazol, senolytics (navitoclax) and regulators of mitochondrial function and autophagy are under evaluation.[44] Finally, the search for a future regenerative and curative treatments will include cell therapy using mesenchymal stem cells and alveolar epithelial progenitors. However, due to the complexity and heterogeneity of human cells involved in the homeostasis of the lung and the multiple factors that influence their differentiation and function, cell therapy will require extensive safety testing before translation in clinical practice.

But the greatest challenge for novel effective targeting treatment in ultra-rare ILDs remains the feasibility, practicality and affordability of traditional randomized controlled trials (RCTs due to small sample sizes and geographically dispersed populations.[40] Therefore, future innovation in designing clinical trials will pivot on pragmatic platforms and umbrella trial designs that allow testing of multiple therapies across ILDs (REMAP-ILD initiative).[40,45] Advances in rare disease research will be greatly facilitated by the formation of global consortia and networks, such as the ERN-LUNG, to better standardize care, enable the sharing of biobanks and data science, and fostering collaboration with patient advocacy groups.

CONCLUSIONS

Ultra-rare ILDs are entering a new era of diagnostic and therapeutic precision. The merging of molecular insights, AI-driven tools, and collaborative networking is improving diagnostic awareness and certainty and accelerating the translation of science in clinical practice. Despite the considerable challenges that ultra-rare ILD's face for equitable care access and trial feasibility, the future holds promise for achieving these unmet needs and providing individualized, precise and biology-driven patient care.

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