Modern Rheumatology Case Reports, **00**, 2021, 1–5
DOI: https://doi.org/10.1093/mrcr/rxab026
Advance access publication date: 22 September 2021
Case Report

Haemophagocytic lymphohistiocytosis in a patient with familial Mediterranean fever and miliary tuberculosis: a case report

Emir Cerme[a], Mert Oztas[b], Ilker Inanc Balkan[c], Esin Aktas Cetin[d] and Serdal Ugurlu[b,*]

[a]Department of Internal Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey
[b]Department of Internal Medicine, Division of Rheumatology, Istanbul University-Cerrahpasa, Istanbul, Turkey
[c]Department of Infectious Diseases and Clinical Microbiology, Istanbul University-Cerrahpasa, Istanbul, Turkey
[d]Institute of Experimental Medicine (DETAE), Department of Immunology, Istanbul University, Istanbul, Turkey

Correspondence: Serdal Ugurlu; serdalugurlu@gmail.com; Department of Internal Medicine, Division of Rheumatology, Istanbul University-Cerrahpasa, Kocamustafapasa Street 53, Istanbul 34098, Turkey.

ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a lethal complication of several infections, especially viral origin. Mycobacterium tuberculosis infection can also lead to HLH, yet it is an uncommon trigger. Considering the role of increased cytokines in HLH, autoinflammatory conditions, such as familial Mediterranean fever (FMF), might contribute to its development. Nevertheless, the possible relationship between FMF and HLH has been suggested only in some case reports. We present a case of FMF who admitted to the hospital with consitutional symptoms and chest pain regarding to recurrent pericarditis. On a blood test, pancytopenia and elevated acute phase reactants were seen. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography demonstrated positive FDG uptake sites on both the right and left surrenal glands, the visceral layer of pericard, and reactive lymphadenomegalies at multiple mediastinal regions. Bone marrow biopsy revealed haemophagocytosis. Methylprednisolone treatment was initiated. Despite immunosuppressive treatment, clinical and biochemical parameters deteriorated; thus, a thorax computed tomography was executed. Findings were consistent with miliary tuberculosis infection. M. tuberculosis was detected in blood culture and bronchoalveolar lavage culture material. Also, bone marrow and surrenal biopsy material revealed necrotising caseating granuloma.

KEYWORDS: Cytokine storm; familial Mediterranean fever; haemophagocytic lymphohistiocytosis; macrophage activation syndrome; tuberculosis

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening histiocytic disorder characterised by cytokine storm and increased inflammation. It usually presents with fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, hyperferritinemia, high C-reactive protein (CRP), and sedimentation levels [1]. The underlying mechanisms of uncontrolled immunological responses similar to autoinflammatory disorders can either be genetically transmitted or acquired. Two types of HLH have been described: primary (familial) and secondary forms. The most common causes leading to secondary HLH are infections (mainly viral), malignancies (mostly lymphoma), autoimmune/autoinflammatory disorders, and some other diseases [2]. Among autoinflammatory disorders, FMF was reported only in two cases [3, 4]. Although infections are the common triggers of HLH, M. tuberculosis has rarely been reported [5]. The main approach to the management of secondary HLH is to treat underlying pathology. Nevertheless, additional immunosuppressive therapies are usually needed to prohibit increased immune response.

Case presentation

A 46-year-old male patient was admitted to Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Emergency Department, with fever, dyspnoea, night sweating, and weight loss. Physical examination revealed no sign of infection and no heart murmur, and bilateral lung auscultation sounds were normal. Abdominal tenderness was not observed. Musculoskeletal examination was normal. He denied the use of tobacco, alcohol, or illicit substances. He was diagnosed with familial Mediterranean fever (FMF), showing M694V homozygosity in exon 10 of MEFV gene at age 23, and was diagnosed with ankylosing spondylitis (AS) at age 25. His brother and his son also were diagnosed with FMF. He had a history of receiving etanercept (ETN) for the treatment of AS and has been receiving anakinra for treatment of FMF since 2014. He did not have any travelling history. He stated he was admitted to a community hospital with the same complaints 2 weeks ago. The electrocardiogram (ECG) exhibited common irregular ST segment elevations. Laboratory analysis indicated pancytopenia [haemoglobin: 10.8 gr/dl (13.6–17.2), Platelet (PLT): 137,000/μl (156,000–373,000), White Blood Cell (WBC): 2,700/μl (4300–10,300), Neut: 2,000/μl (2100–6,100)] and elevated acute-phase reactants [CRP: 222 mg/l (0–5), Erythrocyte Sedimentation Rate (ESR): 45 mm/h (0–15)] despite normal fibrinogen level. Febrile neutropenia was considered as febrile neutropenia and cefepime 2 g (iv) q8hr was immediately initiated. Given the presence of cough and night sweating, a thorax CT was performed and

Received 8 July 2021; Accepted 12 August 2021
© Japan College of Rheumatology 2021. Published by Oxford University Press. All rights reserved.
For permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/mrcr/advance-article/doi/10.1093/mrcr/rxab026/6373648 by Istanbul University Library user on 21 October 2021

the findings were consistent with atypic pneumonia. Considering ECG abnormalities and recent admissions to hospital with same complaints, he was diagnosed with pericarditis and received nonsteroidal anti-inflammatory drugs. An echocardiogram was used, which revealed an ejection fraction of 55% and pericardial effusion of 13 mm at the left ventricule posterior wall with no sign of tamponade. Viral serology tests (HbsAg, Anti-HCV, Anti-HIV, Toxoplasma IgM, EBV VCA IgM, and CMV IgM) were negative. Anti-Hbs: 40 IU/ml (<10 considered negative). The Rose Bengal test was negative. The tuberculin skin test was negative. The QuantiFERON TB test was also negative. Rheumatoid factor and antinuclear antibody were negative. Protein electrophoresis revealed polyclonal gammopathy with a mildly elevated serum IgA level [552 mg/dl (70–400)]. HLH was considered as a possible diagnosis, yet the underlying aetiology was that either infection or malignancy could not be revealed. He was given methylprednisolone 60 mg q24h iv for 3 days. Within 3 days of steroid treatment, despite a decreased CRP level, elevated serum transaminases persisted, and the fibrinogen level also decreased. On the first day of methylprednisolone therapy, FDG positron emission tomography/computed tomography (CT) was performed to determine if there was a malign lesion. It revealed positive uptake regions on right adrenal gland with suvmax of FDG uptake was 12, on left adrenal gland with suvmax of FDG uptake was 13, on visceral pericardium with suvmax of FDG uptake was 14 and reactive lymphadenomegalies at multiple mediastinal regions and bilateral supraclavicular regions (Figures 1 and 2). In order to rule out the malignancies of gastrointestinal system, gastroscopy and colonoscopy were performed and totally normal findings were seen. A bone marrow biopsy was performed to confirm HLH, and bone marrow aspiration demonstrated haemophagocytosis (Figure 3). Flow cytometry analysis of bone marrow aspiration indicated no haematological malignancy finding. After excluding the possibility of pheochromocytoma, adrenal tru-cut biopsy was performed. While receiving 60 mg iv q24h methylprednisolone for 7 days, despite the decreasing of acute-phase reactants (CRP: 12 mg/l, ESR: 22 mm/h) and improvement in leukocyte level (WBC: 6700/µl, Neut: 5200/µl), hypofibrinogenemia worsened (fibrinogen: 129 mg/dl), platelet level decreased (PLT: 75,000/µl), and transaminases levels increased (Alanine Aminotransferase (ALT): 354 IU/l, Aspartate Aminotransferase (AST): 164 IU/l). Pulse methylprednisolone 1 g iv q24h was administered. Despite pulse steroid treatment for 3 days, fever, hypofibrinogenemia, and elevation in transaminases persisted (ALT: 521 IU/l, AST: 273 IU/l, fibrinogen: 103 mg/dl). Neither blood culture nor urine culture indicated any bacteremia. Cefepim was stopped due to the elevated transaminases. Cyclosporine 100 mg po q8h combined with dexamethasone 10 mg/m^2 therapy was promptly initiated. On the fourth day of the therapy, hypofibrinogenemia ameliorated (fibrinogen: 223 mg/dl), although low platelet count persisted (PLT: 40,000/µl). After 7 days, the cyclosporine dose was adjusted due to the prerenal type acute renal failure and intravenous fluid resuscitation was administered. Primer adrenal insufficiency was suspected because of hyponatremia, hypotension despite intravenous fluid resuscitation and hyperkalaemia, so fludrocortisone 0.1 mg q24h was administered (sodium: 129 mmol/l; potassium: 5.4 mmol/l). Poor performance status and fever persisted and thorax CT was executed. It showed multiple nodular lesions at the upper lobes of bilateral lungs, which can be associated with miliar tuberculosis (Figure 4). Bone marrow biopsy specimen and adrenal tru-cut biopsy exhibited necrotising caseating granuloma. Immunohistochemical test of bone marrow biopsy indicated no malignancy. Bronchoalveolar lavage was immediately performed; transbronchial biopsy was positive for acid-fast bacilli. Anti-TB treatment was initiated with rifampin 600 mg/d, isoniazid 300 mg/d, ethambutol 1500 mg/d, and pyrazinamide 1500 mg/d. Additionally, M. tuberculosis was detected in blood culture and bronchoalveolar lavage culture material. The patient died on the 17th day of anti-TB treatment.

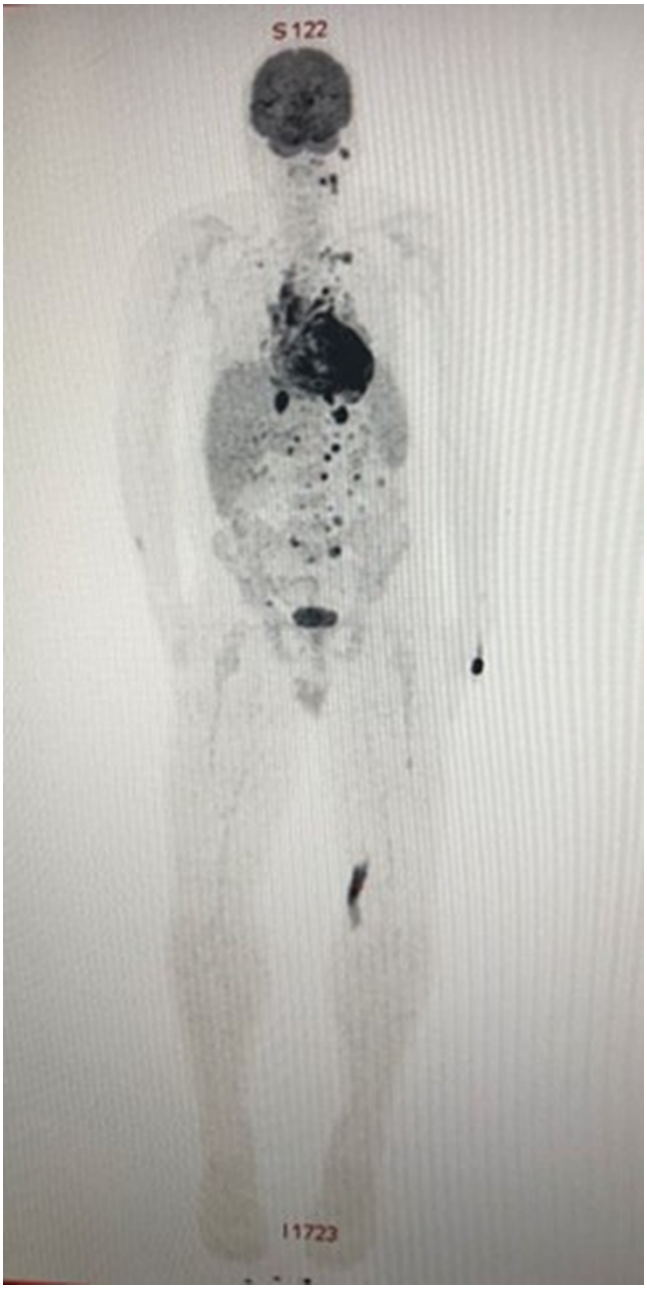


Figure 1. FDG-positron emission tomography demonstrated reactive lymphadenomegalies at multiple mediastinal regions and bilateral supraclavicular regions.

Downloaded from https://academic.oup.com/mrcr/advance-article/doi/10.1093/mrcr/rxab026/6373648 by Istanbul University Library user on 21 October 2021

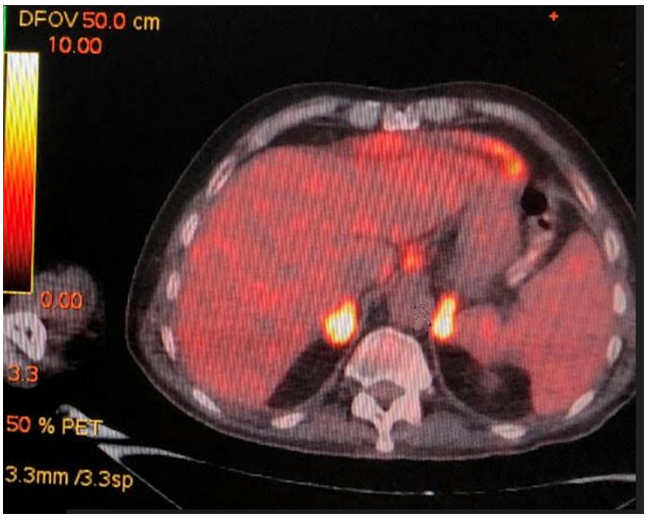


Figure 2. FDG-positron emission tomography demonstrated positive uptake sites on bilateral adrenal glands.

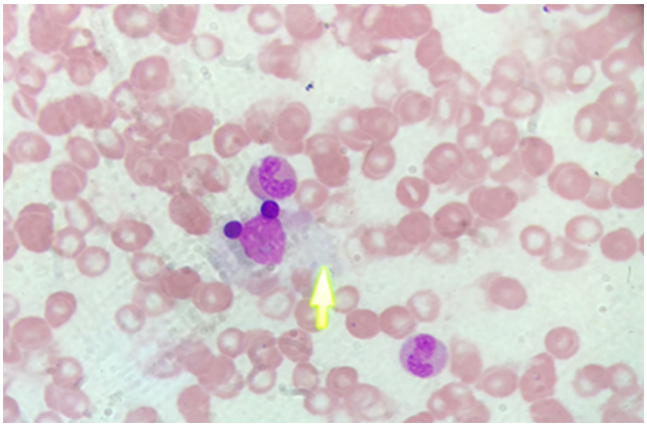


Figure 3. Bone marrow aspiration exhibited haemophagocytosis.

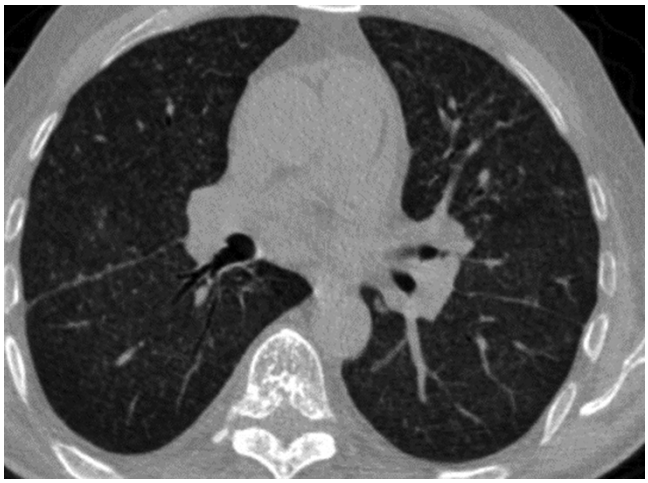


Figure 4. Thorax CT revealed multiple small nodules compatible with miliary pattern of TB.

Discussion

We reported a case with concomitant FMF showing M694V homozygosity in the MEFV gene and recent miliary tuberculosis infection presented as HLH.

HLH is a histiocytic disorder characterised by uncontrolled T-lymphocyte activation, which promotes the proliferation of macrophages, leading to 'cytokine storm' and uncontrolled phagocytosis of platelets and erythrocytes [6]. Cytokines such as interferon-gamma, interleukin (IL) 12, and IL-18 play an important role in activating HLH [7, 8]. It is demonstrated that elevated serum IL-18 and interferon-gamma levels correlate with disease activity [8]. Pro-inflammatory cytokines IL-1ß, tumour necrosis factor alpha (TNF-alpha), and IL-6 also elevate during HLH attack [9, 10]. Uncontrolled inflammation occurs mainly due to the impaired function of natural killer (NK) cells and cytotoxic T lymphocytes [11].

TNF-alpha has a pivotal role in host response to M. tuberculosis infection [12]. It triggers the secretion of inflammatory cytokines and leads to the recruitment of immune cells, especially macrophages that result in granuloma formation [13, 14]. It has been shown that using TNF-alpha blockers could lead to the reactivation of latent M. tuberculosis infection [12]. Compared to TNF-binding monoclonal antibodies, such as infliximab and adalimumab, which recognise both monomeric and trimeric TNF, ETN is only dimeric soluble TNF receptor [12]. Also, infliximab and adalimumab impede T-lymphocyte activity and interferon-gamma secretion thereby ETN does not [12, 15]. In addition, some studies indicated a greater risk of M. tuberculosis infection among patients who received infliximab than among ETN-treated patients [16–18]. Nevertheless, ETN has been shown to increase the risk of M. tuberculosis activation as in our case [16–18].

Fever of unknown origin that is unresponsive to the antimicrobial therapy, general fatigue, pancytopenia and hyperferritinemia should raise the suspicion of HLH. The presence of at least five out of following eight criteria may be diagnostic for HLH [19]:

1. Fever: peak temperature >38.5°C for 7 or more days.
2. Splenomegaly: spleen palpated >3 cm below the left costal margin.
3. Cytopenia involving two or more cell lines: haemoglobin <9.0 g/dl, or platelet <100,000/µl, or absolute neutrophil count <1000/µl.
4. Hypertriglyceridemia or hypofibrinogenaemia: fasting triglycerides >2.0 mmol/l, or more than 3 standard deviations (SD) above the normal value for age, or fibrinogen <1.5 g/l, or more than 3 SD below the normal value for age.
5. Haemophagocytosis: demonstrated in bone marrow, spleen, or lymph node; no evidence for malignancy
6. Low or absent NK cell activity.
7. Ferritin >500 µg/l.
8. Soluble CD25 (soluble IL-2 receptor) >2400 U/ml.

Age over 30 years, hyperferritinaemia, disseminated intravascular coagulation, and increased ß2-microglobulin levels are poor prognostic criteria.

HLH can be seen in the course of monogenic autoinflammatory disorders (AIDs) [20]. Deregulation of innate immune system and increased IL-1ß secretion play an important role in

Downloaded from https://academic.oup.com/mrcr/advance-article/doi/10.1093/mrcr/rxab026/6373648 by Istanbul University Library user on 21 October 2021

the pathogenesis of AIDs [20]. Nucleotide-binding oligomerisation domain-like receptors play a central role in recognising endogenous stress signals and pathogen-associated molecular patterns [21, 22]. Enhanced NLRP3 activity triggers a cascade system that results in increased secretion of IL-1ß [21, 23]. Pyrin is a molecule that inhibits inflammasome activation and cascade system and limits the production of IL-1ß [21, 24]. MEFV gene mutation in FMF results in the dysregulation of pyrin and uncontrolled IL-1ß secretion and inflammation [23]. IL-1ß was also found elevated during HLH episode [8]. IL-18 is another cytokine that was demonstrated as elevated in patients with FMF [25–27]. It is indicated that IL-18 enhances the secretion of TNF-alpha and IL-1ß and also contributes to the activity of macrophages in patients with rheumatoid arthritis in some studies [28]. Some studies suggested that IL-18 level correlates with disease activity in patients with FMF [25]. Moreover, a recent study demonstrated that patients with M694V mutation had higher serum levels of IL-1ß and IL-18 [25, 29]. The genetic test of our case also demonstrated M694V homozygosity in the MEFV gene and, given the relationship between the aforementioned cytokines and HLH, this mutation might contribute to the development of HLH [7–10].

Two cases of FMF-associated HLH have been reported in English literature. L-Rossi Semerano *et al.* [3] first reported that a 4-year-old boy without any underlying disease was admitted to the hospital with persistent fever, fatigue, pancytopenia, low fibrinogen level, clotting abnormalities, hepatosplenomegaly, severe hepatic impairment, and serositis. Genetic testing revealed M694V homozygosity in the MEFV gene. Methylprednisolone (2 mg/kg/day) and azathioprine (2.5 mg/kg/day) provided an improvement. Azathioprine was replaced by cyclosporine (6 mg/kg/day) with clinical efficacy. Colchicine was finally added. Nuray Uslu *et al.* [4] described HLH in a child with Crohn's disease and FMF. He was described as carrying compound heterozygote MEFV mutations (M694V/E148Q). One year after colchicine had started, he was admitted to the hospital with clinical findings of HLH.

Our case also had M694V homozygosity in the MEFV gene. He had two relapsing pericarditis attacks within 3 weeks, which could be because of either FMF episode or M. tuberculosis infection. Pericarditis attack did not repeat during antituberculosis and immunosuppressive treatment, yet pericardial effusion sampling was not performed.

NK cell function deficiency is mainly described for familial HLH. Familial HLH patients show this defect at the diagnosis. Also, patients with infection-related HLH may exhibit decreased NK activity during inflammation, which is reconstituted at the time HLH is resolved [20].

To determine the poor performance status resulted from either uncontrolled HLH or miliary tuberculosis, peripheral blood flow cytometry was evaluated. Among NK cells, the $CD16^{+}CD56^{dimensional}$ subgroup is the major population. It shows cytotoxic activity; meanwhile, the $CD16^{-}CD56^{bright}$ population secretes cytokines, especially interferon-gamma [11]. We were expecting to see a decreased NK count and its cytotoxic activity. But NK count was normal and cytotoxic activity (CD16, CD107a, and IFN-gamma) was increased. The subtype of NK that releases inflammatory cytokines ($CD\ 56^{+}$) was also found as proportionally high. Those findings were interpreted as compatible with the recovering term of HLH. Despite recovering from HLH, the patient died because of a severe miliary tuberculosis infection.

Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) should also be discussed. TB-IRIS is an excessively increased immune response to alive or dead bacilli of M. tuberculosis, which is usually concomitant with HIV infection. More rarely, it has been described in HIV-uninfected patients [2]. It is suggested that aberrant NLRP3 and AIM2 inflammasome activity may play a role in the pathogenesis of TB-IRIS as in AIDs [30]. Also, the interplay between serum IL-18 level and TB-IRIS has been shown in some studies [31]. TB-IRIS may be seen during or after the completion of anti-TB treatment. Four criteria must be met to establish the diagnosis of TB-IRIS [32, 33]:

1. Initial improvement of TB-related symptoms and/or radiographic findings after adequate anti-TB treatment for a certain time;
2. Paradoxical deterioration of TB-related symptoms and/or radiological findings at the primary or new locations during or after anti-TB treatment;
3. Absence of conditions that reduce the efficacy of anti-TB drugs (e.g. poor compliance, drug malabsorption, and drugs side effects);
4. Exclusion of other possible causes of clinical deterioration.

We did not consider TB-IRIS in the case, given the laboratory results and clinical course, which did not improve during treatment.

We also reviewed three cases of M. tuberculosis-associated haemophagocytic syndrome presenting with adrenal mass reported in English literature. Shin *et al.* [34] reported a 50-year-old male who was admitted to the hospital with weight loss and fever. He was diagnosed with HLH associated with tuberculosis. During antituberculosis treatment, toxic hepatitis and adrenal insufficiency developed. Our case also had hypoglycaemia and hypotension during dexamethasone treatment and thus received fludrocortisone 0.1 mg q24h.

Other two cases were reported by Campo *et al.* [35]. These cases had disseminated tuberculosis, which also affected adrenal glands, and had died before any anti-TB treatment or immunosuppressive was started.

Conclusion

Secondary HLH is a life-threatening disorder that can be associated with infections and autoinflammatory disorders. AIDs and HLH have similar pathogenesis of uncontrolled inflammation. Tuberculosis or FMF would have been the underlying disease of the case with HLH, although rarely reported. The management of secondary HLH is based on treating the underlying disease. Immunosuppressive treatment is usually required for the effective control of inflammation, even though sometimes not sufficient as in our case.

Conflict of interest

None declared.

Downloaded from https://academic.oup.com/mrcr/advance-article/doi/10.1093/mrcr/rxab026/6373648 by Istanbul University Library user on 21 October 2021

Patient consent

Written informed consent for the publication of this report was obtained from the patient by the corresponding author.

Ethical approval

Ethical approval is not applicable.

References

[1] Kaito K, Kobayashi M, Katayama T *et al.* Prognostic factors of hemophagocytic syndrome in adults: analysis of 34 cases. *Eur J Haematol* 1997;**59**:247–53.

[2] Janka G, Imashuku S, Elinder G *et al.* Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. *Hematol Oncol Clin North Am* 1998;**12**:435–44.

[3] Rossi-Semerano L, Hermeziu B, Fabre M *et al.* Macrophage activation syndrome revealing familial Mediterranean fever. *Arthritis Care Res (Hoboken)* 2011;**63**:780–3.

[4] Uslu N, Demir H, Balta G *et al.* Hemophagocytic syndrome in a child with severe Crohn's disease and familial Mediterranean fever. *J Crohns Colitis* 2010;**4**:341–4.

[5] Brastianos PK, Swanson JW, Torbenson M *et al.* Tuberculosis-associated haemophagocytic syndrome. *Lancet Infect Dis* 2006;**6**:447–54.

[6] Larroche C, Mouthon L. Pathogenesis of hemophagocytic syndrome (HPS). *Autoimmun Rev* 2004;**3**:69–75.

[7] Osugi Y, Hara J, Tagawa S *et al.* Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. *Blood* 1997;**89**:4100–3.

[8] Takada H, Nomura A, Ohga S *et al.* Interleukin-18 in hemophagocytic lymphohistiocytosis. *Leuk Lymphoma* 2001;**42**:21–8.

[9] Henter JI, Elinder G, Söder O *et al.* Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood* 1991;**78**:2918–22.

[10] Ishii E, Ohga S, Aoki T *et al.* Prognosis of children with virus-associated hemophagocytic syndrome and malignant histiocytosis: correlation with levels of serum interleukin-1 and tumor necrosis factor. *Acta Haematol* 1991;**85**:93–9.

[11] Lee H, Kim HS, Lee J-M *et al.* Natural killer cell function tests by flowcytometry-based cytotoxicity and IFN-γ production for the diagnosis of adult hemophagocytic lymphohistiocytosis. *Int J Mol Sci* 2019;**20**:5413.

[12] Saliu OY, Sofer C, Stein DS *et al.* Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *J Infect Dis* 2006;**194**:486–92.

[13] Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *Lancet Infect Dis* 2008;**8**:601–11.

[14] Roach DR, Bean AG, Demangel C *et al.* TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 2002;**168**:4620–7.

[15] Godfrey MS, Friedman LN. Tuberculosis and biologic therapies: anti-tumor necrosis factor-α and beyond. *Clin Chest Med* 2019;**40**:721–39.

[16] Wallis R, Broder M, Wong J *et al.* Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004;**38**:1261–5.

[17] Askling J, Fored CM, Brandt L *et al.* Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum* 2005;**52**:1986–92.

[18] Dixon W, Hyrich K, Watson K *et al.* Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010;**69**:522–8.

[19] Henter JI, Horne A, Aricó M *et al.* HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;**48**:124–31.

[20] Rigante D, Emmi G, Fastiggi M *et al.* Macrophage activation syndrome in the course of monogenic autoinflammatory disorders. *Clin Rheumatol* 2015;**34**:1333–9.

[21] Mitroulis I, Skendros P, Ritis K. Targeting IL-1β in disease; the expanding role of NLRP3 inflammasome. *Eur J Intern Med* 2010;**21**:157–63.

[22] Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. *Annu Rev Immunol* 2009;**27**:229–65.

[23] Masters SL, Simon A, Aksentijevich I *et al.* Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu Rev Immunol* 2009;**27**:621–68.

[24] Consortium IF. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997;**90**:797–807.

[25] Gohar F, Orak B, Kallinich T *et al.* Correlation of secretory activity of neutrophils with genotype in patients with familial Mediterranean fever. *Arthritis Rheum* 2016;**68**:3010–22.

[26] Simsek I, Pay S, Pekel A *et al.* Serum proinflammatory cytokines directing T helper 1 polarization in patients with familial Mediterranean fever. *Rheumatol Int* 2007;**27**:807–11.

[27] Haznedaroglu S, Ozturk M, Sancak B *et al.* Serum interleukin 17 and interleukin 18 levels in familial Mediterranean fever. *Clin Exp Rheumatol* 2005;**23**:S77–80.

[28] Dai SM, Matsuno H, Nakamura H *et al.* Interleukin-18 enhances monocyte tumor necrosis factor α and interleukin-1β production induced by direct contact with T lymphocytes: implications in rheumatoid arthritis. *Arthritis Rheum* 2004;**50**:432–43.

[29] Van Gorp H, Huang L, Saavedra P *et al.* Blood-based test for diagnosis and functional subtyping of familial Mediterranean fever. *Ann Rheum Dis* 2020;**79**:960–8.

[30] Tan HY, Yong YK, Shankar EM *et al.* Aberrant inflammasome activation characterizes tuberculosis-associated immune reconstitution inflammatory syndrome. *J Immunol* 2016;**196**:4052–63.

[31] Tan HY, Yong YK, Andrade BB *et al.* Plasma interleukin-18 levels are a biomarker of innate immune responses that predict and characterize tuberculosis-associated immune reconstitution inflammatory syndrome. *Aids* 2015;**29**:421–31.

[32] Lanzafame M, Vento S. Tuberculosis-immune reconstitution inflammatory syndrome. *J Clin Tuberc Other Mycobact Dis* 2016;**3**:6–9.

[33] Geri G, Passeron A, Heym B *et al.* Paradoxical reactions during treatment of tuberculosis with extrapulmonary manifestations in HIV-negative patients. *Infection* 2013;**41**:537–43.

[34] Shin BC, Kim SW, Ha SW *et al.* Hemophagocytic syndrome associated with bilateral adrenal gland tuberculosis. *Korean J Intern Med* 2004;**19**:70–3.

[35] Campo E, Condom E, Miro MJ *et al.* Tuberculosis-associated hemophagocytic syndrome. A systemic process. *Cancer* 1986;**58**:2640–5.

Downloaded from https://academic.oup.com/mrcr/advance-article/doi/10.1093/mrcr/rxab026/6373648 by Istanbul University Library user on 21 October 2021