Mixed Langerhans Cell Histiocytosis and Erdheim-Chester Disease in a Girl: A Rare and Puzzling Diagnosis

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Objective: The objective of this study was to report the case of a girl diagnosed as suffering from multisystem, BRAF V600E–positive refractory Langerhans cell histiocytosis (LCH) and coexistent Erdheim-Chester disease (ECD) with perirenal, intracranial involvement and the dramatic response to clofarabine treatment.

Observations: Histiocytoses are rare diseases with a broad clinical spectrum. Recent evidence supports a molecular and clinical overlap between LCH and ECD, and mixed LCH/ECD is now a separate entity. However, only a few pediatric cases of mixed disease have been reported in the literature.

Conclusions: In a child with refractory, multisystem histiocytosis and atypical presentations, mixed LCH/ECD should be suspected in the differential diagnosis.

Key Words: mixed histiocytosis, Erdheim-Chester disease, Langerhans cell histiocytosis, child, clofarabine

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Histiocytoses are a rare and heterogenous group of diseases thought to originate from aberrant dendritic and macrophage progenitor cells.[1,2] The current classification of histiocytoses consists of 5 main groups based on histology, phenotype, and molecular alterations, and clinical and imaging characteristics. The "L" (Langerhans) group encompasses the Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), and extracutaneous juvenile xanthogranuloma and mixed LCH/ECD.[2]

LCH is the most common form of histiocytoses in the pediatric population, whereas ECD is mainly the disease of the elderly, and only about 10 cases of children with pure ECD have been reported in the literature.[3] But there is a growing evidence for molecular and clinical overlap between LCH and ECD.[1,2,4] Although the pattern of skeletal and visceral involvement differs, both diseases could lead to similar clinical pictures such as diabetes insipidus or neurodegenerative disease. In previously reported cases of pediatric ECD, central nervous system was the most common site of presentation after the skeletal lesions and this was a major difference between ECD and LCH.[3] Recent studies have revealed that nearly 20% of adults with ECD also have LCH lesions and that both diseases have common clonal mutations involving the genes of the MAPK pathway.[5–7] However, this coexistence of LCH and ECD has been reported mainly in adults, and only a few pediatric cases are present in the literature.[8–10]

In this article, we report the case of a child with multisystem, risk organ positive (RO^+) LCH and sequentially diagnosed ECD with perirenal and intracranial involvement. In this case also, the BRAF V600E mutation was found to be positive in both LCH and ECD lesions, and a dramatic response to clofarabine therapy was achieved.

CASE REPORT

A 2.5-year-old girl was referred with a diagnosis of hemolytic anemia. History revealed that she had had profound anemia and hepatosplenomegaly for about 2 months and was transfused with erythrocyte suspension twice. On admission, she was pale with massive hepatosplenomegaly. She had no systemic lymphadenopathy. Complete blood count, blood chemistry, and peripheral blood smear were normal, except for normocytic anemia. On abdominal USG, hepatosplenomegaly with normal parenchymal structure was reported. Bone marrow aspiration was cellular, and erythroid and myeloid activity was appropriate for age. With a diagnosis of nonimmune hemolytic anemia, she was given corticosteroids for about 6 weeks, but, during tapering of corticosteroids, a right orbital swelling occurred. Noncontrast cranial CT examination revealed multiple lytic lesions of the calvaria and fascial bones with expansile soft tissue masses around. In addition, bilateral retro-orbital soft tissue masses located inferiorly to the optic nerve and occupying intraconal retro-orbital fat tissue were depicted causing right exophthalmos (Figs. 1A, B). Skeletal survey demonstrated additional lytic lesions on the ribs and pelvis. Biopsy of the orbital mass was reported to be consistent with LCH (CD1a and Langerin positive). She was diagnosed as suffering from LCH, multisystem disease (multiple bone, liver, spleen, bone marrow involvement), and LCH-IV study induction course (vinblastine and prednisone) was started. Response to induction course was poor with a partial regression in orbital mass and resolution of anemia. Repeated abdominal ultrasound revealed recently developed bilateral renal cortical nodular lesions, bilateral renal infundibulopelvic fibrosis resulting in bilateral megacalyces, and calcium milk deposits leveled in calyces (Fig. 2). Second induction course of LCH-IV study protocol was scheduled, and a renal biopsy was taken, as the renal radiologic findings were not compatible with LCH. It was reported to be consistent with non-Langerhans histiocytoses, primarily ECD with CD68 positivity and CD1a negativity. Considering the mixed LCH and ECD disease, cranial MRI was ordered. Contrast-enhanced cranial MRI demonstrated bilateral retro-orbital intraconal solid lesions with partial regression, multifocal calvarial lytic lesions with regressed perilesional soft tissue components, and the diffuse infiltration and thickening of the tentorium cerebelli constricting dural sinuses (Fig. 3). Differential diagnosis included IgG4-related pachymeningitis and retroperitoneal fibrosis, but was excluded with normal serum levels of gammaglobulines. Review of cranial CT and radiograph images revealed sclerosis and thickening of the facial skeleton but not of the long bones. Renal/perirenal involvement along with inracranial dural infiltrations and multiple lytic and facial sclerotic bone lesions supported the ECD and LCH

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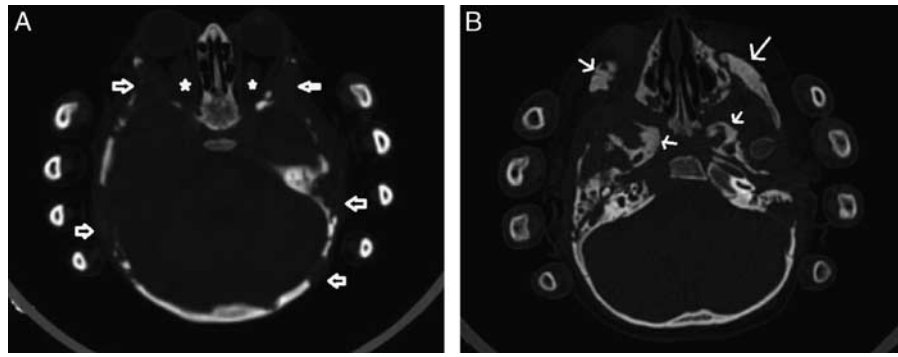


FIGURE 1. A, Axial section of cranial CT revealing multiple lytic lesions (arrows) and bilateral retro-orbital—intraconal masses (asterix). B, Sclerosis and thickening of the fascial bones are seen on CT image signed with arrows.

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coexistence. *BRAF V600E* mutation was found to be positive on biopsy specimens of both LCH (orbital mass) and ECD (kidney) lesions. As the response was also poor after the second induction course with progressive renal pelvic fibrosis and skeletal and CNS findings were stable on imaging, she was discussed on the local tumor board for refractory disease. Clofarabine was started for salvage treatment considering the toxicity profile of cladribine in addition to difficulty in off-label access to the drug in our country. After 6 courses of clofarabine treatment, no pathologic FDG uptake was seen on positron emission tomography-CT scan, and abdominal USG revealed regression of fibrosis, hydrocalyces, and the renal cortical nodular lesions (Fig. 4) Clofarabine was continued for another 3 courses with substantial response on abdominal USG and cranial MRI. She was still on LCH-IV study maintenance treatment with methotrexate and mercaptopurine for about 6 months, and, on recent evaluation, no pathologic FDG activity was seen on positron emission tomography-CT with significant regressions on intracranial and renal lesions.

DISCUSSION

Diagnosis of "mixed" LCH and ECD in a child is very challenging. Although the entity was depicted in the revised classification of histiocytoses at 2016, until now, only 3 pediatric cases were reported as far as we know (Table 1). In all these cases, diagnosis of multisystem or multifocal LCH preceded the diagnosis of ECD with a delay of 2 months to 6 years. In the first case reported by Kim and colleagues, diagnosis of LCH with multifocal bone and intracranial lesions was revised due to poor response to induction chemotherapy. In this case, review of pathology and discovery of sclerotic bone lesions on the lower extremities resulted in the diagnosis of mixed histiocytosis.[8] Varadi et al[9] reported a young boy diagnosed as suffering from LCH with multifocal bone and skin involvement, and, despite initial response to chemotherapy, progression to multisystem, high-risk disease led to the revision of clinical picture and diagnosis of concomitant ECD with sclerotic bone lesions and involvement of bone marrow. Recently, Hao and colleagues reported an 11-year-old-boy, previously treated for multisystem LCH and xanthogranuloma. Six years after the first diagnosis, he was diagnosed to have also ECD with osteosclerotic bone lesions and multiple intracranial

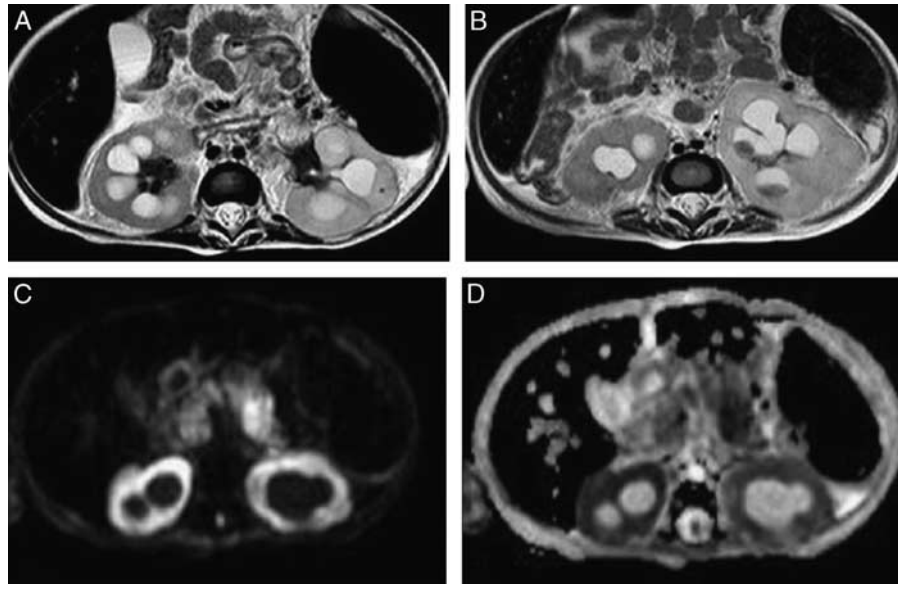


FIGURE 2. T2-weighted MRI images show pelvi-infundibular hypointensity and fibrosis resulting in megacalyces (A) and dependent calcium milk (B). Diffusion-weighted image (C) and apparent diffusion coefficient map (D) demonstrate restricted diffusion of renal parenchyma.

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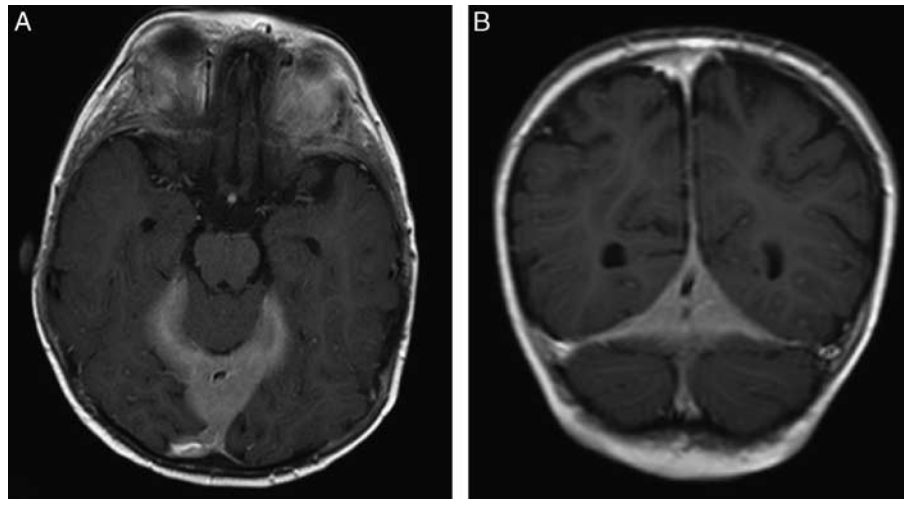


FIGURE 3. Contrast-enhanced T1-weighted axial (A) and sagittal (B) images present the diffusely enlarged and diffusely enhancing thickening of the tentorium cerebelli also constricting the dural sinuses.

masses.[10] Similarly, our case also first diagnosed as multisystem, high-risk LCH and poor response to treatment with progressive perirenal/peripelvic fibrosis, intracranial lesions involving dural structures, and sclerosis on the facial bones directed us to the diagnosis of coexistent ECD for about 6 months after the admission. The delay in diagnosis of all cases may be attributed to the combination of overlapping clinical features and heterogenous courses of LCH and ECD with a low level of suspicion with regard to the rarity of ECD in the pediatric population.

The pattern of bone involvement is different between ECD and LCH. Lytic bone lesions are the most common finding of LCH with bone disease, whereas symmetric osteosclerosis is one of the major diagnostic criteria for ECD, and only 4% of ECD cases lack this finding. Sclerotic bone lesions of ECD are mostly seen on the long bones of the appendicular skeleton, but, in about 50% of patients, thickening of the facial/skull bones and axial skeleton was reported.[11–14] In parallel with the adult series, sclerotic bone lesions on long bones were also reported in all pediatric cases reported before, but, in our case, only sclerosis of the facial bones was present.

Infiltration of perirenal tissues with retroperitoneal fibrosis and hydonephrosis has been reported in about 30% of patients with ECD and not in other histiocytoses.[12] However, in a more recent study by Cohen-Aubert and colleagues, 58% of 165 ECD patients (and 68% of 88 BRAF V600E cases) were reported to have retroperitoneal fibrosis. Moreover, the presence of retroperitoneal fibrosis was found to be an independent negative prognostic factor in this study.[13] In previous pediatric cases, no renal involvement was described, and our case seems to be the very first with histologically proven perirenal involvement with hydronephrosis and megacalyces.

CNS involvement of LCH occurs mainly in the form of soft tissue masses accompanying the bone lesions or degenerative changes on the posterior fossa, but CNS findings of ECD may vary from retro-orbital, cerebral, or cerebellar gadolinium-enhanced parenchymal lesions to more specific pachymeningeal expansile infiltrations. CNS lesions have been reported in 25% to 50% of adults with ECD, but all reported pediatric cases with LCH and ECD had some form of CNS involvement of ECD.[8–10,12–15] In our case also, dural, meningeal infiltrations involving tentorium cerebelli were thought to be consistent primarily with ECD.

Treatment of refractory multisystem or mixed histiocytosis is controversial. Although the cladribine and cytarabine combination has been shown to be effective, toxicity is an important concern.[16] Clofarabine has been reported to be promising with a measurable response and acceptable toxicity in about 70% of patients with heavily pretreated histiocytoses.[17] Recently, the presence of *BRAF V600E* mutation was defined to be the major link between LCH and ECD supporting the idea of a common progenitor for

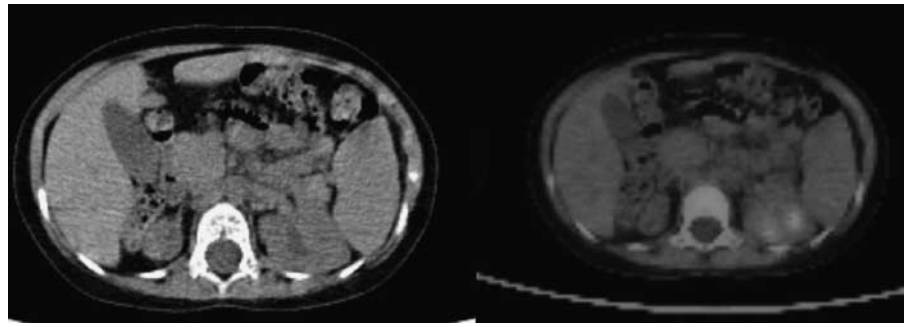


FIGURE 4. PET-CT images reveal the complete regression of the renal parenchymal infiltrates along with renal pelvis entrapment because of the retroperitoneal fibrosis. PET indicates positron emission tomography.

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TABLE 1. Reported Cases of Children With Mixed LCH/ECD

References	Age at Onset	Sex	Time Between LCH and ECD Diagnosis	LCH Organ Involvement	ECD Organ Involvement	LCH/ECD Histologic Diagnosis	*BRAF* Status of LCH/ECD	Treatment	Last Update
Kim et al[8]	3 y	Boy	2 mo	Multifocal bone	Multifocal bone CNS	Bone/CNS	+/+	VBL; PRED cladribine cytarabine	PR, AWD at four months of cladribine and cytarabine treatment
Váradi et al[9]	20 mo	Boy	8 mo	Multifocal bone, skin, liver, spleen	Multifocal bone, BM, CNS	Bone/BM	+/+	VBL; PRED Pred+Indo IFN vemurofanib	CR, NAD at 18th month of vemurafenib treatment
Hao et al[10]	11 y	Boy	6 y	Multifocal bone DI	CNS	Bone/CNS	+/+	VBL PRED etoposide, 6MP cladribine dabrafenib	PR, AWD at four months of dabrafenib treatment
Present case	2.5 y	Girl	6 mo	Multifocal bone liver, spleen BM	CNS perirenal fibrosis facial bones	Bone/ Kidney	+/+	VBL-PRED clofarabine 6MP+MTX	PR, AWD at sixth month of maintenance treatment

6MP indicates 6-mercaptopurine; BM, Bone marrow; CNS, central nervous system; CR, complete response; DI, diabetes insipidus; IFN, interferon; MTX, methotrexate; NAD; nonactive disease; PR, partial response; PRED, prednisone; VBL, vinblastine.

both diseases,[6,7] and the presence of mutations was associated with resistance to first-line therapy.[1,6,18] In a large series of mixed histiocytoses by Hervier and colleagues, in 9 patients with available tissue samples, both lesions of ECD and LCH were found to be positive for *BRAF V600E* mutation. In parallel with these data, *BRAF V600E* mutation was reported to be positive in both ECD and LCH lesions of all pediatric cases including the present one (Table 1). *BRAF V600E* inhibitor vemurafenib is a potential therapy for mutation-positive cases, but a recent report of Donadieu et al[19] suggests that vemurafenib does not eradicate the neoplastic clone with reactivations after cessation of the drug and might be used as a bridging therapy before hematopoietic stem cell transplantation in multisystem high-risk LCH. In our case, we choose to keep off-label vemurafenib use as a third-line option in case of refractoriness to salvage therapy or future possible relapses.

In summary, diagnosis and treatment of mixed histiocytoses are difficult during childhood, but the clinical and biological features seem to be very similar to those of the adult population. This case reveals that perirenal involvement of ECD might also be diagnosed in children with ECD. In addition, it should be noted that clofarabine is a good alternative for treatment of refractory, multisystem histiocytoses considering the unsustained remissions with targeted therapy in BRAF-positive cases. We think that increasing awareness and clinical suspicion will probably lead to recognition of more cases with LCH and ECD in childhood.

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