A unique case of a myelodysplastic/myeloproliferative neoplasm with distinct histiocytic and dendritic cell outgrowths

Jamie Macagba Slade · Sherri Korman · Basharith Khan ·
Shriram M. Jakate · Vijaya B. Reddy · Ira J. Miller

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Abstract Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH) are rare histiocytic disorders with multisystem involvement. Both are considered distinct entities with characteristic clinical, radiological, and pathological features. A limited number of cases have been reported of patients with ECD in association with LCH. We report a case, for the first time to our knowledge, of a patient with ECD, coexisting LCH, a third histiocytosis of less defined lineage, and a myelodysplastic/myeloproliferative neoplasm (MDS/MPN).

Keywords Erdheim-Chester disease · Langerhans cell histiocytosis · Myelodysplastic/myeloproliferative neoplasm

Introduction

Histiocytosis refers to a spectrum of diseases characterized by the excessive proliferation of histiocytes which often present with multisystem involvement. Broadly, the histiocytic disorders can be classified into the Langerhans cell histiocytoses and non-Langerhans cell histiocytoses based on cell lineage. The Langerhans histiocytoses comprise a spectrum of diseases formerly known as Hand-Schuller-Christian disease (multifocal, unisystemic form), Letterer-Siwe disease (multifocal, multisystemic form), eosinophilic granuloma (unifocal form), and Hashimoto-Pritzker disease (congenital self-healing reticulohistiocytosis) [1]. The non-Langerhans histiocytoses include juvenile xanthogranuloma, Rosai-Dorfman disease

(RDD), and Erdheim-Chester disease (ECD) among others [2, 3]. LCH is a neoplasm of antigen presenting cells (dendritic cells). The cells in ECD are phagocytic histiocytes [4].

Langerhans cell histiocytosis (LCH) is a rare condition that can be encountered in any age group, but is most often diagnosed in childhood. The incidence in adults is estimated to be only one to two cases per million, compared to an incidence of three to five cases of LCH per million children [5, 6]. Unisystemic LCH (55 % of cases) occurs in patients of any age, each having unifocal or multifocal involvement of a single organ or tissue such as the bone, skin, lymph node, lungs, or central nervous system. Multisystemic disease involves two or more organ systems and carries a worse prognosis [7]. Acute disseminated multisystem disease is most commonly seen in children under 3 years of age. In adults, LCH is frequently a chronic, indolent disease involving a single organ. The most common form of LCH in adults is isolated pulmonary involvement which is strongly associated with cigarette smoking. The usual clinical presentation of LCH in the skin of adults is an erosive rash in the groin and other intertriginous sites resembling a candida diaper rash, or it can involve the scalp and be mistaken for seborrheic dermatitis [6, 8, 9]. When multiple organ systems are affected, the most commonly involved organs in adults are the lungs, skin, axial skeleton, skull, and pituitary gland [8]. *BRAF*^{V600E} mutations have been found in 57 % of LCH cases [10]. Recently, Brown et al. reported the mutually exclusive activating somatic *BRAF*V600E and *MAP2K1* gene mutations in LCH [11].

ECD is a rare non-LCH first reported by the Austrian pathologist Jakob Erdheim and the American pathologist William Chester [12]. In 1930, Chester described a “lipoid granulomatosis” in the bone, visceral organs, and fat in two middle-aged patients [13]. Forty years later, Henry Jaffe reported a similar case and introduced the eponym “Erdheim-Chester disease” [14]. Since then, several hundred cases have been reported in the literature.

J. M. Slade (✉) · S. Korman · B. Khan · S. M. Jakate ·
V. B. Reddy · I. J. Miller

Department of Pathology, Rush University Medical Center, 1750 W
Harrison St, Room 570 Jelke, Chicago, IL 60612, USA
e-mail: jamie_m_slade@rush.edu

ECD is an unusual systemic condition most commonly involving the bone, skin, lung, heart, retroperitoneum, pituitary, and less commonly liver and kidney. It has a slight predilection for males, and most patients are middle-aged adults [15]. Patients present with varied symptoms reflecting the distribution and extent of organs involved. About one third are asymptomatic and have an indolent course. Bone pain is the most common initial complaint. Typically, patients present with symmetric sclerotic lesions in the long bones [16]. Prognosis is poor in patients with extraskeletal involvement [2]. Classical radiological findings helpful in diagnosis are retroperitoneal infiltration with a “hairy kidney” and “coated aorta” appearance [16]. More than half of ECD patients die within 3 years of diagnosis, most commonly of pulmonary or cardiac failure [2]. In one study, *BRAF*^{V600E} mutations were detected in 13 of 24 (54 %) cases of ECD [17]. Most recently, Emile et al. discovered 46 of 80 (57.5 %) ECD patients with *BRAF*^{V600E} mutations as well as an additional 10.9 % of patients with a mutation in *PIK3CA* and 3.7 % of patients with a mutation in *NRAS* [18].

Although ECD is rare, its recognition has recently increased, as reflected in the rise in frequency of case reports. Because of its multisystem involvement and insidious presentation, diagnosis can be confounding and may be delayed for many years. Both LCH and ECD can involve multiple organ systems and may be clinically difficult to differentiate from other systemic conditions. These two entities are distinguished from each other by their clinical, radiological, and pathological features. We report an unusual case of a patient who presented with a rash consistent with cutaneous LCH with an atypical pattern of involvement, and over the course of a few months she was found to have ECD involving the bone marrow, as well as a third histiocytosis with a nonspecific immunophenotype in the small intestine, and an underlying myelodysplastic/myeloproliferative neoplasm (MDS/MPN).

Clinical history

A 61-year-old Caucasian woman with a past medical history of hypertension presented to the dermatology clinic at our hospital with a scalp and truncal rash (Fig. 1a) for the preceding 8 months. Large, pink, scaly, psoriasiform plaques on the scalp, neck, chest, abdomen, back, groin, and gluteal cleft were noted on exam. Her review of systems was significant for a 30-lb unintentional weight loss over the last 9–12 months. Eight months prior to coming to our clinic, she had been diagnosed with LCH based on skin biopsy and treated with PUVA therapy (30 sessions) and topical steroids, which led to some improvement, but was discontinued due to prohibitive cost and nausea from the PUVA.

A repeat punch biopsy at our institution from the abdominal rash showed a superficial dermal infiltrate of histiocytic cells with

pagetoid spread into the overlying epidermis (Fig. 1b). The histiocytic cells were positive for CD68, CD1a, and S100 supporting the diagnosis of LCH (Fig. 1c–e). As the patient was unable to tolerate PUVA, she was started on topical steroids, oral prednisone (60 mg daily), and oral methotrexate (10 mg weekly). Within a month of treatment, she developed lower extremity edema with grade 3 ulcers as well as anemia (Hb 9.8 g/dL), thrombocytopenia (platelets 69 th/μL), and leukocytosis (WBC 75.5 th/μL) with atypical monocytes noted on her complete blood count. Therefore, methotrexate was held and the dose of prednisone reduced. The patient was referred to the hematology service at another hospital for evaluation of her abnormal laboratory test results. A repeat complete blood count showed leukocytosis (WBC 59.7 th/μL), anemia (Hb 9.2 g/dL), and thrombocytopenia (platelets 79.9 th/μL). Bone marrow biopsy and aspirate smears revealed moderately hypercellular marrow with neutrophilic and monocytic hyperplasia and decreased erythropoiesis (myeloid to erythroid ratio of more than 20 to 1), as well as single and clustered, large, atypical histiocytes showing erythrophagocytosis and emperipolesis (Fig. 2a–c). These abnormal histiocytes were positive for CD68 and negative for CD1a and S100. The peripheral blood showed marked neutrophilia (52.29 th/μL) with atypical hypogranular and hypersegmented forms and an absolute monocytosis (2.62 th/μL) with nuclear and cytoplasmic immaturity (Fig. 2d), but no increase in blasts. The red blood cells showed a normocytic, normochromic anemia with mild anisopoikilocytosis. The bone marrow biopsy was reviewed at our institution and a diagnosis of MDS/MPN, likely chronic myelomonocytic leukemia, with associated ECD was rendered.

Three days later, she was admitted to the intensive care unit at our institution for increasing weakness, hypoxic respiratory failure, hyponatremia (sodium 175 meq/L), anemia (Hb 9.9 g/dL), thrombocytopenia (platelets 70.0 th/μL), leukocytosis (WBC 78.0 th/μL), and signs of sepsis. Her anemia was transfusion-dependent requiring multiple transfusions throughout her course. She was diagnosed with diabetes insipidus and treated with supplemental oxygen, D5W along with desmopressin (DDAVP), and broad spectrum antibiotics. CT scan of the abdomen and pelvis showed enlarged kidneys with mild perinephric fat stranding as well as smooth, long segment soft tissue encasement of the aorta (Fig. 3). These findings are consistent with the classical radiological findings of a “hairy kidney” and “coated aorta” in ECD. Although no complaints of bone pain were reported, a bone scan reported uptake in the distal right femur.

CT scan of the chest showed bilateral diffuse pulmonary reticular nodular thickening, scattered emphysematous changes, and thickening of the intralobular septa. She underwent a bronchoscopy which revealed rare atypical histiocytes and was positive for *Pneumocystis jirovecii* pneumonia (PJP) for

Fig. 1 **a** Photographs of the truncal rash showing large, pink, and scaly psoriasiform plaques. **b** Low power magnification of a punch skin biopsy of the left lateral abdomen showing a superficial dermal infiltrate of histiocytic cells with pagetoid spread into the overlying epidermis. The

histiocytes showed typical features of Langerhans cells including indented nuclei with moderately abundant, slightly eosinophilic cytoplasm (*inset*). **c** The histiocytic cells were positive for CD68, **d** CD1a, and **e** S100 supporting the diagnosis of LCH

which trimethoprim/sulfamethoxazole was initiated. Because of her presenting leukocytosis, thrombocytopenia, and anemia, an inpatient hematology consultation was obtained. A repeat bone marrow biopsy was performed which showed similar findings to the previous biopsy. The patient's clinical history of diabetes insipidus, radiographic findings in the aorta and kidneys, and morphologic findings in the bone marrow established a final diagnosis of Erdheim-Chester disease with evidence of an underlying MDS/MPN. The karyotype was normal, and *JAK2V617F* mutational analysis and FISH for

BCR/ABL translocation were negative. *BRAF*^{V600E} gene mutation analysis and immunohistochemical analysis of the bone marrow and duodenum were negative.

Due to the patient's recent onset of nausea, anorexia, and abdominal fullness, an esophagoduodenoscopy (EGD) was performed. Gross findings of the EGD were unremarkable. However, the endoscopic duodenal biopsy revealed an atypical histiocytic infiltration of the submucosa. The histiocytes were positive for CD68, negative for CD1a, and positive for S100—an abnormal but nonspecific immunoprofile (Fig. 4).

Fig. 2 **a** Bone marrow biopsy showing an interstitial infiltration of single and clustered large, atypical histiocytes (arrows). **b** Bone marrow aspirate showing monocytosis (arrowheads) with immaturity with admixed

neutrophils. **c** An iron stain showing the emperipolesis of neutrophils (arrow) and occasional lymphocytes. **d** The peripheral blood showing neutrophilia

These histiocytes did not show emperipolesis, as seen in RDD.

The patient was transferred to the hematology service with plans for treatment with IFN- α . However, she developed

systemic toxicities with 5 doses of IFN- α and could not tolerate further treatment. Her respiratory function worsened, and she developed bowel obstruction and became severely malnourished. She died within a month after being diagnosed with ECD.

Fig. 3 CT scan displaying classical finding of the appearance of a “hairy kidney”—an irregular border around the kidney due to retroperitoneal infiltration of the perirenal fat (arrowheads) as well as a “coated aorta” showing soft tissue encasement and aneurysmal dilatation of the aorta with an intraluminal thrombus (arrows)

Discussion

We presented here a case of a 61-year-old woman who succumbed to multisystemic involvement by three different histiocytic proliferations with distinct morphologies and immunophenotypes, and evidence of an underlying MDS/MPN. Cases of LCH and concurrent non-LCH disorders, specifically RDD or ECD have been reported. We found 12 cases in the English literature of concurrent LCH and RDD [19–22]. The majority of these cases had a predominance of RDD with a lesser component of LCH and with occurrence of both diseases in the same affected organ. Only one of the 12 cases exhibited concomitant RDD and LCH in different anatomical locations [22].

A total of 45 cases of concurrent LCH and ECD, including our present case, have been found (Table 1). The patients' ages

Fig. 4 **a** H&E of a duodenal biopsy showing submucosal infiltration by a dense sheet of abnormal histiocytes. The histiocytes were medium-sized with abundant foamy cytoplasm, some with indented nuclei (*inset*). **b** Immunostain for CD68 highlights the histiocytic infiltrate. **c**

Immunostain for CD1a is negative and **d** positive for S100—an abnormal but nonspecific immunoprofile for Erdheim-Chester disease and Langerhans cell histiocytosis

ranged from 2 to 75 years with a median age of 43 in 23 cases reported by Hervier et al. [40] and a mean age of 45 years in the remaining 22 cases. There was no evident gender bias (F:M of 25:20). All 45 cases were biopsy proven diagnoses of LCH. Thirty-six of 45 cases were biopsy proven diagnoses of ECD with the remaining nine cases diagnosed based on radiologic findings [24, 25, 31, 38, 40]. Complete blood counts, which were provided in five cases, excluding our current case, showed a mild to moderate anemia in all five cases [25, 28, 31, 35, 36]. There were no reports of monocytosis or neutrophil dysplasia in any of the remaining cases to raise suspicion of a MDS/MPN, as seen in our patient. LCH involving the skin was present in 20 cases, excluding our current case. The majority of the cases of cutaneous LCH were described as ulcerative lesions involving the intertriginous areas, vulva, scalp, and thighs. In contrast, our patient had an unusual presentation of LCH with large, pink, scaly, and psoriasiform plaques on the trunk and scalp.

The largest series of concurrent LCH and ECD cases (termed “mixed histiocytosis”) was recently reported in 23 patients by Hervier et al. The study compared the phenotype of patients with concurrent LCH and ECD to that of patients

with isolated LCH and isolated ECD and found that the phenotype of patients with mixed histiocytosis was closer to that of isolated ECD than to isolated LCH. Additionally, Hervier et al. indicated that the association of LCH and ECD is linked to the *BRAF*^{V600E} mutation which was identified in 9 (82 %) of 11 ECD lesions and in 11 (69 %) of 16 LCH lesions [40]. Haroche et al. investigated the frequency of *BRAF*^{V600E} mutations in different types of histiocytoses including ECD, LCH, Rosai-Dorfman disease, juvenile xanthogranuloma, histiocytic sarcoma, xanthoma disseminatum, interdigitating dendritic cell sarcoma, and necrobiotic xanthogranuloma. They detected *BRAF*^{V600E} mutations in 13 of 24 (54 %) cases of ECD and 11 of 29 (38 %) cases of LCH, but none in the other histiocytoses [17]. Additionally, Emile et al. discovered 46 of 80 (57.5 %) ECD patients with *BRAF*^{V600E} mutations as well as an additional 10.9 % of patients with a mutation in *PIK3CA* and 3.7 % of patients with a mutation in *NRAS* [18]. In another study, Badalian-Very et al. [10] identified *BRAF*^{V600E} mutations in 35 of 61 (57 %) cases of LCH. More recently, Brown et al. reported the mutually exclusive activating somatic *BRAF*^{V600E} and *MAP2K1* gene mutations in LCH [11]. Immunomorphological features also

Table 1 Summary of reported cases of coexistent Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH)

Cases	Age	Sex	Location ECD	Location LCH	CBC abnormalities
1 Brower et al. 1984 [23]	66	M	Distal tibia	Proximal tibia	Not provided
2 Waite et al. 1988 [24]	57	F	Distal tibia, distal femur	Parietal bone	Not provided
3 Strouse et al. 1992 [25]	36	M	Tibia	Tibia	Anemia (Hgb 13.4 g/dL)
4 Kambouchner et al. 1997 [26]	58	M	Femur, tibia, fibula, lung, omentum, peritoneum	Mandible	Not provided
5 Adle-Biassette et al. 1997 [13]	34	F	Bone, skin, brain, lung, retroperitoneum	Skin, vulva	Not provided
6 Vital et al. 1999 [27]	46	F	spleen, kidney Femur, brain, spinal cord, skin, vulva	Skin, vulva	Not provided
7 Scully et al. 2000 [28]	41	M	Femur, tibia, humerus, tarsal, mandible, maxilla, soft tissue, kidney	Femur	Thrombocytosis (Plt $515 \times 10^3/\text{mm}^3$) Anemia
8 Bisceglia et al. 2003 [29]	44	M	Brain	Mandible, scapula	Not provided
9 Bisceglia et al. 2003 [29]	35	M	Femur, tibia, humerus, brain, lung	Skin	Not provided
10 Andrade et al. 2004 [30]	40	F	Breast bone, retroperitoneum kidney, orbit	Hard palate	Not provided
11 Narvarte et al. 2004 [31]	40	F	Orbit, femur, lung	Femur	Anemia (Hgb 12.4 g/dL)
12 Furmanczyk et al. 2007 [32]	63	F	Tibia, femur	Femur	Not provided
13 Granier et al. 2008 [33]	65	M	Lung, pleura, retroperitoneum heart	Brain	Not provided
14 Kerzl et al. 2008 [34]	63	F	Femur, skin	Skull, femur	Not provided
15 Aouba et al. 2009 [35]	27	M	Hip synovium	Lymph node	Not provided
16 Tsai et al. 2010 [36]	34	F	Tibia fibula, soft tissue, kidney, skin	Skin	Elevated neutrophil count ($10.4 \times 10^9/\text{L}$) Anemia (Hgb 9.5 g/dL)
17 Naruse et al. 2010 [37]	31	M	Femur, tibia, knee, pituitary	Femur	Anemia (Hgb 8.1 g/dL)
18 Pineles et al. 2011 [4]	26	F	Skin, orbit	Skull	Not provided
19 Pineles et al. 2011 [4]	32	F	Pituitary, orbit	Distal femur, skull, bone marrow	Not provided
20 Caoduro et al. 2013 [38]	63	F	Femur, tibia, right orbit, aorta	Skin	Not provided
21 Yin et al. 2013 [39]	27	F	Retrobulbar mass	Scalp, skull, femur	Not provided
22 to 44 Hervier et al. 2014 [40]	Median age=43 (range=2 to 75)	11 M, 12 F	Bone, cardiac, large vessel, mucocutaneous, pulmonary, retroperitoneal, epiploon	Lytic bone, mucocutaneous, pulmonary, digestive, CNS, pituitary, orbit	Not provided
45 Current case	61	F	Bone marrow	Skin	Anemia (Hgb 9.9 g/dL) Thrombocytopenia (Plt 70.0 th/ μL) Leukocytosis (WBC 78.0 th/ μL) Monocytosis (2.62 th/ μL)

suggest overlapping pathogenesis of the histiocytoses. A subset of cases with combined RDD and LCH found in a lymph node showed rare transitional cells with morphologic features of RDD but with immunohistochemical features of LCH cells (CD1a and langerin expression) [21]. In our present case, the histiocytes found in the duodenum had morphologic features of ECD but immunohistochemical features of LCH, while the abnormal marrow histiocytes showed emperipolesis-like RDD but lacked S100 expression. The various histiocytoses are considered to be proliferations of differentiated cells. Cases with multiple lineages may represent proliferations of less committed tumor stem cells.

Our case likely represents the end of the spectrum with origin in the marrow hematopoietic stem cell. There have been several case reports of patients with LCH developing a second hematological malignancy, such as MDS and MDS/MPN either prior to, concurrent with, or subsequent to their LCH diagnosis [41–49]. Iwasaki et al. recently reported an 82-year-old male with cutaneous LCH who died from chronic myelomonocytic leukemia (CMML) diagnosed 10 months later and identified 37 cases of LCH with a coexistent hematological malignancy reported between 2000 and 2013 [42]. The most common malignancies identified were lymphoblastic leukemia (ALL) in 11 patients, MDS in 8 patients, and acute myeloid leukemia (AML) in 8 patients, and included CMML in 3 patients and juvenile myelomonocytic leukemia (JMML) in 1 patient. Eleven of the 15 patients with skin-limited LCH and known outcome had a fatal course. Yohe et al. described four cases of concurrent or subsequent LCH in patients with acute leukemia of ambiguous or myeloid lineage [41]. In the two cases successfully tested, they did not find a *BRAF*^{V600E} mutation. However, none of their cases had skin involvement. Edelbroek et al. noted a frequent association between LCH presenting in the skin in adults and a second hematological malignancy [43]. In 18 patients presenting to their hospitals with an initial diagnosis of cutaneous LCH, 5 developed hematological malignancies, including myelomonocytic leukemia (2 cases), histiocytic sarcoma (1 case), diffuse large B-cell lymphoma (1 case), and peripheral T-cell lymphoma (1 case). Their literature review revealed 74 adult patients presenting with cutaneous LCH between 1974 and 2011, of which 6 had a second hematological malignancy. The pathophysiological link between LCH and increased risk of hematological malignancy remains unclear. Given the frequency of secondary tumors of myelomonocytic origin, it has been speculated that LCH and these neoplasms develop from a common bone marrow precursor that may follow different paths of differentiation [43]. Chromosome 7 abnormalities have been documented in LCH, MDS, and AML [42, 45, 46], and clonal gene rearrangement of the T-cell receptor γ -chain has been detected in concurrent lesions of LCH and T-cell derived leukemia, suggesting more than just a chance correlation.

Histiocytic proliferations in association with MDS/MPN parallel other clonal lineage outgrowths, such as mastocytosis and plasmacytoid dendritic cell neoplasms, that can accompany a myeloproliferative neoplasm. For example, mastocytosis may be limited to the skin in cutaneous mastocytosis, most commonly urticaria pigmentosa, or may manifest as systemic mastocytosis, most commonly involving the bone marrow or gastrointestinal tract. In up to 30 % of cases of systemic mastocytosis, an associated hematological clonal non-mast cell disorder (AHNMD) occurs, predominantly myeloid neoplasms and most commonly chronic myelomonocytic leukemia [50]. Also, blastic plasmacytoid dendritic cell neoplasm, derived from the precursors of plasmacytoid dendritic cells, can occur as an isolated disease most frequently involving the skin and bone marrow, or may occur in the context of another hematologic neoplasm. Approximately 10 to 20 % of cases are associated with hematologic malignancies such as myelodysplastic syndrome, chronic myeloid leukemia, chronic myelomonocytic leukemia, and acute myeloid leukemia [50]. Furthermore, in patients with chronic myelomonocytic leukemia, nodal proliferations of plasmacytoid dendritic cells (originally called plasmacytoid T or “T-zone” cells, and then plasmacytoid monocytes), have been recognized for over two decades [51–54]. Interestingly, when the skin is involved in CMML, about half the cases have infiltrates showing plasmacytoid dendritic cell lineage [55].

The chronic, indolent nature of LCH in adults begs the question of whether LCH in adults may be more generally associated with unrecognized marrow stem cell abnormalities.

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Conflict of interest The authors declare that they have no conflict of interest.

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