



Diverse cutaneous manifestations of Erdheim-Chester disease in a woman with a history of Langerhans cell histiocytosis

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INTRODUCTION

Erdheim-Chester disease (ECD) is a rare, systemic, non-Langerhans cell histiocytosis (non-LCH). Diagnosis is based on a combination of specific radiologic, histologic, and clinical findings. Although there have been hundreds of prior reports of ECD, very few cases have described the spectrum of potential cutaneous manifestations.¹⁻⁴ Most of these cases describe ECD skin findings as xanthelasmalike lesions surrounding the periorbital area,^{1,2} whereas 2 patients were reported to have a red-brown papular eruption affecting the chest and lower extremities.^{3,4} We discuss a case of a 45-year-old woman with an extensive childhood history of LCH who then presented more than 20 years later with a new eruption of polymorphous skin lesions distributed over the face, trunk, arms, and legs. These lesions were clinically varied yet histologically all consistent with xanthogranulomas. Upon further workup, the patient was found to have specific radiographic findings pathognomonic for ECD and a *BRAF* V600E mutation, which has been reported in both LCH and ECD. Our case is unique, in that this patient was affected by both diseases within her lifetime. Identification of the *BRAF* V600E mutation suggests the possibility of a common origin between LCH and ECD.

CASE REPORT

A 45-year-old woman presented with complaints of a new widespread eruption across her face, arms, and legs. The patient described an occasionally pruritic, nonpainful, papular rash that would erupt

Abbreviations used:

ECD:	Erdheim-Chester disease
LCH:	Langerhans cell histiocytosis
PET-CT:	Positron emission tomography—computerized tomography

sporadically without a known trigger and resolve to leave hyperpigmented macules. A review of systems was noncontributory, including no episodes of fever, chills, night sweats, or weight loss. The patient's medical history was significant for childhood LCH that manifested as eosinophilic granuloma of the cranium, treated at age 3 with surgery, radiation, and vincristine. She also had recurrent disease treated with prednisone and methotrexate between the ages of 9 and 24. The patient had no other chronic medical problems, no allergies, and no relevant family history and was not taking any medications. On physical examination, erythema was noted on her face, arms, chest, and back. Upon closer inspection, the erythema was composed of numerous, pinpoint, pink-to-red papules (Fig 1). In addition, examination found yellow papules coalescing into thin plaques along her bilateral temples and periorbital regions (Fig 1) and scattered 2- to 4-mm red brown papules across her arms and legs. Biopsies performed on the arm, leg, and face, found foamy cells and multinucleated cells in the dermis without 2-toned cytoplasm. Immunohistochemistry found positive CD68 and negative CD1a and S-100 staining, consistent with non-LCH histiocytosis (Fig 2). The patient was subsequently referred to the hematology department

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Fig 1. Clinical photographs of ECD.

for further evaluation of an underlying hematologic malignancy given the xanthogranulomas on histology, but findings from a thorough workup (a complete blood count, comprehensive metabolic panel, lactate dehydrogenase, peripheral blood flow cytometry, serum protein electrophoresis, serum immunofixation electrophoresis, β -2 microglobulin, quantitative immunoglobulins, and serum free light chains) were normal. A positron emission tomography–computerized tomography (PET-CT) scan was performed to evaluate for multiorgan involvement.

The PET-CT scan was significant for multifocal ^{18}F fludeoxyglucose avid sclerotic changes in the sternum, sacrum, and bilateral symmetric uptake in the femoral and tibial bones, and the diagnosis of ECD was made based on these pathognomonic radiologic findings (Fig 3). Given recent findings of the high prevalence of *BRAF* V600E mutation in ECD patients and potential therapeutic implications,^{5,6} the tissue was tested for this mutation and found to be *BRAF* V600E positive. The patient was then enrolled in an open-label, phase II clinical trial

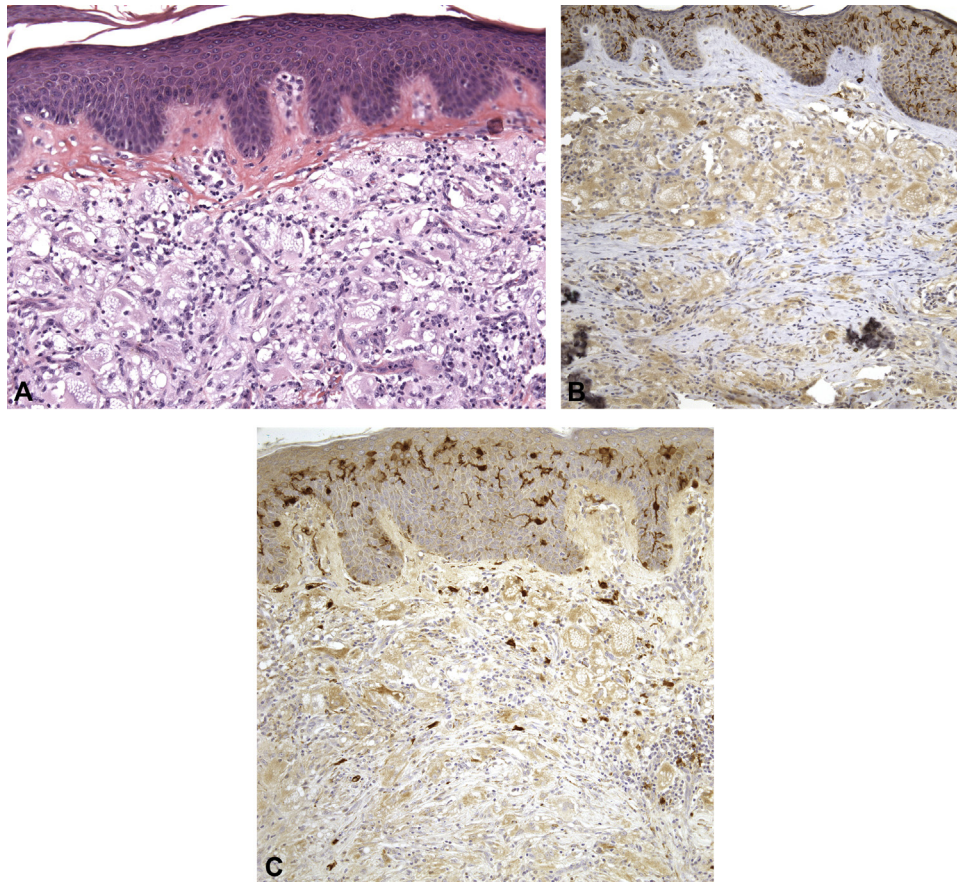


Fig 2. Histology photographs of ECD. (A, Hematoxylin-eosin stain; original magnification: $\times 20$. B, CD1a stain; original magnification $\times 20$. C, S-100 stain; original magnification: $\times 20$.)



Fig 3. Characteristic radiographic findings of ECD from PET-CT. A, CT image shows bilateral osteosclerotic changes of the femur and tibia. B, PET image with FDG uptake in the bilateral femur and tibia.

of vemurafenib in patients with *BRAF* V600E mutation—positive cancers, but her participation was discontinued because of the development of severe myalgias and arthralgias during the trial.

DISCUSSION

ECD is a rare, non-LCH, neoplasm that is diagnosed by clinical, histologic, and radiologic findings. Previously reported cases of ECD have a slight male predominance, disease onset typically in the fifth to seventh decades of life¹ and bone pain as the most common presenting symptom.^{2-4,7} Patients with ECD have pathognomonic changes of bilateral symmetric sclerosis of the diaphyseal regions of the long bones on plain radiographs and symmetric technetium Tc 99m labeling of the distal long bones with bone scintigraphy.^{1-4,7} Biopsies (taken typically from bone) show foamy histiocytes without any Birbeck granules with immunohistochemistry positive for CD68 and negative for CD1a and S-100.^{3,4,7}

Although our patient did have the characteristic histologic and radiologic findings that established the diagnosis of ECD, the initial cutaneous manifestations of ECD were different from those previously described in the literature. Although ECD has been reported to significantly affect the cardiovascular, pulmonary, renal, and central nervous systems,^{3,7} involvement of the skin is relatively uncommon, with approximately 28% of reported cases having any skin manifestations.¹ The most commonly described dermatologic findings in ECD include xanthomalike papules and periorbital xanthelasmalike skin lesions.^{2,8} Other reports describe red-brown papular lesions affecting the extremities and trunk.^{9,10} Our reported patient with ECD manifested a diverse array of cutaneous manifestations, all with identical histologic findings.

Although there is no standardized treatment for ECD, a recent consensus guideline for the diagnosis and treatment of ECD reported interferon- α as first-line therapy with the largest amount of supporting evidence.^{1,7,11,12} Treatment with interferon- α was identified as an individual predictor of survival of ECD patients.¹ Another treatment currently being investigated is the use of vemurafenib in ECD patients with a *BRAF* V600E mutation.⁶ Recent studies have shown a high prevalence of the *BRAF* V600E mutation in up to 54% to 100% of tested ECD patients and 38% to 68% of LCH patients.⁵ In addition, no such mutation has been found in any of the other tested histiocytoses, including Rosai-Dorfman disease, juvenile xanthogranuloma, histiocytic sarcoma, xanthoma disseminatum, interdigitating dendritic cell sarcoma, and necrobiotic xanthogranuloma,

which suggests a common origin between ECD and LCH.⁵ Vemurafenib is a serine/threonine kinase inhibitor that inhibits the *RAS-ERK* cellular signaling pathway, which is constitutively activated by the *BRAF* V600E mutation.⁶ Although marked response of ECD to vemurafenib has been reported in several cases, the drug is still being studied to determine the safety, optimal duration of therapy, and potential adverse drug reactions.⁶ Treatment continues to pose a challenge, as there is no standardized regimen or any modality that has demonstrated disease eradication. However, the discovery of the highly prevalent *BRAF* V600E is a promising treatment target.

Early diagnosis of ECD could potentially limit disease morbidity and mortality by initiating early treatment. Our case is unique to previously reported cases of ECD, as our patient presented initially with a clinical array of cutaneous lesions and pathognomonic radiographic findings. Her history of childhood LCH raises a question of whether there is a common origin linking the 2 histiocytoses, ECD and LCH.

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