

Case of Erdheim–Chester presenting with xanthelasma-like eruption and osteolytic bone lesions: A case report

SAGE Open Medical Case Reports
JCMS Case Reports
Volume 7: 1–4
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DOI: 10.1177/2050313X19845217
journals.sagepub.com/home/sco



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Abstract

Erdheim–Chester disease is a rare multisystemic non-Langerhans cell histiocytosis presenting 95% with skeletal lesions. Erdheim–Chester disease is due to mutations in the RAS-MEK-ERK pathway where 50% are due to BRAF-V600E mutations. Typical histopathological, clinical, and radiologic features are necessary for the diagnosis of Erdheim–Chester disease. Prognosis depends on the extent of the systemic involvement, and central nervous system involvement has a poorer outcome. We present a 30-year-old Moroccan woman with diabetes insipidus, bone marrow, and asymmetrical axial osteolytic bone lesions. Biopsies were consistent with Erdheim–Chester disease. Despite no treatment, the patient has demonstrated clinical improvement.

Keywords

Erdheim–Chester, non-Langerhans histiocytosis, xanthelasma, vemurafenib, interferon- α

Introduction/background

Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis (non-LCH) characterized by a multiorgan accumulation of CD68+, CD1a–, and S100– histiocytes with fibrosis. ECD has a clonal systemic proliferation of non-LCH with mutations in the RAS-MEK-ERK pathway where 50% have BRAF-V600E mutations.^{1–5} Less than 1000 cases have been described.^{1,6,7} Diagnosis is most common in adults with an average age of onset between 55 years and 60 years with a slight male predilection.^{1,8} ECD most commonly presents with painful and symmetrical osteosclerosis of long bones along with diabetes insipidus (DI), exophthalmos, and xanthelasma.^{1,2,8–10} ECD is a chronic disease, and prognosis depends on the severity of organ involvement: central nervous system (CNS) involvement is associated with worse prognosis.^{1,8,9,11,12}

We present a case of ECD with an atypical presentation and evolution, along with a review of the literature for management and treatment.

Case report

A 30-year-old Moroccan woman presented with a 2.5-year history of progressive papular skin lesions. These appeared during her pregnancy in 2013, at 30 weeks of gestation.

Multiple millimetric xanthelasma-like papules appeared on flexural surfaces, face, around the eyelids, and lips. The patient had no systemic symptoms and no other health issues. She first consulted in Morocco where a skin biopsy revealed non-LCH with positive CD68 and negative CD1a and S-100 markers.

In March 2015, she developed skin lesions on her torso, abdomen, vulva, chin, and cheeks. These were asymptomatic or slightly pruritic in flexural areas. Except for light fatigue, polydipsia, and polyuria, the rest of her systemic review was negative. Investigations included a second skin biopsy, blood, and urine exams along with imaging. The skin biopsy showed a dermal infiltration of nodular pattern associating xanthomatized histiocytes admixed with multinucleated Touton-like giant cells. Immunohistochemical results were identical to the previous biopsy. The water deprivation test

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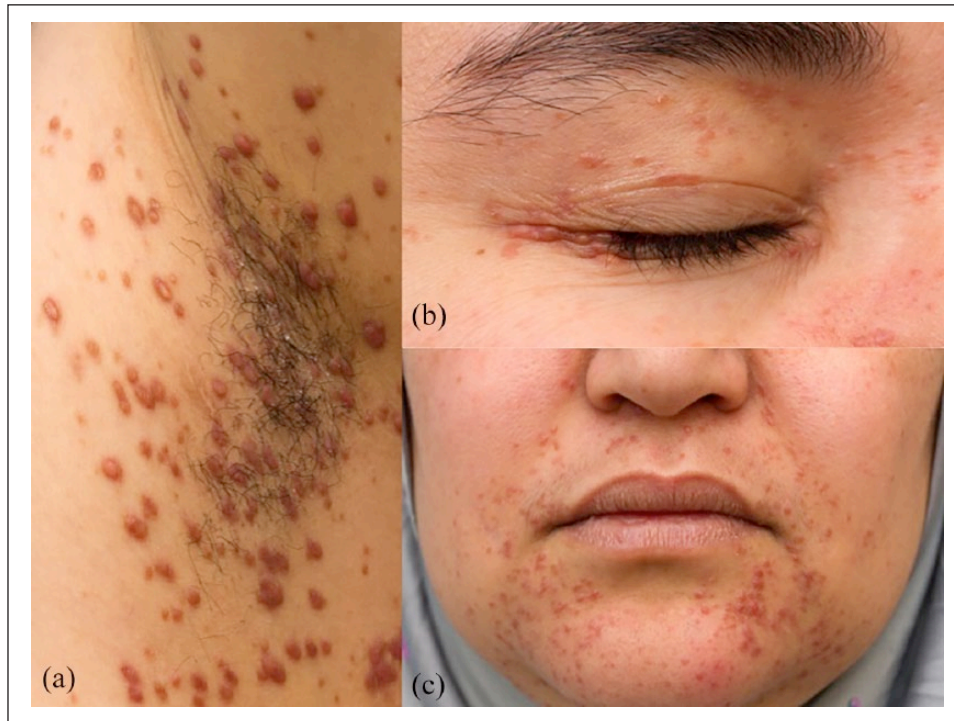


Figure 1. Multiple brown, skin-color, and yellowish waxy xanthelasma-like papules on the (a) left axilla. (b) Right eyelid. (c) Peribuccal region.

was positive for DI, and desmopressin was initiated. The other tests were normal. The patient was diagnosed with xanthoma disseminatum (XD).

On her June 2015 follow-up, there were new erythematous papules (0.2–1 cm in size) on her torso, axilla, and superior and inferior lips (Figure 1). In the fall of 2015, new-onset nasal congestion led to a nasal endoscopy, which revealed papules on the right nasal fossa septum. A third skin biopsy was done, and the histopathology was identical to her previous biopsies (Figure 2). The investigation was completed with a brain magnetic resonance imaging (MRI), bone scan with computed tomography (CT) scan and pelvic radiograph, echocardiogram, and evaluations by oncology and ophthalmology teams. Imaging revealed osteolytic lesions in the inferior half-right sacrum, left ilium, the superior half of sternum, distal left humerus, 12th posterior right rib, fifth lumbar vertebra, cranial vault, and left temporal-mandibular articulation. There were no osteosclerotic bone lesions. The brain MRI did not reveal any CNS lesions. However, ophthalmology examination showed bilateral optic tract compression with a slight decrease in bitemporal visual fields.

The bone marrow biopsy showed thickened trabecular bone with osteosclerosis over 30% of biopsy length. Bone marrow cellularity was markedly increased to almost 100% related to xanthogranulomatous histiocytic infiltrate associated with some Touton-like giant cells (Figure 3). The histiocytes were positive for CD68, and negative for CD1a, S100,

CD34, Factor XIIIa, and BRAF-V600E mutation. With multiple bone and cutaneous lesions, systemic symptoms, and bone marrow infiltration, the patient was diagnosed with ECD. The patient declined treatment. Monitoring was planned with repeat bone scans, blood tests, and yearly ophthalmology examinations.

At her most recent follow-up in November 2017, DI was stable with desmopressin. CT and bone scans have shown a complete regression of all the osteolytic bone lesions, except for the cranial vault's lesions, which have decreased in size. Her visual fields showed improvement in 2017. The patient has remained healthy; she is pregnant and due March 2019. Her next imaging is postponed until after her pregnancy.

Discussion

ECD is a rare multisystem non-LCH diagnosed by clinical, radiological findings, and compatible histopathologic features. The majority of patients present with painful symmetrical osteosclerosis of long bones: metaphysis and diaphysis predominantly.^{2,8,13} The following systems are often involved in ECD: CNS, cardiovascular, renal, retro-orbital, endocrine, and respiratory.⁸ Cutaneous manifestations occur in 33% of patients most commonly as xanthelasma.^{1,7,8} Some have an atypical presentation, such as red-brown pinpoint papules on the face, or brown-red slightly pruritic papules on the trunk.^{14,15} ECD is a chronic disease and prognosis is variable depending on the severity of organ involvement. Patients

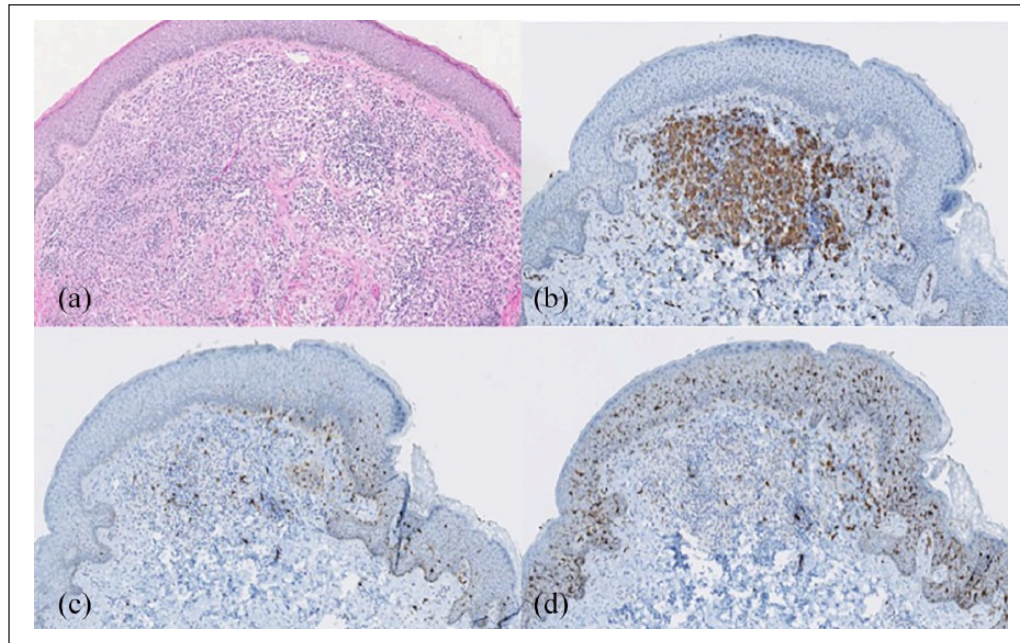


Figure 2. Histopathological examination of an abdominal skin lesion composed of a dense upper dermis nodular infiltrate consisting of histiocytes with multinucleated giant cells. (a) Hematoxylin–eosin stain (magnification 10×). (b) CD68+ histiocytes (magnification 10×). (c) S100– histiocytes (magnification 10×). (d) CD1a– histiocytes (original magnification, 10×).

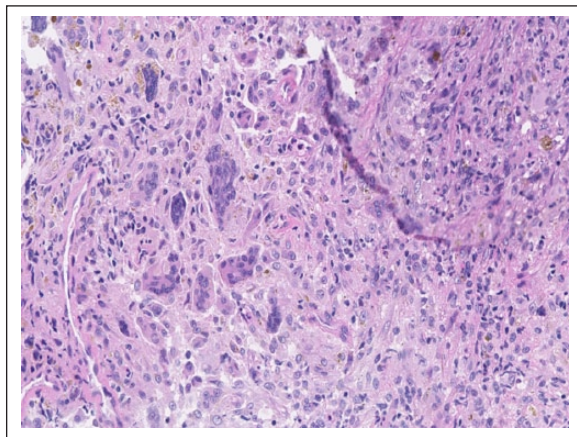


Figure 3. Bone marrow biopsy showing a dense infiltrate composed of histiocytes with multinucleated giant cells (hematoxylin–eosin stain, magnification 40×).

with CNS involvement, such as cerebellar or pyramidal symptoms, have a worse prognosis.^{1,8,9,11,12}

XD is another rare non-LCH of unknown etiology and also with a male predilection.¹⁶ The classical presentation includes mucocutaneous xanthomas and DI.^{13,17} Xanthomas are composed of CD68+, CD1a–, and S100– histiocytes and cutaneous xanthomas often disseminate and can coalesce into larger plaque nodules.^{16,17} 40%–60% of XD patients have mucosal xanthomas, which are often found in the respiratory and upper gastrointestinal tracts.^{13,16} DI, the most common CNS presentation, is found in 40% of cases.^{13,16}

Unlike ECD, bone involvement is not characteristic in XD.^{13,17}

Our patient has an atypical ECD. She is younger than the average ECD patient, and she presented with asymptomatic and asymmetrical axial osteolytic lesions instead of the classical and painful osteosclerosis of long bones. Few cases of ECD with axial bone lesions have been described.^{18,19} However, these patients were symptomatic and received treatment.^{18,19} Our patient had spontaneous regression of almost all of her osteolytic bone lesions and improvement of her visual fields. To our knowledge, this phenotype with a spontaneous improvement of bone lesions and visual fields has not been described.

There are no official dermatology guidelines for the management of ECD, but consensus guidelines and management approaches were published in 2014.^{8,9} An investigation algorithm was proposed: all patients should have several biopsies with BRAF-V600E mutation tested on more than one anatomical site, blood tests for renal insufficiency, cytopenia, inflammation, endocrine profile, chest-abdominal-pelvic CT, echocardiogram, positron emission tomography (PET), and cardiac and brain MRI.⁸ Treatment guidelines are based on case series or case reports.

In the past, multisystem involvement was first treated with interferon- α (INF- α).^{2,8} Other treatments included cladribine, anakinra, infliximab, imatinib, corticosteroids, radiotherapy, and surgery.^{7,8} However, with the increase in the knowledge of pathogenesis, BRAF and MEK inhibitors are being used.⁸ For patients with multisystemic involvement and BRAF-VE600E+ mutations, first-line treatment includes

usage of INF- α or BRAF inhibitors such as vemurafenib.⁸ Recently, the Food and Drug Administration (FDA) approved vemurafenib as a first-line treatment for BRAF-V600+ECD after the release of the VE-BASKET Study.²⁰

Treatment is suggested for all, but asymptomatic patients without neurologic involvement can undergo expectant observation with medical follow-up every 3 to 6 months.⁸ In our case, the patient was symptomatic with CNS involvement (pituitary and ophthalmic), but declined treatment. The optimal duration of therapy is unknown, and current recommendations suggest treating patients indefinitely, and doing a PET every 3 to 6 months.^{8,10} The prognosis remains uncertain, and there is no curative treatment. The overall 5-year survival is estimated at 68% for patients treated with INF- α .⁸ Also, in the VE-BASKET study, 86% had a 2-year progression-free survival rate.²⁰ With advances in the knowledge of ECD pathogenesis, more targeted-therapies can be studied.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MA-H reports personal fees from Novartis Pharma Canada Inc, outside the submitted work.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

A written and informed consent was obtained to use the patient's information and images for medical-scientific publication purposes.

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