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Diabetes insipidus, bone lesions, and new onset red-brown papules in a 42 year-old male

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Case Summary

History

A 42-year old Caucasian male was referred to the National Institutes of Health for evaluation. His symptoms began approximately 10 years prior to referral with pituitary dysfunction that manifested as diabetes insipidus, secondary hypogonadism and hyperprolactinemia, treated with desmopressin and testosterone gel. Eight years later, he began to experience vertigo, dizziness, diplopia, and difficulty focusing and tracking. This was followed by progressive left-sided weakness, poor coordination and balance difficulties. Magnetic resonance imaging (MRI) without contrast revealed multiple non-specific white matter lesions. Subsequent evaluation failed to identify an underlying infection or inflammatory etiology. Systemic corticosteroid therapy was initiated with minimal improvement. The patient was tapered off corticosteroids two months later and noted new asymptomatic skin lesions on his bilateral upper and lower extremities, leading to re-initiation of systemic steroids and introduction of interferon alpha. He denied fevers, chills, weight loss or difficulty breathing.

Physical Examination

The patient was a well appearing Caucasian male. Cutaneous examination was notable for approximately twenty 2-3 mm, firm, reddish-brown papules scattered on the trunk and extremities, with greater density on the anterior thighs (Fig 1). Diascopy revealed a yellowish hue. Ophthalmologic examination was notable for nystagmus, saccadic pursuit and mild dysmetria. Neurologic examination revealed unsteady tandem gait, abnormal finger-to-nose pointing and left-sided dysdiadochokinesia. Left arm strength was diminished (4/5). The oral mucosa was unremarkable. No lymphadenopathy was appreciated.

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Note: Dr. Kornik evaluated this patient during an elective rotation at the NIH

Histopathology

A punch skin biopsy of a papule on the left thigh was obtained, and histology revealed a moderately dense dermal infiltrate of epithelioid histiocytes characterized by rounded to slightly elongated nuclei with inconspicuous nucleoli and moderate to abundant eosinophilic cytoplasm (Fig 2A). CD68 and CD163 immunohistochemistry highlighted the lesional histiocytes (Fig 2B). Lesional cells also showed strong, diffuse staining for Factor XIIIa (Fig 2C). CD1a and S-100 immunostains were negative.

Other significant diagnostic tests

Radiographs of the upper and lower extremities revealed sclerotic lesions involving the metaphyseal and diaphyseal regions of the long bones with sparing of the epiphyses. Positron emission tomography - computed tomography (PET/CT) scan showed multiple foci of increased uptake in the lower extremity, including the bilateral femurs and tibiae corresponding to areas of sclerosis on CT scan. Multiple similar areas of abnormal uptake were detected on whole body bone scan (Fig 3). MRI of the brain showed small focal white matter hyperintensities of the cerebral hemispheres, as well as signal abnormalities in the pons and cerebellum (Fig 4). Chest CT did not show evidence of pulmonary disease. Transthoracic echocardiogram and serum lipid panel were unremarkable.

Diagnosis

Erdheim-Chester Disease (ECD) with cutaneous, skeletal, and central nervous system (CNS) involvement

Follow-up

The patient's medical condition continued to deteriorate over the next several months despite treatment with peginterferon alfa 2a 135 mcg/week. Whereas he was walking independently during his first visit, one year later the patient required the use of a wheelchair or walker at all times. Neuro-ophthalmologic evaluation revealed saccadic dysmetria and end gaze nystagmus consistent with cerebellar disease as well as vestibulo-ocular reflex deficit which correlated with brainstem involvement. Disease progression in the pons, brainstem and cerebellum was confirmed by radiographic imaging. All other organ systems involved were stable in comparison to the patient's first visit to the NIH.

Subsequent to the patient's first evaluation at the NIH, Haroche *et al.* reported the BRAF V600E mutation in 54% of patients with Erdheim-Chester disease, but not in other forms of non-Langerhans cell histiocytosis.¹ Based on this new finding, molecular testing was performed on the patient's biopsy specimen. DNA was extracted from paraffin-embedded tissue sections using the Qiagen QIAamp DNA FFPE Tissue Kit. The percentage of tumor cells was ~20%. The DNA was subjected to COLD-PCR using a single primer set encompassing codons 599-601 of the BRAF gene. The product was subjected to pyrosequencing on a Qiagen PyroMark Q24 system. A c.1799 T>A (p.V600E) mutation was detected. All positive and negative control reactions were adequate.

Discussion

ECD is a rare multisystem disorder of non-Langerhans cell histiocytes described by Jacob Erdheim and William Chester in 1930.^{2, 3} The disease course is highly variable, ranging from asymptomatic bone lesions to life-threatening multi-organ involvement^{2, 3} and is associated with an overall 5-year survival of 68%.⁴ Due to the varied clinical presentation, the differential diagnosis is broad (Table I) and diagnosis requires a high index of suspicion and integration of clinical, radiographic and histologic findings.^{2, 4, 5, 6} Skeletal lesions primarily affecting the lower limbs are the most common manifestation of the disease,^{3, 4}

leading to bone pain in approximately one-half of patients.³ The radiographic features of bone involvement are specific and demonstrate symmetric sclerosis involving the distal portion of the long bones.^{3, 7} Bone scintigraphy, PET and MRI may be used to evaluate osseous structures as well.² In 5-8% of patients, lytic bone lesions develop which simulates Langerhans cell histiocytosis (LCH), myeloma or metastatic disease if a complete skeletal survey is not performed.³

Almost any organ system is susceptible to histiocytic infiltration and nearly all (98%) patients with ECD exhibit extraskeletal manifestations.⁴ Cutaneous manifestations develop in approximately one-third of patients but are often non-specific. The most commonly reported skin findings are xanthomatous lesions³ which may be clinically indistinguishable from the lesions of xanthoma disseminatum and papular xanthoma.⁶ Other reported cutaneous signs are pruritic eruptions, cutaneous masses,³ yellow-red papules, nodules, indurated erythematous plaques⁵ and infiltration of the vulva and clitoris.² In addition to the skin, the heart, lungs, central nervous system, endocrine glands² and gastrointestinal system⁸ may be affected. Infiltration of the retroperitoneum can lead to bilateral hydronephrosis⁴ and sheathing of the aorta.² The most common causes of death are heart failure, respiratory distress, pulmonary fibrosis³ and CNS disease.⁴

Neurologic involvement can lead to significant functional impairment and is an important prognostic factor since it has been shown to be an independent predictor of mortality.⁴ Diabetes insipidus and exophthalmos are two characteristic signs of intracranial involvement that occur secondary to histiocytic infiltration of the pituitary and retro-orbital tissues, respectively, and are found in approximately one-third of patients.³ Non-LCH should be considered in the differential diagnosis of any patient with unexplained diabetes insipidus.

Histology is essential and is characterized by xanthomatous or xanthogranulomatous infiltration of various tissues with lipid-laden macrophages³ that display immunoreactivity with CD68 and factor XIIIa.^{9, 10} ECD can be differentiated from LCH by the lack of S100 and CD1a staining.^{2, 3} Ultrastructural examination is notable for the absence of Birbeck granules, a cardinal feature of Langerhans cells.³

The pathogenesis of ECD is poorly understood and studies are limited by small numbers of patients.² Tran *et al.* reported elevated circulating levels of interleukin-1beta, IL-6 and tumor necrosis factor-alpha (TNFα) in a pediatric patient with ECD.¹¹ Dagna *et al.* assessed spontaneous and stimulated cytokine release in isolated mononuclear cells from a biopsy specimen of a patient with ECD and found spontaneous secretion of IL-6 and IL-8, as well as stimulated production of TNFα.¹⁰ The presence of IL-8, a chemoattractant for polymorphonuclear cells and monocytes, was a novel finding. Similarly, Haroche *et al.* described immune activation involving IL-1 and IL-6 in addition to interferon-alpha and monocyte chemotactic protein-1, implicating disruption of the Th1 immune response.²

Currently, there is no established first-line therapeutic regimen for ECD. Corticosteroids are the most commonly reported treatment. More recently, therapy with IFNα was shown to confer a greater likelihood of survival.⁴ Other reported treatment regimens include chemotherapy (vinca alkaloids, anthracyclines and cyclophosphamide), imatinib mesylate, sunitinib, anakinra, methotrexate, bisphosphonates, autologous hematopoietic stem cell transplantation and radiation therapy.^{3, 4, 12} The recent discovery of a BRAF^{V600E} mutation in 54% of patients with ECD suggest the possibly utility of targeted therapy with vemurafenib, a BRAF inhibitor recently approved for treatment of metastatic melanoma.¹³

KEY TEACHING POINTS

ECD is a multisystem non-Langerhans cell histiocytosis characterized by histiocytic infiltration of the bones, viscera, CNS and skin requiring comprehensive skeletal, visceral and neurologic evaluation. Hallmark skeletal lesions are symmetric distal osteosclerosis of the long bones with sparing of the epiphyses.

Cutaneous involvement most commonly consists of xanthelasma and xanthoma-like lesions. Histology reveals lipid-laden macrophages expressing CD68 and factor XIIIa, and lacking S100 and CD1a expression.

The recent report of BRAF V600E mutations in 54% of patient with Erdheim Chester disease suggests a potential new therapeutic approach. However, further research is needed to better understand the pathophysiology of this rare disease.

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Abbreviations

ECD	Erdheim-Chester disease
LCH	Langerhans cell histiocytosis
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography - computed tomography
TNFα	Tumor necrosis factor-alpha

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Figure 1. Cutaneous Erdheim-Chester disease. Isolated red-brown papule on the thigh (**A**); close-up image (**B**)

Figure 2.

Histology findings in cutaneous Erdheim-Chester disease. H&E stained tissue section revealed a moderately dense infiltrate of epithelioid histiocytes in the dermis. A mild superficial perivascular lymphocytic inflammatory infiltrate is present (**A**) (original magnification, 200x). CD163 immunohistochemistry (**B**) (original magnification, 200x). Factor XIIIa immunohistochemistry (**C**) (original magnification, 200x).

Figure 3.

Bony involvement in Erdheim-Chester disease. Whole body bone scan after the administration of Technetium-99 showing several areas of abnormal increased uptake in the skeleton. Most prominent is bilateral heterogeneous increased uptake in the distal half of both femurs extending to the condyles, in the proximal portion of the tibiae, and in the distal portion of the tibiae.

Figure 4. CNS involvement in Erdheim-Chester disease. Brain MRI showing include extensive patchy signal abnormality throughout the pons extending into the middle cerebellar peduncles and numerous small foci of signal abnormality throughout the white matter (arrows).

Table I**Differential Diagnosis of Erdheim-Chester disease**

Xanthoma disseminatum
Juvenile Xanthogranuloma
Langerhans cell histiocytosis
Sinus histiocytosis with massive lymphadenopathy
Sarcoidosis
Amyloidosis
Gaucher disease
Niemann-Pick disease
Mastocytosis
Paget's disease
Fluoride intoxication
Adult progressive diaphysial dysplasia
Whipple disease
Mucopolysaccharidoses
Hermansky-Pudlak syndrome
Malakoplakia

Table from Caputo *et al.* *J Am Acad Dermatol.* 2007⁶