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Erdheim-Chester disease; a 31-year-old woman presented with bone pain and ophthalmologic involvement: a case report

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Abstract

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic disorder with no actual known incidence rate. It primarily affects multiple organs via increased expression of proinflammatory cytokines, eventually leading to histiocyte activation and infiltration at multiple sites. A 31-year-old virgin female presented with progressive generalized bone pain and blurred vision. She underwent a comprehensive clinical and paraclinical evaluation. Based on the final results, the diagnosis of ECD was established. We started treatment mainly using Interferon- α and corticosteroids, estrogen, levothyroxine, and desmopressin acetate. In adults with a mysterious chronic disease affecting multiple organs, we should always consider ECD as a differential diagnosis. Although ECD is still rare, the detection rate of this disease has increased significantly in recent decades. A comprehensive clinical and paraclinical evaluation is necessary to make a definitive diagnosis and determine the extent of the disease.

Keywords: Erdheim-Chester disease, Histiocytic disorder, Bone pain, Ophthalmologic complication

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Introduction

Erdheim-Chester disease (ECD) is a rare multiorgan disease with no actual known incidence rate, affecting mainly men with an average age of 55-60 years (1, 2). It is considered as a clonal myeloid disorder triggered by somatic mutations of signaling molecules such as BRAF, eventually leading to increased expression of proinflammatory cytokines that result in histiocyte activation and infiltration at multiple sites (3,4).

Clinical symptoms vary depending on organ involvement. Impairment of the skeletal system presenting with bone pain (especially in the lower limbs) is reported as the most common clinical manifestation (1). Other methods, including the cardiovascular system, pulmonary system, central nervous system, integumentary and endocrine system, may be affected.

Considering the nonspecific symptoms and rarity of ECD, the establishment of a diagnosis is a difficult endeavor. Therefore, when a patient is highly suspicious of ECD, a comprehensive and complete workup is required,

including basic laboratory tests, imaging, and pathological studies.

Here, we present a case of ECD in a 31-year-old woman who presented with generalized bone pain and blurred vision.

Case Presentation

A 31-year-old virgin female was admitted to our center complaining of generalized bone pain, especially in the lower extremities, which had been progressively occurring for 1.5 years and literally interfered with her daily activities. The patient mentioned proximal weakness of the upper and lower limb muscles, gait disturbances, and ataxia. She was awake and alert and looked older than her documented age. Cranial nerve examination was normal. Muscle strength was symmetrical 4/5+ and 3/5+ in the upper and lower limbs, respectively. However, gait assessment was impossible because the patient could not walk. Deep tendon reflex was 2+ symmetrical in the upper limbs and 3+ in the lower limbs. Other neurological

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■ Implication for health policy/practice/research/medical education

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic disorder that affects multiple organs. This disease was diagnosed in a 31-year-old virgin woman with progressive generalized bone pain and blurred vision. The use of interferon- α along with corticosteroids, estrogen, levothyroxine and desmopressin acetate was prescribed. It should be noted that ECD should always be considered as a differential diagnosis in adults with a mysterious chronic disease..

examinations were normal. In addition, tenderness was noted in the thoracolumbar vertebrae and lower limbs. An eczematous rash without xanthomas, xanthelasmas, or other skin abnormalities was pointed out on the legs and back.

She noted progressive blurred vision from last year. The pupils were midsize and reactive to light, and visual acuity at presentation was 1/10 in both eyes. However, previous examinations about seven months ago estimated visual acuity at 6/10, which may indicate a progressive course. We found the cornea, anterior and posterior chamber, and lens normal in both eyes, except for bilateral macular dystrophy and edema, along with bilateral optic disk edema.

She reported experiencing amenorrhea six years ago and polyuria and polydipsia for the last three months. Additionally, she mentioned approximately 8-10 kg of weight loss in the past six months. She also had a urinary tract infection that recurred in the previous year.

Considering the chronic multisystem involvement, we performed further comprehensive investigations.

Complete baseline laboratory tests were performed (Table 1). The appropriate endocrine tests were done based on the history suggestive of polyuria, polydipsia, and amenorrhea (Table 1). The final results were literally consistent with diabetes insipidus, central hypothyroidism, secondary adrenal insufficiency, hypogonadotropic hypogonadism, and growth hormone deficiency.

Cardiovascular system related assessments were normal. Regarding muscle weakness, we performed electromyography and nerve conduction velocity (EMG-NCV), which revealed no abnormalities.

The patient underwent magnetic resonance imaging (MRI) of the brain, orbit, spine, and pelvis for further evaluation. We found an abnormal enhancing lesion extending to the infratemporal fossa and pterygoid muscles (Figure 1). Mucosal thickening of the sphenoid, maxillary, and ethmoid sinuses was noted with enhancement in the postcontrast images, which could be indicative of infiltrating lesions (Figure 1). Increased thickness of the pituitary stalk (7 mm) was observed (Figure 1). In the fluid-attenuated inversion images (FLAIR) and the T2-weighted sequences, confluent hyperintensity was noted in the posterior part of the pons and the middle cerebellar peduncle and in the superior part of the cerebellar vermis (Figure 1).

Table 1. Initial laboratory investigation

Test	Value	Reference
Hb	10.6	11.5–16.5 g/dL
WBC	11000	3500–11000/ μ L
PLT	383000	150000–450000/ μ L
MCV	76.2	Fl
Serum Iron	28	23–165 μ g/dL
Ferritin	55.1	10–124 ng/mL
ESR	82	0–22 mm
CRP	6	Up to 6
Na	160	136–146 mEq/L
K	3.5	3.5–5.1 mEq/L
Urine analysis /SG	1002	
Ca	8.8	8.5–10.4 mg/dL
P	3.7	3.5–5 mg/dL
Vit D3	34.3	30–100 ng/mL
Prolactin	131	4.79–23.3 ng/mL
IGF-1	31.86	83–305 ng/mL
T4	4	5.10–14.10 μ g/dL
T3	0.45	0.8–2.05 ng/mL
TSH	3.71	0.27–4.2 IU/mL
LH	0.16	14–48 mIU/mL
FSH	0.56	25.8–134.8 mIU/mL
Estradiol	39.95	< 58 pg/mL
ACTH	<5	10–60 pg/mL
Cortisol	6.44	4–22 μ g/dL

Hb: Hemoglobin, WBC: White blood cells, PLT: Platelet, MCV: Mean corpuscular volume, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Na: Sodium, K: Potassium, SG: Specific gravity, Ca: Calcium, P: Phosphorus, Vit D3: Vitamin D3/Cholecalciferol, TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, ACTH: Adrenocorticotropic hormone, IGF-1: Insulin like growth factor-1, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum Glutamic Pyruvic Transaminase, ALP: Alkaline phosphatase, BUN: Blood urea nitrogen, Cr: Creatinine.

On spinal MRI, the vertebral body of C4 was hypointense in both T1- and T2-weighted sequences with inhomogeneous contrast enhancement, which was hyperintense and sclerotic on radiograph (Figure 2). MRI of the pelvis revealed abnormal signal intensity in the right ilium and sacral wing (Figure 2).

The radiography of upper and lower extremities demonstrated osteosclerosis (Figure 3).

The patient underwent bone mineral density testing, which revealed severe osteoporosis. Considering panhypopituitarism, treatment with corticosteroids, estrogen, levothyroxine, and desmopressin spray was started. Bisphosphonates and calcium supplements were prescribed. Considering the significant thickening of the sphenoidal and ethmoidal sinuses and the pelvic

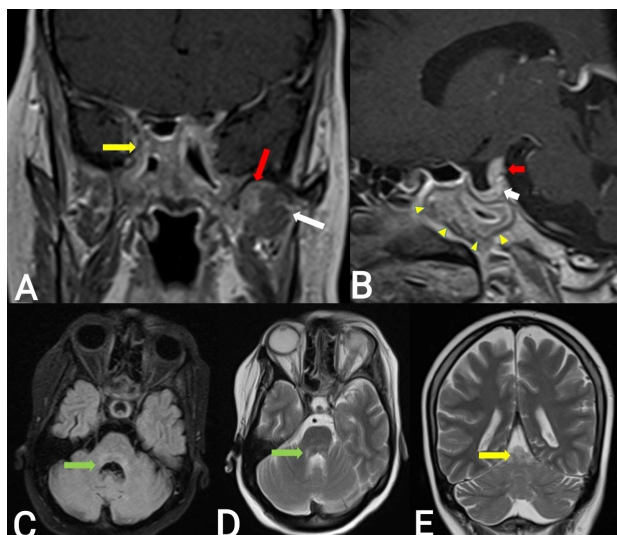


Figure 1. In the left image, coronal T1 post-contrast MRI (A) long yellow arrow shows an infiltrative enhancing lesion that filled the sphenoid sinus. The long white arrow shows normal pterygoid muscle and the long red arrow shows muscle involvement with enhancing lesion. In the right image, sagittal post-contrast MRI (B) yellow arrowheads show an infiltrative enhancing lesion that filled the sphenoid sinus. The short white arrow shows a normal pituitary gland and the short red arrow shows thickening of pituitary stalk. In the axial FLAIR (C) and T2-weighted (D) MRI sequences, long green arrows show an abnormal signal change in the middle cerebellar peduncle. In the coronal T2-weighted image (E) long yellow arrow shows abnormal signal change at the upper part of the vermis. These findings could explain the disequilibrium of the patient.

lesion, a biopsy of the sphenoidal sinus was performed by transsphenoidal surgery and a biopsy of the pelvic lesion was completed. The specimens were sent for further pathologic studies.

Microscopic observation showed tissue infiltration by histiocytes with foamy (xanthomatous) cytoplasm in the fibrotic background (Figure 4).

Immunohistochemistry (IHC) revealed a positive result for CD68 and cyclin-D1. Other markers including CD-1a, Langerin, S-100, and BRAF-V600E were negative.

Based on the clinical findings and subsequent investigations, a diagnosis of ECD was established and the patient was treated with interferon- α . She is now

being carefully followed up. The therapeutic response was completely satisfactory, with significant improvements compared with the initial presentation.

Discussion

In adults with a mysterious chronic disease affecting multiple organs, we should always consider ECD as a differential diagnosis. Unexplained bone pain and abnormal radiological findings associated with various systemic impairments, including the cardiovascular system, central nervous system, and skin, should alert us to consider this diagnosis. Although ECD is still rare, the detection rate of this disease has increased significantly in recent decades.

In our case, one of the main complaints was progressive, persistent pain in the lower extremities, as well as the typical bone involvement in this disease evidently. Intraconal masses with compressive effect on the optic nerve may cause optic disk edema and atrophy, which was noted in our case (5). Although xanthelasma is the typical skin lesion in ECD, we found only a nonspecific reddish eczematous rash in our patient (6).

However, there is no specific laboratory finding in ECD. Still, typical indicators of chronic inflammatory disease, such as elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) and/or anemia, may be found (7). There is evidence that the incidence of myeloid neoplasms, such as myeloid dysplastic syndrome and myeloproliferative neoplasms is higher in people with ECD (8). Therefore, it is important to carefully screen for concurrent myeloid disease in these patients, especially if we find abnormal platelet or lymphocyte counts during initial evaluations. Since endocrine abnormalities are not that rare in ECD, it is recommended to check the relevant endocrine tests (9). Especially when endocrine involvement is suspected based on the history and clinical evaluation. As previously reported, at least two hormonal axes are impaired in patients with pituitary dysfunction (9). We found clinical evidence and impaired tests consistent with diabetes insipidus, central hypothyroidism, secondary adrenal insufficiency, hypogonadotropic hypogonadism,

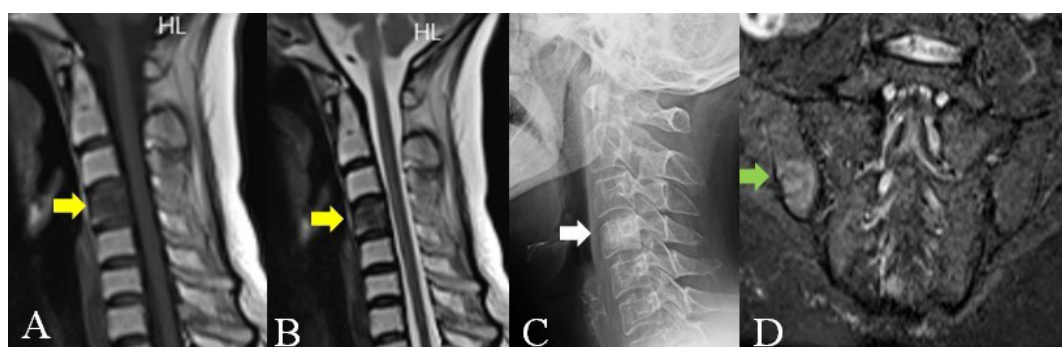


Figure 2. In the sagittal T1-weighted (A) and T2-weighted (B) MRI sequences, short yellow arrows show an abnormal hyposignal change in the C4 vertebral body bone marrow. In the cervical x-ray sclerotic lesion compatible with MRI findings is evident at C4 vertebrae body. The short green arrow shows an abnormal signal change at the right iliac bone wing (D).

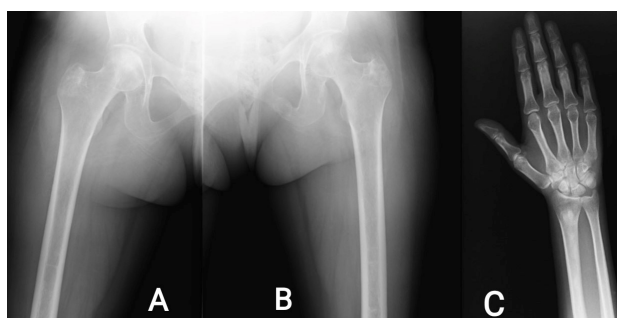


Figure 3. (A&B) bilateral symmetric osteosclerosis in head of femur. osteosclerosis in radius bone (C).

growth hormone deficiency, and hyperprolactinemia.

Imaging is one of the most essential tools for the diagnosis of ECD. The most important radiologic finding in patients with skeletal involvement is bilateral symmetric osteosclerosis of the diaphysis and metaphysis (typically in the long bones) (10). Increased thickness of the pituitary stalk on MRI of the brain, as we found in our case, and other findings such as infiltrating lesions may be suggestive of ECD (9).

Tissue biopsy is essential to confirm the diagnosis of ECD. The characteristic histopathologic clues are infiltration of foamy or lipid-laden histiocytes occasionally accompanied by Touton giant cells associated with fibrosis and an inflammatory background (11). The histiocytes are negative for CD1a and CD207 and positive for CD68, CD163, and factor XIIIa on IHC staining (11).

Due to the fact that database for confirming a clear therapeutic guideline is limited, there is an absolute need for well-designed prospective clinical trials. Nevertheless, known treatment options include 1) Corticosteroids, 2) Biologic agents such as interferon- α , anti-cytokine agents (Anakinra, Infliximab), 3) Chemotherapy, 4) BRAF inhibitors, 5) MEK inhibitors, 6) mammalian/mechanistic target of rapamycin (mTOR), 7) Radiotherapy and 8) Surgery (12). Interferon- α , particularly the pegylated form, may be recommended as an efficient treatment option along with targeted agents (13). Glucocorticoids have shown therapeutic effectiveness in ECD; however, they have not been shown to provide a survival benefit (13). Of note, radiotherapy is literally used as adjuvant therapy, especially in patients with lesions that have a compressive effect (14). Surgery is basically suitable for intracranial and orbital lesions (15).

Conclusion

Erdheim-Chester disease as a rare non-Langerhans histiocytic disorder could be considered as one of the differential diagnoses of chronic multisystemic diseases, especially when infiltrative disease is suspected. A comprehensive initial evaluation including history and clinical assessment, laboratory tests, imaging, and pathologic studies is required to make a definitive diagnosis and identify the extent of the disease. Nevertheless,

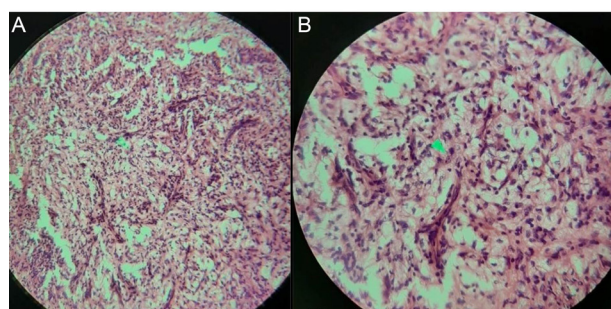


Figure 4. (A&B) Microscopic observation showed tissue infiltration by histiocytes with foamy (xanthomatous) cytoplasm in fibrotic background. Scattered inflammatory cells were also observed (focuses: A: $\times 100$, B: $\times 250$).

further studies are needed to increase knowledge of the pathogenesis, diagnostic clues, and treatment options for ECD.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical Approval

The case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient provided written informed consent for the publication of this report. The authors have strictly adhered to ethical considerations, including avoiding plagiarism, data fabrication, and double publication.

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