Erdheim Chester Histiocytosis: About a New Case Revealed after Ten Years History of Diabetes Insipidus

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Abstract
Erdheim-Chester Disease (ECD) is a rare form of non-Langerhans cell histiocytosis characterized by the proliferation of lipid-rich histiocytes and foam-like tissue cells. Here, we present a case report of a 31-year-old male patient with ECD who initially presented with nonspecific symptoms including diabetes insipidus. Histopathological analysis confirmed the diagnosis, showing typical histological features of ECD. Treatment with Anakinra and corticosteroids led to significant improvement in symptoms. Additionally, we provide a comprehensive literature review summarizing the clinical manifestations, diagnostic criteria, pathological features, and treatment options for ECD. This case highlights the importance of considering ECD in the differential diagnosis of patients presenting with multisystem involvement and underscores the challenges in managing this rare disease.

Introduction
Erdheim Chester disease (ECD) is a non-Langerhansian rare histiocytosis, with around 700 cases described worldwide since its discovery for the first time in 1930 by Jakob Erdheim and William Chester. It is a multisystem disease, characterized by a proliferation of abnormal histocytes CD68 positive and CD1a negative, including a retroperitoneal and perirenal fibrosis, a peri-aortitis, an osteosclerosis of the lower limbs and sometime an exophthalmia or a diabetes insipidus. However, cases may be non-typic and confusing [1-3].

Case data
We report the case of the patient B.K aged of 31 years old, followed for diabetes insipidus with an enlarged pituitary stalk evolving for 10 year, posing an etiological diagnostic problem. Sarcoidosis have been first discussed without a lot of clinical and biological arguments, conducing to the introduction of corticotherapy, with a morphological response (regression of the stalk enlargement on the MRI). The patient has been regularly followed and 9 years after, an expansion of the pituitary stalk led us to reevaluate him.

More Information
DOI: 10.59324/ejmhr.2024.2(2).27
Keywords:
Erdheim Chester disease, diabetes insipidus, retroperitoneal fibrosis.

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A thoraco-abdominal CT scan has demonstrated a retroperitoneal infiltration: left peri-renal and peri-pancreatic, which leaded us to discuss Erdheim Chester disease. A bone scan scintigraphy revealed multifocal involvement, including the shoulders, elbows, femurs, costal arch, and the right sacroiliac joint. A cutaneous localization as a xanthelasma on the lower eyelids is describe with recurrent outbreaks of headache associated to fever.
Figure 3: Bone Scan Scintigraphy Revealed Multifocal Involvement, Including the Shoulders, Elbows, Femurs, Costal Arch, and the Right Sacroiliac Joint

The definitive diagnosis was obtained by an immunohistochemical study on biopsy of the bone marrow and the Xanthëlasma, finding squamous histocytes expressing CD68, weakly PS100, without expression of CD1a and nuclear expression of D1 cylinder.

Figure 4: Photography of the Patient Demonstrating a Cutaneous Localization as a Xanthëlasma on the Left Lower Eyelids

Figure 5: Immunohistochemistry Showing Diffuse Cytoplasmic CD68 Expression

Figure 6: Immunohistochemistry Revealing Nuclear Cyclin D1 Expression within the Histiocytes
After a multidisciplinary discussion, the patient was started on Anakinra due to the unavailability of interferon alpha, which was the first-line treatment, and is regularly followed up in clinic.

Discussion
ECD is a type of histiocytosis originally named "lipid-like granulomatosis" by Jakob Erdheim and William Chester. It has also been referred to as "lipoid granulomatosis," "cholesterol granulomatosis," and multiple osteosclerotic histiocytosis, among other names. In 1972, Jaffe officially named the condition "Erdheim-Chester disease." This rare disease predominantly affects males, with a male-to-female ratio of 1.5 to 1, and typically presents between the ages of 40 and 70, with a median age of onset at 53 years. Pathologically, ECD is characterized by the proliferation of lipid-rich, foam-like tissue cells, primarily in bones. Around 50% of patients also experience infiltration in organs beyond the bones. Despite its rarity, approximately 700 cases of ECD have been reported worldwide since its discovery.
Histiocytosis encompasses a spectrum of xanthogranulomatous diseases resulting from the proliferation and accumulation of reactive or neoplastic histiocytes. Classification of such diseases is complex, but ECD falls into class II (non-Langerhans cell histiocytosis) with involvement of multiple organ systems. The WHO classified ECD as a tumor with uncertain biological behavior among soft tissue and bone tumors in 2013 and as a histiocytic and dendritic cell tumor among hematopoietic system tumors in 2017 [4-5].

The etiology and pathogenesis of ECD remain uncertain. While the WHO (2017) classifies it as a tumor of histiocyte origin, the debate continues regarding whether ECD represents a neoplastic or reactive proliferative disorder [6-8].

ECD primarily affects bone tissue in over 95% of cases, with the long bones of the limbs being the most commonly involved sites. However, it can also affect various other anatomical locations, including the cardiovascular system, central nervous system, lung, and orbit. Additional affected areas reported in literature include the urinary tract, retroperitoneum, gastrointestinal tract, skin, adrenal gland, breast, thyroid, and other regions. Patients with ECD may present with systemic symptoms such as fever, weight loss, and night sweats, with clinical manifestations varying depending on the location of the lesions. Diabetes insipidus is the most common neurological manifestation of ECD. Pulmonary lesions can cause symptoms like cough and dyspnea, while cardiovascular involvement may result in pericardial pain, cardiac tamponade, heart failure, and myocardial infarction. Renal lesions may lead to abdominal pain, dysuria, and renal insufficiency, and gastrointestinal involvement may present with long-term diarrhea, fatigue, and weight loss. Orbital lesions may be characterized by exophthalmos, diplopia, visual impairment, and other ocular symptoms [9-13].

The diagnosis of ECD relies on a combination of clinical presentation, characteristic imaging findings, and histopathological analysis of lesion biopsies. Diagnostic criteria encompass several key features:

1. Rarity of the disease, typically affecting individuals aged 55-60 years but can also occur in children, with bone involvement being predominant (>95%), along with cardiovascular, retroperitoneal,
central nervous system, pulmonary, and cutaneous manifestations.

2. Histomorphological similarity to Disseminated Juvenile Xanthogranulomatosis (DJXG), featuring hyperplastic histiocytes with foamy cytoplasm, Touton giant cells, and fibrosis, often intermixed with other inflammatory cells.

3. Immunohistochemical profile positive for CD68, CD163, Factor Vila, and CD14, while negative for S100, CD1a, and Langerin.

4. Characteristic symmetric sclerotic changes seen on X-ray in the metaphysis of long bones.

5. Presence of BRAF (V600E) mutation in the majority of cases (>50%), with a minority showing mutations in the PIK3CA and NRAS genes.

Histologically, ECD is characterized by lipid-rich, foam-like tissue cell proliferation accompanied by lymphocyte, plasma cell, and Touton giant cell infiltration, often with variable fibrosis. Immunohistochemical staining typically reveals positivity for CD68 and CD163, with negativity for CD1a, Langerin, and often S-100. Radiographically, symmetrical osteosclerosis is observed in the diaphysis or metaphysis of bilateral long bones, particularly around the knee joint. CT imaging may depict pseudo-tumor-like lesions in affected internal organs, irregular masses in the breast and muscles, and soft tissue infiltration around the aorta forming the "coated aorta" sign in cardiovascular involvement [14-16].

To the author’s knowledge, there is no universally accepted standard treatment for ECD. Treatment primarily involves targeting the cytokine/chemical factor network. Interferon-α (IFN-α) or pegylated IFN-α is often the initial therapeutic choice, with additional options including Anakinra and infliximab. IFN-α, in particular, has demonstrated efficacy in reducing tissue cell infiltration and alleviating pain, thereby prolonging overall patient survival. Given that over half of ECD patients harbor BRAF V600E mutations, further investigation into this pathway is crucial for advancing targeted therapy. Vemurafenib, a BRAF inhibitor, has shown promising results in ECD treatment, with studies indicating objective and sustained therapeutic effects in patients with BRAF V600E mutations. Biological agents such as infliximab, a TNF-α inhibitor, have also shown efficacy in managing cardiac involvement in ECD patients. Additionally, IL-6 inhibitors like Actemra have demonstrated effectiveness in ECD treatment, particularly in reducing inflammatory markers [8, 13-16].

**Conclusion**

At follow-up, our patient presented a bilateral hydronephrosis due to a retroperitoneal fibrosis leading to an acute renal failure treated by a JJ catheter. Discontinuation of anakinra unmasked a neurological involvement of Erdheim-Chester disease, presenting with vestibular syndrome and severe headaches, which responded well to high-dose corticosteroid therapy with Solumedrol at 60mg/day.

Despite advancements in treatment modalities, the prognosis of ECD remains challenging, largely due to delayed diagnosis and advanced disease stage at presentation. Internal organ involvement, including the central nervous system, cardiovascular system, digestive system, lung, and kidney, significantly impacts prognosis.

**References**


