

## Case report

# Erdheim-Chester disease with multisystemic involvement: a diagnostic challenge

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### ABSTRACT

Erdheim–Chester disease (ECD) is a rare, non-inherited, non-Langerhans form of histiocytosis of unknown origin, first described in 1930. This entity is defined by a mononuclear infiltrate consisting of lipid laden, foamy histiocytes that stain positively for CD68. Individuals affected by this disease are typically adults between their 4th and 6th decades of life. The multi systemic form of ECD is associated with significant morbidity, which may arise due to histiocytic infiltration of critical organ systems. Among the more common sites of involvement are the skeleton, central nervous system, cardiovascular system, lungs, kidneys (retroperitoneum) and skin. The most common presenting symptom of ECD is bone pain. Bilateral symmetric increased tracer uptake on <sup>99m</sup>Tc bone scintigraphy affecting the periarticular regions of the long bones is highly suggestive of ECD. However, definite diagnosis of ECD is established only once CD68(+), CD1a(–) histiocytes are identified within a biopsy specimen with aid of clinical and radiological data. Here we present a rare case of Erdheim-Chester disease in a 46 year male patient based on clinical data, radiological data, histopathological and immunohistochemistry findings.

**Keywords:** CD 68(+), CD1a(-), Erdheim-Chester disease, Multisystem involvement, Non-Langerhans cell histiocytosis, Pathological fracture, Sclerotic bone lesion

### INTRODUCTION

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell, lipid-laden histiocytosis with specific histological and radiological findings.<sup>1</sup> First described in 1930 by William Chester as a novel lipo granulomatous disorder, it was later termed Erdheim-Chester disease after the pathologist Erdheim, with whom he worked.<sup>2</sup> Till now roughly 550 cases have been described in the literature.<sup>1</sup> The disease usually becomes apparent in adulthood between 40 and 60 years with an average age of onset of 53 years. In fact, Erdheim-Chester is a rare non-Langerhans cell histiocytosis of unknown etiology. “Respiratory distress, extensive pulmonary fibrosis, and cardiac failure are the most common causes of death”.<sup>2,3</sup> However, recent detection of a mutation in the BRAF

(BRAFV600E) proto-oncogene has been identified in the majority of ECD patients.<sup>4</sup> This recent identification of the clonal nature of the disorder has changed this understanding of the pathogenesis of the disease.<sup>4</sup>

The diagnosis of ECD depends on the combination of clinical presentations and imaging features, which are confirmed with histopathological findings. Skeletal involvement is highly pronounced and it occurs in up to 95% of ECD patients and bone pain is the most common presenting symptom.<sup>4</sup> Other extra skeletal involvement includes infiltration of the eyes causing exophthalmos, papilledema, xanthelasma and papulonodular skin lesions, endocrinal infiltration and diabetes insipidus, severe lung disease, renal failure, retroperitoneal region involvement, dysuria, abdominal pain, cardiomyopathy

and central nervous system (CNS) disorders.<sup>5,6</sup> The diagnosis is based on almost pathognomonic radiographic signs characterized by bilateral, symmetrical osteosclerosis involving metaphyseal and diaphyseal regions, with sparing of the epiphyses, combined with histological features.<sup>5</sup>

The differential diagnosis of ECD includes many conditions presenting with symptoms and findings similar to ECD such as Langerhans cell histiocytosis, Rosai-Dorfman disease, Wegener's granulomatosis, multiple sclerosis, Paget disease, neuro sarcoidosis, amyloidosis, metabolic disorders such as Gaucher's disease and mucopolysaccharidoses, cerebrotendinous xanthomatosis, Whipple's disease, chronic recurrent multifocal osteomyelitis, Takayasu arteritis, primary hypophysitis, malignancy and mycobacterial infections.

### CASE REPORT

Here we present a case of 46 year old male patient who presented with complain of bilateral thigh pain and unable to walk after a trivial trauma due to slippage in bathroom. Patient initially consulted some private hospital, where radiographs were taken, and diagnosis of bilateral shaft femur fracture was done and then patient was referred to this institute.

A detailed past history was evaluated upon admission which revealed that patient had bilateral loss of vision, initially of left eye following trauma and then of right eye due to retinal detachment. Patient also gave history of hospital admission for pneumonia and liver abscess in past. On examination patient had pallor, bilateral blindness and presence of scar mark over anterior abdomen wall at right hypochondrial region suggesting previous operation mark. Local examination of bilateral thigh showed swelling, bony crepitation and tenderness. Distal pulsation and toes and ankle joint movements were normal. Radiological investigations were done.

- X-ray of pelvis with bilateral lower limbs were taken which showed spirally displaced fracture in mid shaft of left femur along with multiple sclerotic lesions noted involving neck of femur with cortical thinning. (Figure 1 and 2) - Usg abdomen revealed hepato-splenomegaly and liver abscess, slightly bulky pancreas and minimally edematous bowel loop.

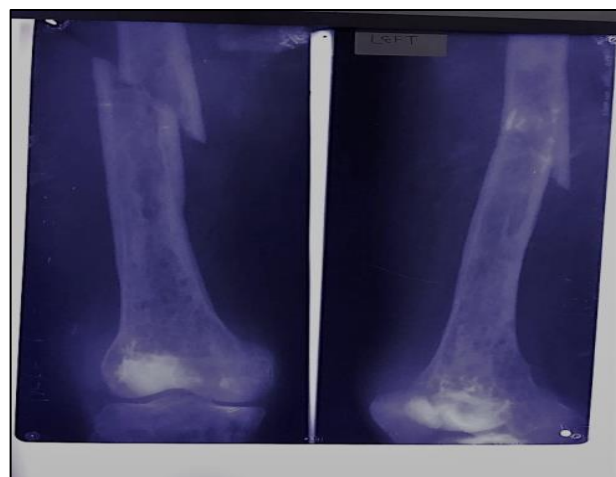
As there was bilateral mid shaft femur fracture following a minor trauma, the patient was diagnosed of bilateral pathological fracture without neurological deficit. Patient was operated for fracture and biopsy was taken from the fracture site for pathological evaluation.

All routine investigations of complete blood count(CBC), renal function test (RFT), liver function test (LFT), random blood sugar (RBS) and serology were done. There was mild leukocytosis, hypoalbuminemia,

hypoproteinemia. Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels were elevated.



**Figure 1: X-ray femur: spirally displaced fractures noted involving mid shaft of femur.**

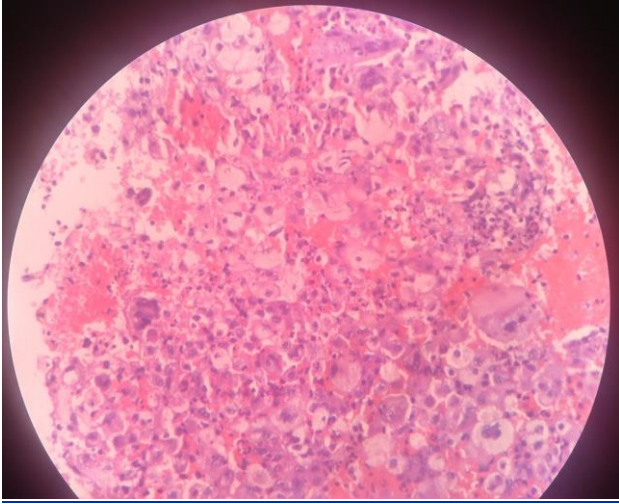


**Figure 2: X-ray femur: spirally displaced fractures noted involving both mid shaft of femur.**

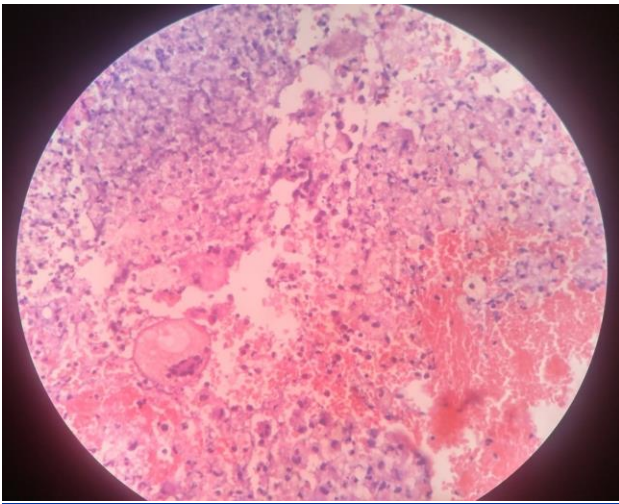
All viral markers were negative. Hb electrophoresis was normal. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) of patient were within normal range. Serum Ca<sup>++</sup> was also normal. Bone marrow examination findings were normal. Urine examination showed absence for Bence - Jones protein. Rest all parameters were normal.

Authors received biopsy sample and microscopic examination showed necrosed bony trabeculae, plenty of foamy histiocytes at places forming sheets, few histiocytic and touton giant cells, areas of hemorrhage and necrosis, disintegrated polymorphonuclear cells, lymphocytes, few plasma cells along with focal fibrosis and vascular proliferation. Histiocytes did not show any grooving. Eosinophils were not seen. Authors performed special stain: PAS stain did not show intracytoplasmic

PAS positivity/fungal organism and ZN stain did not show acid fast bacilli. (Figure 3 and 4) Immunohistochemistry was performed, in which histiocytic cells were positive for CD 68 and Vimentin, focally positive for S100 and negative for CD1a.



**Figure 3: H and E stain; 40X view: Section showed plenty of foamy histiocytes and tuon giant cells, areas of hemorrhage and necrosis, disintegrated polymorphonuclear cells, lymphocytes, few plasma cells along with focal fibrosis and vascular proliferation.**



**Figure 4: H and E stain; 40X view: Section showed plenty of foamy histiocytes and tuon giant cells, areas of hemorrhage and necrosis, disintegrated polymorphonuclear cells, lymphocytes, few plasma cells along with focal fibrosis and vascular proliferation.**

From above details we concluded that features were suggestive of xantho granulomatous histiocytic lesion favoring possibility of Erdheim Chester Disease considering clinical and radiological details. Various radiological investigations were done after

histopathological diagnosis to confirm it as well as to delineate the extent of disease.

HRCT thorax was done which showed few fibrotic strands noted involving apical segment of right upper lobe and apico-posterior segment of left upper lobe, patchy area of consolidation with surrounding atelectatic bands involving posterobasal segment of left lower lobe, mild pleural effusion on right side with underlying subsegmental collapse of posterobasal segment of right lower lobe. Lung window showed multiple ill-defined bizzare shaped small cysts with surrounding ground glass opacities and fissural thickening and para septal emphysema involving apical segment of right upper lobe.

Few sub centimeters sized non-necrotic lymph nodes noted in pre/paratracheal, prevascular, pre/subcarinal regions and aortopulmonary window. Cardiac size was within normal limits.

## DISCUSSION

Erdheim-Chester disease (ECD) is a rare & incurable illness till date with multisystem involvement with some infiltrative predominance in the bone of the lower and upper extremities. This is the feature that we wish to emphasize in the present case report. It shows male predominance (sex ratio 1.2–1.5) and is most often diagnosed during fourth to sixth decade of life.

The bone lesions are bilateral, symmetric and localized in the distal limb bones, mainly in the lower limbs, involving diaphysis-metaphysis junction with no or little involvement of the epiphysis. Clinically, their manifestations consists of local pain, swelling and edema.<sup>7</sup> These aspects were present in this patient. This patient presented with bilateral loss of vision, as ECD is known to associate with frequent involvement by ocular pathology.<sup>8</sup>

Pulmonary infiltration is usually less common and it consists of diffuse reticulonodular infiltration of both lungs, resulting in progressive dyspnea. This latter symptom may also be caused by myocardial or pericardial infiltration due to the disease, but can also be due to pleural effusions resulting from pleural infiltration by the disease.<sup>9</sup> In this patient, Lung window showed multiple ill-defined bizzare shaped small cysts with surrounding ground glass opacities and fissural thickening, paraseptal emphysema was also noted involving apical segment of right upper lobe. There was also mild pleural effusion on right side. From the pathological point of view, Erdheim-Chester disease is due to a proliferation of foamy histiocytes causing fibrotic changes in various tissues, mainly the skeleton. This disease can be distinguished from Langerhans cell histiocytosis (LCH) on the basis of morphology in which histiocytes shows grooving and presence of eosinophils, usually affect younger people and in radiological examination purely lytic lesion in long bones. These findings were absent in this case.



Xantho granulomatous osteomyelitis also occurs in young individual with raised ESR and CRP. In this patient both ESR and CRP levels were normal. Metabolic storage disorder is another entity for discussion. It presents in childhood with massive hepato-splenomegaly. PAS stain is positive. All these features were not there in this case. In Sinus histiocytosis with massive lymphadenopathy also called Rosai Dorfman syndrome, bone involvement is very rare. Erdheim-Chester disease is a multi-system illness with predominantly bone involvement which was clearly illustrated in this patient. The course of the disease is highly variable, but long delay between the successive progressions are common, as seen in this case and can vary from months to years (more than 15).<sup>10</sup> The diagnosis is usually challenging due to the rarity of the disease and clinical overlapping with many other conditions.

The diagnosis in this case study was made based on characteristic features including clinical details, radiological findings and histopathological findings. Mutation of the proto-oncogene BRAF (BRAFV600E) has been found in more than 50% of cases. Currently, interferon- $\alpha$  is the most extensively studied agent in the treatment of ECD and serves as the first line of treatment. The rarity and variable presentation of this disease usually leads to delayed diagnosis and to high morbidity and mortality rates from associated complications.

## CONCLUSION

Erdheim-Chester disease is a systemic “histiocytosis” caused by non-Langerhans cells and typically foamy histiocytes, mainly involving bones and the retroperitoneal space. Although the course may be protracted, the overall prognosis is relatively poor. ECD is an orphan multi-systemic disease both diagnosis and treatment are challenging however the challenge for diagnosis requires a high degree of suspicion. As in this case, Authors made diagnosis of Erdheim-Chester disease by aid of clinical history, radiological investigation, histopathological examination and immunohistochemistry markers. Treatment and management of the disease are of greater complexity. Since no definite cure exists, the goals of treatment should be prolonging life and maximizing their quality. Psychological consulting is important because success of the physical treatment usually results in the maintenance of a chronic condition. As such, it may be accompanied by various difficulties, deficits and secondary complications as we discussed in this case report. The physical component of treatment should be supervised by a multidisciplinary team of specialists, whose expertise should correlate with the patient's distribution of the disease.

With time, better understanding of the immunology and molecular biology that underlie this condition will ultimately lead to the emergence of novel therapeutic

approaches. Recently, there has been some evidence for a role of the oncogenetic BRAFV600E mutation in this histiocytosis pathogenesis.<sup>4,5</sup> These findings might suggest new avenues for the mechanisms responsible for the disease and potential therapeutic possibilities.

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