



Case Report

# Erdheim-Chester Disease: A Case Report and Review of the Literature

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Received : 10 May 2020

Accepted : 23 May 2020

Published : 18 June 2020

**DOI**

10.25259/JCIS\_68\_2020

**Quick Response Code:**



## ABSTRACT

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans' cell histiocytosis characterized by xanthogranulomatous infiltration of foamy histiocytes surrounded by fibrosis. ECD may be asymptomatic or present as a multi-systemic disease with life-threatening manifestations, most commonly involving the skeletal system. Immunohistochemical staining demonstrates cells that are CD68+, CD1a-, and S100- with an absence of Birbeck granules. We report a case of a 69-year old male patient who presented with neurological symptoms – eventually thought to be separate to his diagnosis of ECD. It represents the ability to diagnose ECD based just on radiological findings in an otherwise asymptomatic individual.

**Keywords:** Erdheim-Chester Disease, Histiocytosis, Hairy kidney sign, Coated aorta sign

## INTRODUCTION

The first case of Erdheim-Chester disease (ECD) was described in 1930 by Jakob Erdheim, an Austrian pathologist, and William Chester, an American pathologist.<sup>[1]</sup> It is a rare, systemic form of non-Langerhans' cell histiocytosis and is of unknown etiology.<sup>[2]</sup> It primarily affects adults between their 5<sup>th</sup> and 7<sup>th</sup> decades of life but patients between the ages of 7 and 84 years have been diagnosed.<sup>[3]</sup> There is a slight male predominance with some studies suggesting an earlier diagnosis in female compared to male patients.<sup>[4]</sup> ECD may be asymptomatic or present as a multi-systemic disease with life-threatening manifestations affecting the skeleton, central nervous system, respiratory, cardiovascular and renal systems, as well as the retroperitoneum and skin. In symptomatic patients, bone pain is the most common initial presentation. Extra-skeletal manifestations are seen in up to 50% of cases.<sup>[3]</sup>

ECD is characterized by xanthogranulomatous infiltration of foamy histiocytes surrounded by fibrosis.<sup>[5-8]</sup> They lack Birbeck granules (a characteristic intracellular organelle found in Langerhans' cells) and immunohistochemical staining is positive for CD68 and negative for CD1a.<sup>[9]</sup> The World Health Organization has proposed a classification system for histiocytic disorders; Class I is Langerhans' cell histiocytosis (LCH) and Class II are the non-Langerhans' histiocytoses and include juvenile xanthogranuloma (JXG), Rosai-Dorfman disease, and ECD.<sup>[10]</sup> LCH encompasses the conditions previously known as Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma.<sup>[3]</sup> Class III includes the malignant histiocytic disorders.<sup>[10]</sup> LCH and ECD share common properties and overlap can occur in up to 12% of ECD cases.<sup>[11-15]</sup> However, ECD differs from LCH in the immunohistochemical and microscopic

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characteristics in that the histiocytes only in the latter stain positive for S100 protein and electron microscopy of their cytoplasm demonstrates Birbeck granules in more than 20% of cells.<sup>[16]</sup>

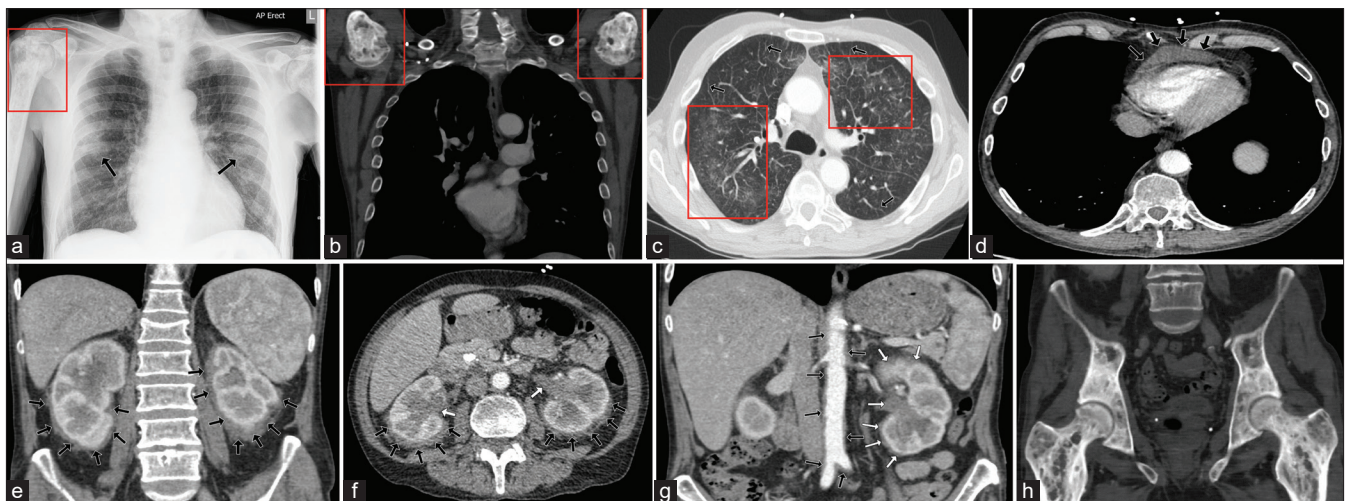
## CASE PRESENTATION

A 69-year-old gentleman presented with recurrent episodes of left arm and leg weakness over 1 week, which was diagnosed as crescendo transient ischemic attacks (TIA). His only medical history was previous alcohol excess, which he had overcome. On admission, the chest radiograph reported bilateral interstitial coarse reticulation, predominantly in the right mid zone. Incidental note was made of coarsening of the trabecular pattern and ill-defined sclerosis of the proximal humeri. Computed tomography (CT) of the head, performed for the TIAs, reported no acute intracranial abnormality, mild chronic ischemic small vessel disease, and an incidental sphenoid sinus mucous retention cyst. The skull bones were normal.

The blood results during admission revealed a microcytic anemia with a hemoglobin of 100 g/L and a mean corpuscular volume of 76.9 femtoliter. The white cell count, renal function tests, and liver function tests, including alkaline phosphatase

(ALP), were normal (apart from low albumin, 22 g/L). The coagulation screen, total cholesterol, glucose, and prostate-specific antigen were also all within normal limits.

Due to the microcytic anemia and humeral findings on the chest radiograph, in addition to some weight loss, a CT scan of the chest, abdomen, and pelvis were requested to rule out malignancy. As demonstrated in Figure 1, the findings within the chest were a combination of interlobular septal thickening and patchy ground glass opacification, producing a crazy paving pattern, with two ill-defined small solid nodules in the right upper and left lower lobes, respectively. Both kidneys showed diffuse perinephric soft tissue with further soft tissue within both renal pelvices and mild dilatation of the intrarenal collecting system. Bony appearances revealed coarsening of the trabeculae and a mixed pattern of sclerosis and lucency within the proximal humeri, scapulae, proximal femora, and acetabulae bilaterally. The case was forwarded to the neuroradiology multidisciplinary team meeting and on discussion of the findings; a diagnosis of ECD was made by the radiologist. It was felt that the patient's neurological symptoms were unrelated to the incidental radiological findings of ECD and he was referred on to a consultant neurologist at a specialist center.



**Figure 1:** 69-year-old male patient who presented with left sided weakness secondary to a TIA. A history of weight loss and anaemia triggered further imaging investigation with a whole body CT, which subsequently lead to the diagnosis of Erdheim-Chester Disease. (a) An AP chest radiograph taken on admission, showing bilateral fine reticular and reticulonodular opacification, predominantly in the upper zones with areas of peripheral ground glass opacification, (black arrows). In addition, there are sclerotic changes in the humeri (red box). (b) Contrast enhanced, coronal CT of the chest, in bony window, shows further evidence of the sclerotic changes in both humeri (red boxes). (c) Contrast enhanced axial image of the chest, in lung window, shows interlobular septal thickening (black arrows) and patchy ground glass opacification in both upper lobes in a crazy paving-type pattern (red boxes). (d) Contrast enhanced axial view of the chest, in mediastinal window, showing a pericardial effusion (black arrows). (e) and (f) Contrast enhanced coronal (e) and axial (f) CT images through the abdomen, in soft tissue window, demonstrating diffuse perinephric soft tissue around both kidneys (black arrows) with additional soft tissue within the region of both renal pelvices and mild dilatation of the intrarenal collecting system (white arrows). (g) Contrast enhanced coronal abdominal CT image, in soft tissue window, demonstrating circumferential periaortic fibrosis, giving a 'coated aorta' appearance (black arrows). The perinephric soft tissue thickening is again demonstrated on this coronal image (white arrows). (h) Contrast enhanced coronal image of the pelvis and proximal femora, in bony window, demonstrating coarsened trabeculae with a mixed pattern of dense sclerosis and lucency.

## DISCUSSION

ECD is a rare, xanthogranulomatous form of non-Langerhans' cell histiocytosis, characterized by infiltration of foamy histiocytes and surrounding fibrosis. Diagnosis relies on established radiological and histological criteria, as described below.

### Skeletal involvement

Involvement of the skeleton occurs in up to 96% of ECD patients. Bone pain is the most common initial presentation of ECD, occurring in 50% of cases.<sup>[17]</sup> Bilateral and symmetrical osteosclerosis of the diaphyseal regions of the long bones is characteristic of ECD.<sup>[18]</sup> In contrast, skeletal lesions in LCH are osteolytic and are rarely located on long bones.<sup>[19,20]</sup> Approximately 4% of ECD patients lack radiological findings of osteosclerosis of the femora.<sup>[11]</sup> The axial skeleton and epiphyseal regions are usually spared.<sup>[21]</sup> In a retrospective study of 59 cases of ECD in 1996, Veyssier-Belot *et al.* reported lytic lesions of either the flat bones, such as the ribs and skull, or of the long bones in 5–8% of cases.<sup>[3]</sup>

### Pulmonary involvement

In a multicenter survival analysis of 53 patients by Arnaud *et al.* in 2011, ECD associated pulmonary involvement was reported in 43% of cases.<sup>[22]</sup> Pulmonary involvement in ECD has several characteristic imaging features. Plain film may show reticular shadowing but is often normal. CT may show interlobular septal thickening, diffuse, and localized centrilobular nodular opacities, ground glass opacities, and fissural thickening.<sup>[17,23]</sup> The differential diagnoses of these radiological features may include lymphangitic spread of carcinoma,<sup>[24]</sup> alveolar proteinosis, sarcoidosis, leukemia, lymphoma, amyloidosis, and some interstitial pneumonias.<sup>[25,26]</sup>

### Cardiovascular manifestations

Approximately 75% of ECD patients suffer from cardiovascular involvement<sup>[27]</sup> but it is frequently asymptomatic and detected incidentally on radiological imaging,<sup>[8,28]</sup> as with the other systemic manifestations in this patient. On CT, the most common abnormality is circumferential soft-tissue sheathing of the thoracic and abdominal aorta and its branches. This periaortic fibrosis is also known as the “coated aorta” phenomenon due to periaortic infiltration by histiocytes,<sup>[5,6,29]</sup> pathognomonic of ECD.<sup>[8]</sup> The differential diagnosis of this appearance includes retroperitoneal fibrosis and Takayasu arteritis. ECD associated venous disease is much less common.<sup>[6]</sup>

Pericardial infiltration is the most frequent cardiac manifestation of ECD<sup>[30]</sup> and can occur in up to 45% of patients. This can present as pericarditis and pericardial

effusion, which may lead to cardiac tamponade.<sup>[17,31,32]</sup> A histological sample of the pericardium may reveal infiltration of foamy histiocytes.<sup>[8]</sup>

### Retroperitoneal and renal manifestations

Retroperitoneal involvement is a common feature of ECD, affecting 30–50% of patients.<sup>[5,33]</sup> Nevertheless, Arnaud *et al.* reported ECD associated involvement of the retroperitoneal space in 68% of patients,<sup>[22]</sup> the majority of whom were asymptomatic.<sup>[34]</sup> However, when present, the symptoms include abdominal pain and dysuria. The differential diagnosis of ECD associated retroperitoneal fibrosis includes idiopathic retroperitoneal fibrosis (Ormond's disease) and secondary retroperitoneal fibrosis.<sup>[18,35]</sup> The appearance of the kidneys is often described as “hairy” due to the infiltration of the perirenal fat creating an irregular renal border, which does not undergo enhancement after the administration of iodinated contrast, thereby differentiating it from the kidney itself.<sup>[36]</sup>

### Laboratory findings

Apart from low serum calcium and albumin, this patient also had a microcytic anemia. In over 550 documented cases of ECD, there have only been a few other papers that have reported a microcytic anemia.<sup>[37–41]</sup> It may be a coincidental finding; however, anemia can cause fatigue, which is one of the recognized symptoms of ECD.<sup>[6]</sup> Veyssier-Belot *et al.* reported an increased erythrocyte sedimentation rate in 27% of patients and a mildly increased ALP in 12%.<sup>[3]</sup>

### Histiocyte immunostaining

A histopathological confirmation is necessary to finalize a diagnosis of ECD using a biopsy usually obtained from bone, skin, retro-orbital, or retroperitoneal soft tissue.<sup>[42]</sup> Confirmation of ECD is made on the detection of CD68 positive, non-Langerhans' histiocytes with foamy or eosinophilic cytoplasm nested within a polymorphic granuloma, fibrosis, or xanthogranulomatosis.<sup>[6]</sup> They lack Birbeck granules and stain negatively for CD1a and S100 protein.<sup>[3,6,43]</sup> ECD histiocytes are morphologically and immunohistochemically identical to those seen in JXG.<sup>[22]</sup> Mutational analysis of *BRAF* and *RAS* is considered critical in all ECD patients to guide therapy with *BRAF* inhibition.<sup>[43]</sup>

As this patient was asymptomatic from the manifestations of ECD that were present, neither biopsy nor treatment was offered. This conservative approach to management is accepted in the literature.<sup>[43]</sup> As a result of the rarity of this disease and the absence of any randomized controlled trials, there is no evidence-based treatment for ECD. However, interferon- $\alpha$  is the most extensively studied therapy in ECD and serves as the first-line treatment.<sup>[6,44,45]</sup>



The degree of visceral involvement is a poor prognostic indicator and the strongest independent predictor of mortality. Arnaud *et al.* reported the 1-year and 5-year survival rates to be 96% and 68%, respectively.<sup>[45]</sup> The most common cause of death is lung fibrosis followed by renal failure, secondary to retroperitoneal involvement and heart failure.<sup>[44]</sup>

## CONCLUSION

ECD is a form of non-Langerhans' cell histiocytosis characterized by xanthogranulomatous infiltration of foamy histiocytes surrounded by fibrosis. Its rarity and multi-systemic involvement can make diagnosis challenging and it therefore requires a multidisciplinary approach. To add to the diagnostic dilemma, patients with ECD may be asymptomatic despite the multi-systemic involvement, as in this case. However, recognition of the characteristic radiological features, with diagnostic skeletal, pulmonary, cardiac, renal, and retroperitoneal manifestations, can help to clinch the diagnosis of this rare condition, without histological confirmation.

## Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Merai H, Collas D, Bhagat A, Mandalia U. Erdheim-Chester Disease: A Case Report and Review of the Literature. *J Clin Imaging Sci* 2020;10:37.