

## Erdheim-Chester Disease: Histopathological Perspective of a Rare Condition

### Abstract

Erdheim-Chester disease (ECD) is a rare, multisystem non-Langerhans cell histiocytosis of unknown etiology with characteristic radiological and histopathological features. It usually affects middle-aged individuals with slight male predominance. Radiologically symmetrical sclerotic lesions are seen mainly in the long bones. The histopathological hallmark is infiltration by foamy histiocytes at multiple sites of involvement. Immunohistochemistry (IHC) with CD68 confirms the diagnosis. This case report describes the case of a 60-year old Indian male who presented with complaints of cerebellar ataxia with chorea and autonomic involvement. Radiological and histopathological investigations confirmed ECD with multisystem involvement, involving- CNS, skeletal, pulmonary, cardiovascular, adrenal gland, lymph nodes, retroperitoneal, and perinephric soft tissue. The variable presentations require consideration and ruling out of numerous differential diagnoses such as histiocytosis X (LCH), multiple sclerosis, neuro-sarcoidosis, amyloidosis, metabolic disorders, Rosai-Dorfman disease, malignancies, and mycobacterial infections. No definitive therapy exists for ECD presently, with the prognosis being dependent on the extent and distribution of the extra-skeletal manifestations.

**Keywords:** CD68, Erdheim-Chester, Histiocytosis, Non-Langerhans cell

### Introduction

Erdheim-Chester disease (ECD) is a rare, multisystem non-Langerhans cell histiocytosis of unknown etiology. It is characterized pathologically by xanthogranulomatous infiltrates which are found mainly in the central nervous system, the long bones of the lower extremities, retroperitoneum, heart, lung, kidneys, skin, spleen, liver, and orbit. Clinically and radiologically, it is characterized by symmetric sclerosis of long bones along with increased uptake on bone scans. The ECD diagnosis is dependent upon the combination of imaging features and clinical presentations which are confirmed by histopathologic findings.<sup>[1]</sup>

This disorder was first described in 1930 by American pathologist William Chester as a lipogranulomatous disorder and it was later designated as Erdheim-Chester disease after the Austrian pathologist Jakob Erdheim, with whom he worked.<sup>[2]</sup> It usually affects middle-aged individuals, and it is more common in males as compared to females. ECD may be asymptomatic, or it might exist as an aggressive multi-systemic disease affecting the skeletal, central nervous system, cardiovascular, respiratory, and renal systems and it is also known to

involve the retroperitoneum and skin. The most common complaint among symptomatic patients is bone pain. Extra-skeletal manifestations are seen in up to 50% of cases,<sup>[3]</sup> and it includes clinical features such as - xanthelasma, papilledema, exophthalmos, severe lung disease, diabetes insipidus, papulonodular skin lesions, cardiomyopathy, retroperitoneal fibrosis, and renal failure. Neurological manifestations include ataxia, paresis, seizures, sensory disturbances, and diabetes insipidus.<sup>[1]</sup>

According to the World Health Organization (WHO) proposed classification system for histiocytic disorders; Class I is Langerhans' cell histiocytosis (LCH) and Class II is the non-Langerhans histiocytosis, which includes juvenile xanthogranuloma (JXG), ECD, and Rosai-Dorfman disease. The Class III category includes malignant histiocytic disorders.<sup>[4]</sup>

Up to 12% of ECD cases show some overlapping with LCH, however, a distinction can be made among them through histopathological and immunohistochemical features. ECD is characterized by xanthogranulomatous infiltration of foamy histiocytes often

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surrounded by fibrosis.<sup>[5]</sup> They do not have Birbeck granules (a characteristic intracellular organelle found in Langerhans' cells) and immunohistochemical staining is positive for CD68 and negative for CD1a.<sup>[6]</sup>

A mutation in the BRAF proto-oncogene (BRAF V600E) has been identified in a majority of ECD patients (40–80%) leading to an oncogenic alteration in this already calamitous disease.<sup>[7]</sup>

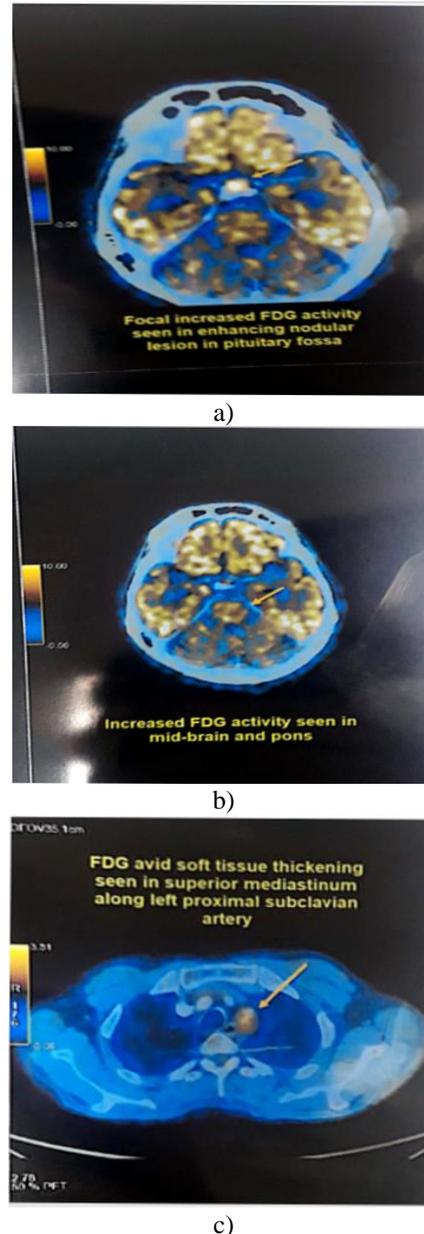
The differential diagnosis for ECD includes Histiocytosis X (LCH), metabolic disorders, neuro-sarcoidosis, amyloidosis, multiple sclerosis, Rosai–Dorfman disease, malignancies, and mycobacterial infections.<sup>[8]</sup>

The prognosis in ECD is dependent on the extent and distribution of the extra-skeletal manifestations and is especially poor in patients with CNS involvement. Severe pulmonary fibrosis, respiratory distress, and cardiac failure are the most common causes of death. Interferon- $\alpha$ , radiotherapy, chemotherapy, corticosteroids, and surgical resection have been used to combat Erdheim-Chester disease. However, no consensus regarding the best treatment has been established.<sup>[9]</sup>

### Case report

A 60-year-old gentleman presented with complaints of loss of balance for 4 years, involuntary jerky movements for 2 years, and emotional lability and scanning of speech for 1 year which was clinically diagnosed as cerebellar ataxia with chorea with autonomic involvement with pituitary macroadenoma. His only history was alcohol consumption for the past 30 years, which he stopped 4 years back. On admission, his CT scan of the neck, chest, and abdomen revealed a soft tissue-enhancing mass lesion in the mediastinum which was seen encasing the arch of the aorta and the origin of the left subclavian artery, along with an ill-defined enhancing soft tissue mass in the retroperitoneum involving bilateral perinephric fat, intrarenal sinus extension and encasing the renal pelvis and renal vessels. The soft tissue lesion was also seen along para-aortic, and pre-aortic regions along with focal encasement of the aorta. Additional findings on the CT scan were linear fibrotic bands in the medial segment of the right middle lobe, left inferior lingual segment and medial basal segment of the lung, calcified sub-centimetric right hilar lymph nodes, a tiny nodule in the right lower lobe lateral basal segment of the lung, borderline hepatomegaly, occlusion of the coeliac axis, short segment moderate/severe stenosis of the superior mesenteric artery at origin, dilatation of inferior mesenteric artery with the formation of collaterals, diffuse atherosclerotic changes, plaques and moderate stenosis of aorta, renal artery and left common iliac artery. Based on these findings a suspicion of lymphoma was considered. His CT Brain showed a fairly well-defined lesion in the pituitary fossa causing cortical erosions, suggestive of a pituitary macroadenoma measuring 1.4x1x1 cm along with chronic ischemic changes and diffuse cerebral cortical atrophy with caudate atrophy. Similar findings were reported on the MRI brain along with atrophy of basal ganglia and dentate nuclei. Following these investigations, a whole-body PET -CT scan was done. PET-CT scan revealed mild

diffuse increased FDG activity in midbrain and pons, focally increased FDG activity in an enhancing nodular lesion in the pituitary fossa -? Macroadenoma, mildly FDG avid soft tissue density lesion in the superior mediastinum, bilateral mild perinephric and renal sinus soft tissue thickening with minimal FDG activity, bilateral bulky adrenal glands with mild diffuse FDG activity, mildly enlarged left paraaortic nodes with minimal FDG activity, mildly FDG avid wall thickening was also detected along the abdominal aorta, aortic bifurcation, renal arteries and left common iliac artery with luminal thickening and mild FDG activity was seen in fracture sites in the right 8,9,10<sup>th</sup> ribs along with intramedullary sclerotic changes in bilateral femoral shafts. Based on the PET-CT scan findings a possibility of Erdheim-Chester disease was favored over neoplastic etiologies/ lymphoma (**Figure 1**).





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Figure 1. Photomicrograph showing PET scan with multi-organ involvement

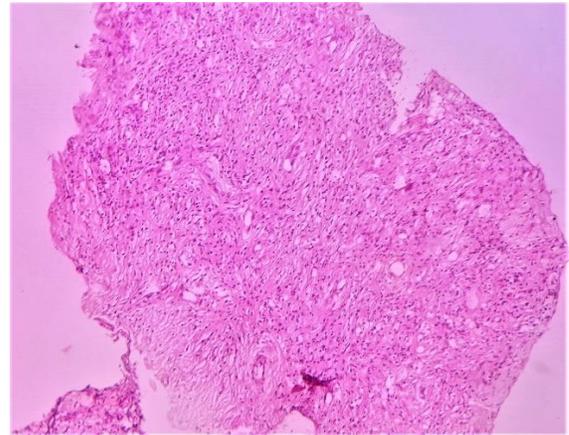


Figure 2. Photomicrograph showing fibrofatty tissue showing numerous histiocytes with clear cytoplasm [H&E X 400]

During admission, the blood investigation results revealed mild microcytic hypochromic anemia along with mild anisocytosis with a hemoglobin level of 13g/dl, mean corpuscular volume of 67fl, and red cell distribution width of 15.9%. The erythrocyte sedimentation rate was slightly raised (33mm/hr.). The liver function tests, white cell count, renal function tests, including alkaline phosphatase (ALP), and blood glucose levels were normal. Routine biochemical and microscopic examination of cerebrospinal fluid was normal. Serum heavy metal analyses (including copper, lead, mercury, and iron) were normal. On hormone estimation, serum parathormone, cortisol, growth hormone, and ACTH were within normal range, however, serum-free testosterone was slightly decreased (6.87pg/ml) while serum prolactin (17.3 ng/ml), FSH (21.5mIU/ml) and LH (12.4 mIU/ml) were raised. Serum tocopherol (vitamin E) and ceruloplasmin levels were within the normal reference ranges. Serum antinuclear antibody (ANA) showed weak positivity, serum anti-thyroid peroxidase (TPO) antibodies were raised (9 IU/ml) while the Gliadin antibody was negative.

Following the aforementioned workup, a biopsy from perinephric fat was taken from the site of increased uptake. We received the biopsy specimen in multiple tissue bits altogether measuring 0.4x0.3x0.2cm. The biopsy bits were greyish-white and were soft to firm in consistency. On histopathological examination, the fragmented biopsy tissue showed fibrofatty and fibro-collagenous tissue with collections of foamy histiocytes associated with minimal inflammatory cells (**Figure 2**). On immunohistochemical study, these foamy histiocytes were positive for CD68 (**Figure 3**). In light of the clinical, radiological, histopathological, and IHC findings a diagnosis of histiocytic neoplasm, consistent with Erdheim Chester disease was made. The patient is presently under medical treatment and should have a close follow-up.

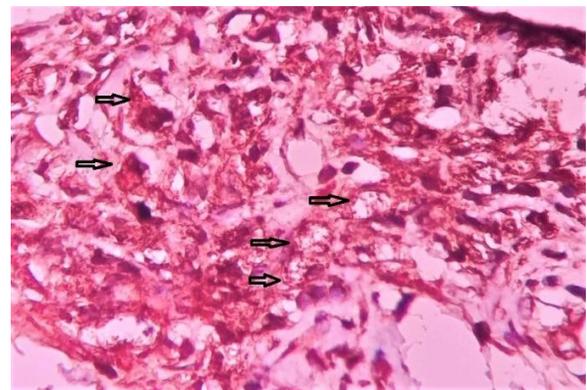


Figure 3. Photomicrograph showing immunohistochemical marker CD68 positivity which is specific for tissue histiocytes.

## Results and Discussion

ECD is a very rare type of non-Langerhans cell neoplasm which is characterized by infiltrates of foamy histiocytes at multiple anatomic sites. The exact etiology of this disorder is not well established however, the majority of these patients harbor a mutation in the BRAF proto-oncogene, indicating a possible clonal disorder.<sup>[10]</sup> Distinct pathognomic radiological and histological features, supported by IHC and clinical findings are required to diagnose this condition and differentiate it from its many mimics.

We reported a case of a middle-aged male who presented with cerebellar ataxia with chorea and autonomic involvement. Other authors have reported cases with widespread involvement of the CNS, including extra-axial and intra-axial brainstem lesions. Common symptoms of ECD involving CNS are central diabetes insipidus followed by cerebellar symptoms and signs, such as ataxia with gait abnormalities, and considering the wide spectrum of CNS lesions, a differential diagnosis of multiple sclerosis is considered. Our patient also had similar neurological complaints.<sup>[11]</sup> On radiological examination, multiple enhancing soft tissue lesions were detected along with enhancing lesions in the midbrain and pons with focally increased FDG activity in an enhancing nodular lesion in the pituitary fossa. This is also consistent

with radiological findings reported by other authors.<sup>[12]</sup> Multiple lymphadenopathies and intramedullary sclerotic changes in bilateral femoral shafts were also noted. Given these findings, a differential diagnosis of lymphoma and ECD was considered. Involvement of the lymph nodes has been very rarely reported in ECD.<sup>[13]</sup> Skeletal involvement occurs in up to 96% of ECD patients, with bone pain being one of the most common symptoms. Bilateral and symmetrical osteosclerosis of the dia-metaphyseal regions of the long bones is characteristic of ECD, and it is seen in our patients also.

CT scan of our patient also showed pulmonary linear fibrotic bands. In a multicentric study by Arnaud *et al.*, it was reported that pulmonary involvement was seen in 43% of ECD cases.<sup>[14]</sup>

Our patient had microcytic hypochromic anemia and increased ESR levels. Few cases of ECD have reported the presence of microcytic anemia and it can also contribute to fatigue and generalized weakness experienced by these patients.<sup>[15]</sup> Raised ESR has also been documented in ECD patients.

Histopathological examination of biopsy from perinephric fat showed infiltration by a collection of foamy histiocytes, which was confirmed by IHC through CD68 positivity in these cells. Perinephric fat involvement has been documented in ECD patients with studies describing a characteristic "hairy" pattern of perirenal fat infiltration on imaging.<sup>[16]</sup>

Histopathology is essential for the confirmation of a diagnosis of ECD using a biopsy which is usually obtained from skin, bone, or retroperitoneal soft tissue. Detection of CD68-positive, non-Langerhans histiocytes with foamy cytoplasm is diagnostic of ECD.<sup>[15]</sup> Our patient presented with multisystem involvement and the extent of visceral involvement is a poor prognostic indicator and the strongest independent predictor of mortality. The most common cause of mortality among ECD patients is lung fibrosis followed by renal failure, heart failure and secondary to retroperitoneal involvement.<sup>[9]</sup>

## Conclusion

ECD is a very rare multisystem non-Langerhans cell histiocytosis. Its diagnosis requires the detection of the characteristic radiological findings and confirmation through histopathological examination and immunohistochemistry. Asymptomatic cases, absence of frank bone involvement, and multisystemic manifestations make the diagnosis highly challenging. CNS, lymph node and cardiovascular involvement provide added difficulties in diagnosis, requiring ruling out a wide gamut of differential diagnoses. We recommend a multidisciplinary approach and thorough workup for the definitive diagnosis of ECD.

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## Conflict of interest

None.

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## Ethics statement

Prior permission was taken from the Institutional Ethics Committee (DPU-IEC) to conduct this study.

Patient consent was taken prior to the commencement of the study.

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