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Exploring Erdheim-Chester Disease: A Histopathological Insight into a Rare Disorder

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Abstract

Erdheim-Chester disease (ECD) is an uncommon, multisystem disorder categorized as non-Langerhans cell histiocytosis, with its cause still unknown. It mostly affects middle-aged individuals, with a slight male predominance. Radiologically, the disease is characterized by symmetric sclerotic lesions in the long bones, while histopathologically, foamy histiocytes are found in various affected areas. The diagnosis is confirmed by immunohistochemistry (IHC) with CD68. This case report presents a 60-year-old male from India who experienced cerebellar ataxia, chorea, and autonomic dysfunction. Imaging and histopathological evaluation confirmed ECD with widespread involvement, affecting the CNS, skeleton, lungs, cardiovascular system, adrenal glands, lymph nodes, retroperitoneal area, and perinephric soft tissue. The clinical manifestations are diverse, making it essential to differentiate ECD from other conditions, including Langerhans cell histiocytosis (LCH), multiple sclerosis, neuro-sarcoidosis, amyloidosis, metabolic disorders, Rosai-Dorfman disease, cancer, and mycobacterial infections. Currently, there is no established treatment for ECD, and the prognosis is dependent on the severity and distribution of the disease outside the skeletal system.

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

Introduction

Erdheim-Chester disease (ECD) is a rare and complex systemic disorder that is part of the non-Langerhans cell histiocytosis group, with no clear cause. It is defined by the presence of xanthogranulomatous infiltrates, which primarily affect multiple organ systems such as the central nervous system, lower limb long bones, retroperitoneum, heart, lungs, kidneys, skin, spleen, liver, and the eyes. On imaging, it typically shows symmetric sclerosis in the long bones, with increased uptake observed in bone scans. Diagnosis of ECD is based on a combination of clinical features, imaging findings, and confirmation through histopathological analysis [1].

The disease was initially recognized in 1930 by William Chester, who described it as a lipogranulomatous condition and was later named after Jakob Erdheim. ECD most commonly occurs in middle-aged adults, with a higher incidence in males. While some individuals may be asymptomatic, others experience an aggressive, multi-organ form of the disease, affecting the bones, brain, heart, lungs, kidneys, skin, and more. Bone pain is the most common symptom. Up to half of those affected have extra-skeletal manifestations such as xanthelasmas, papilledema, exophthalmos, lung disease, diabetes insipidus, skin nodules, heart complications, and kidney failure. Neurological symptoms such as ataxia, seizures, and sensory issues are also common [1-3].

The WHO categorizes histiocytic diseases into three groups: class I (Langerhans cell histiocytosis), class II (non-Langerhans histiocytosis, which includes ECD and

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other disorders), and class III (malignant histiocytoses) [4].

ECD can share features with Langerhans cell histiocytosis (LCH) in some cases, but these conditions can be distinguished by their distinct histopathological and immunohistochemical profiles. ECD is marked by foamy histiocytes with surrounding fibrosis, and unlike LCH, it lacks Birbeck granules. The immunohistochemical staining for ECD shows positivity for CD68 and negativity for CD1a [5, 6].

A significant proportion of ECD cases (40–80%) are associated with a mutation in the BRAF V600E gene, contributing to the disease's progression [7].

The differential diagnosis for ECD includes conditions like LCH, neuro-sarcoidosis, amyloidosis, multiple sclerosis, and other infections [8].

The prognosis of ECD largely depends on the extent of involvement, with poorer outcomes typically seen in cases with central nervous system involvement. Pulmonary fibrosis, respiratory failure, and heart complications are common causes of death. There is no definitive treatment for ECD, although options like interferon-A, radiotherapy, chemotherapy, corticosteroids, and surgery have been explored, with no consensus on the most effective approach [9].

This case report presents a 60-year-old male from India who experienced cerebellar ataxia, chorea, and autonomic dysfunction.

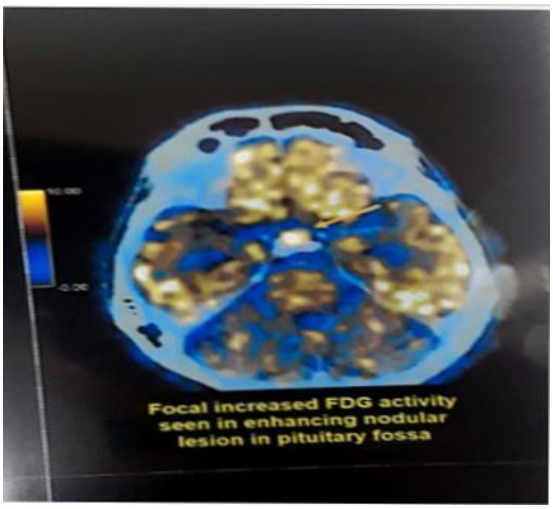
Case Report

A 60-year-old male sought medical attention with a history of balance problems for the past four years, involuntary jerky movements for two years, and changes in speech and emotional instability for one year. He was diagnosed clinically with cerebellar ataxia accompanied by chorea, as well as autonomic dysfunction and a pituitary macroadenoma. His medical background included a 30-year history of alcohol use, which he had ceased four years prior.

Upon admission, imaging studies including CT scans of the neck, chest, and abdomen revealed a mass in the mediastinum, which appeared to encase the aortic arch and the origin of the left subclavian artery. Another mass was observed in the retroperitoneal area, affecting bilateral perinephric fat and extending into the renal sinus, renal vessels, and renal pelvis. Additionally, the scan revealed fibrosis in the right lung and other signs like calcified lymph nodes, a small nodule in the lung, borderline liver enlargement, and occlusion of the celiac artery. These findings raised the suspicion of lymphoma. The CT brain scan showed a lesion in the pituitary fossa with cortical erosion, suggesting a pituitary macroadenoma. It also revealed signs of chronic ischemia, cerebral atrophy, and caudate atrophy. These findings were corroborated by an MRI, which further identified atrophy of the basal ganglia and dentate nuclei.

To gather more information, a whole-body PET-CT was performed. It revealed mildly increased FDG activity in the midbrain and pons, a nodular lesion in the pituitary with focal FDG uptake, and a mild FDG-avid lesion in the mediastinum. Additionally, mild FDG activity was observed in the perinephric tissues and bilateral adrenal glands, with enlargement of left paraaortic lymph nodes. Other findings included vascular thickening along the aorta, renal arteries, and iliac arteries, as well as sclerotic changes in the femoral shafts and FDG activity in fractures of the right ribs.

Based on the imaging results, Erdheim-Chester disease was considered a potential diagnosis over lymphoma or other neoplastic causes, as shown in **Figure 1**.



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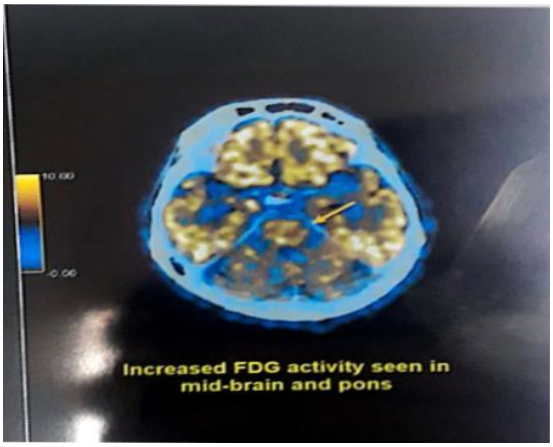

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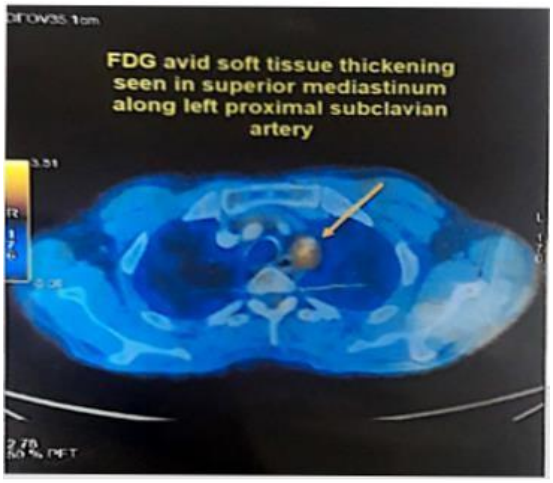

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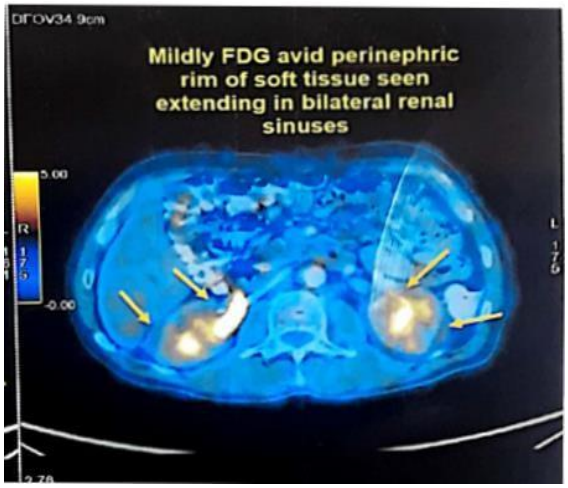

d)

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

A 60-year-old male presented with a history of balance issues over the past four years, involuntary jerky movements for the past two years, and emotional instability along with speech difficulties for the past year. He was diagnosed with cerebellar ataxia and chorea with autonomic involvement, alongside a pituitary macroadenoma. His medical history was notable for chronic alcohol consumption, which he had discontinued four years ago.

Upon admission, a CT scan of the neck, chest, and abdomen revealed a mass in the mediastinum that was enhancing and surrounding the aorta and left subclavian artery. Additionally, another soft tissue mass was seen in the retroperitoneum, involving both perinephric fat and extending into the renal sinus, encasing the renal pelvis and vessels. There was also involvement in the para-aortic and pre-aortic regions, with partial encasement of the aorta. The CT findings also showed fibrotic bands in the lungs, calcified lymph nodes, mild liver enlargement, and significant vascular changes including stenosis of several arteries. The findings raised suspicion for lymphoma.

A brain CT scan showed a lesion in the pituitary fossa suggestive of a pituitary macroadenoma, along with signs of chronic ischemia and cortical atrophy. These results were confirmed by an MRI, which also indicated basal ganglia and dentate nucleus atrophy. A subsequent whole-body PET-CT scan showed multiple areas of increased FDG activity, including in the brain, pituitary fossa, mediastinum, and bilateral perinephric regions. These findings suggested Erdheim-Chester disease as a more likely diagnosis than lymphoma.

The patient's blood tests showed mild anemia with a reduced mean corpuscular volume and increased red cell distribution width. The erythrocyte sedimentation rate was slightly elevated, while other tests such as liver function, renal function, and white blood cell count were normal. Hormone levels were generally within normal ranges, except for slightly low testosterone and elevated prolactin, FSH, and LH levels. Antinuclear antibody testing was weakly positive, and thyroid peroxidase antibodies were raised.

A biopsy was performed from the perinephric fat, where the increased FDG activity was observed. The biopsy specimen consisted of fragmented tissue, which on histopathological examination showed fibrofatty tissue with foamy histiocytes and minimal inflammatory cells. Immunohistochemistry confirmed that these histiocytes were positive for CD68.

Considering the clinical, radiological, histopathological, and immunohistochemical findings, a diagnosis of

Erdheim-Chester disease was confirmed. The patient is currently receiving medical treatment and is being closely monitored (**Figures 2, 3**).

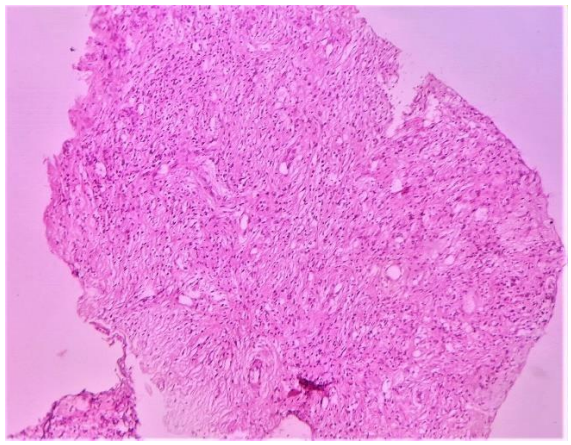

Figure 2. Photomicrograph showing fibrofatty tissue showing numerous histiocytes with clear cytoplasm [H&E X 400]

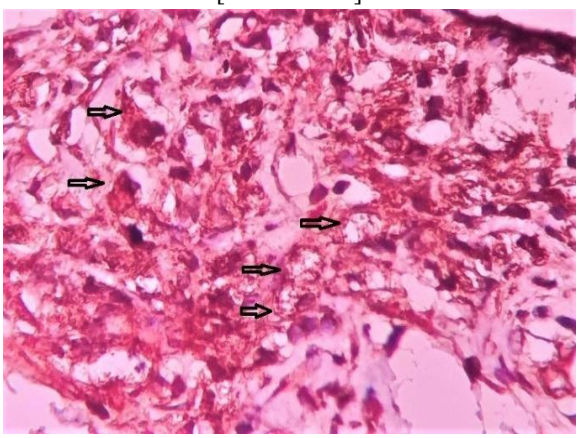

Figure 3. Photomicrograph showing immunohistochemical marker CD68 positivity which is specific for tissue histiocytes.

Results and Discussion

Erdheim-Chester disease (ECD) is an uncommon form of non-Langerhans cell histiocytosis characterized by the infiltration of foamy histiocytes across various tissues. Although the precise cause remains unclear, the majority of cases involve a mutation in the BRAF proto-oncogene, suggesting a potential clonal nature of the disease. Diagnosing ECD requires the identification of unique radiological and histopathological features, supported by clinical and immunohistochemical evidence, to distinguish it from other similar conditions [10-13].

We present the case of a middle-aged male who experienced cerebellar ataxia, chorea, and autonomic dysfunction. Similar cases have shown widespread central nervous system (CNS) involvement, including lesions in the brainstem. CNS symptoms, notably central diabetes insipidus followed by cerebellar dysfunction (including ataxia and gait issues), are frequently observed in ECD. In our case, neurological symptoms aligned with those described in the literature, leading us to consider multiple sclerosis in the differential diagnosis. Radiological findings revealed multiple enhancing soft tissue lesions and abnormal FDG uptake in the midbrain, pons, and pituitary fossa, consistent with previous reports. Additionally, lymphadenopathy and intramedullary sclerotic changes in femoral shafts were present, raising the suspicion of lymphoma or ECD. Lymph node involvement is relatively rare in ECD, however, it has been noted in a few cases. Skeletal involvement, which occurs in nearly all ECD patients, is often marked by bilateral osteosclerosis of the long bones, which was also evident in this patient.

Further CT scans identified fibrotic changes in the lungs. A multicentric study by Arnaud *et al.* found pulmonary involvement in 43% of ECD cases, confirming this as a common feature. The patient also exhibited microcytic hypochromic anemia and elevated ESR, both of which are observed in some ECD cases and may contribute to fatigue and weakness.

Histopathological analysis of a perinephric fat biopsy revealed infiltration of foamy histiocytes, confirmed by immunohistochemistry, which showed CD68 positivity. This finding was consistent with the “hairy” pattern of perirenal fat involvement that has been reported in ECD patients. Biopsy and histopathological examination remain crucial for confirming ECD, with CD68-positive, foamy histiocytes being the key diagnostic marker.

The prognosis of ECD depends heavily on the extent of multisystem involvement. The presence of visceral involvement is a significant predictor of poor outcomes, with lung fibrosis, renal failure, and heart failure being the most common causes of death [14-16].

Conclusion

Erdheim-Chester disease is a rare, multisystemic disorder characterized by non-Langerhans cell histiocytosis. Diagnosis relies on a combination of distinct radiological features, histopathological confirmation, and immunohistochemical testing. The condition can be challenging to diagnose, especially in asymptomatic cases or when bone involvement is absent. Multisystemic

manifestations, particularly involving the CNS, lymph nodes, and cardiovascular system, complicate the diagnosis, requiring a thorough differential diagnosis. A multidisciplinary approach and comprehensive diagnostic evaluation are essential for accurate diagnosis and management of ECD.

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Conflict of Interest: None

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Ethics Statement: None

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