

Erdheim Chester Disease with BRAF V600E Wildtype: A Case Report

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ABSTRACT

Erdheim Chester disease is a rare histiocytic neoplasm characterized by multisystem infiltration of CD68 and CD163 positive, CD1a and S100 negative histiocytes. We report a 65-year-old woman with incidental fluorodeoxyglucose uptake in the right thyroid, retrocrural region, retroperitoneum, perinephric region, adrenal gland, paraaortic lymph node, and left external iliac lymph node on positron emission tomography-computed tomography. Histopathological examination of a CT-guided core biopsy from perinodal soft tissue adjacent to the left external iliac lymph node revealed predominantly histiocytic infiltration with sparse lymphocytes and mast cells in fibrocollagenous tissue. Histiocytes were positive for CD68 and CD163 and negative for CD1a and S100. BRAF V600E mutation and somatic mutations on a 161-gene next-generation sequencing panel, including genes of the MAPK-ERK pathway, were not detected. Based on clinicopathoradiological findings, Erdheim Chester disease was diagnosed. This case highlights diagnostic challenges and the importance of multidisciplinary evaluation.



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INTRODUCTION

Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm characterized by the accumulation of mature histiocytes, chronic inflammation, and fibrosis.¹ More than 1,500 cases have been reported worldwide since its first description by William Chester and Jakob Erdheim in 1930.² ECD is classified among histiocytic neoplasms and recognized through advances in molecular pathology and imaging modalities.³ Its pathogenesis is associated with activation of the MAPK signaling pathway, with the BRAF V600E mutation detected in approximately 50% of cases. These molecular insights have influenced diagnostic approaches and targeted therapeutic strategies.⁴ We report the first case of ECD in Nepal with BRAF V600E wild-type, highlighting diagnostic challenges and the importance of a multidisciplinary approach for accurate diagnosis.

CASE REPORT

A 65-year-old female with a known history of diabetes mellitus, hypertension, chronic liver parenchymal disease, and prior cholecystectomy presented to the Department of Gastroenterology, Hepatology & Endoscopy of our hospital for surveillance of liver disease. She also had a history of a D11 vertebral fracture, which was completely treated. However, for the past 6 months, she had experienced intermittent back pain that was aggravated by heavy household work.

Laboratory findings revealed positive serum antinuclear antibody (ANA), negative serum anti-smooth muscle antibody (ASMA), and a normal serum IgG4 subclass level (0.436 g/L; normal range, 0.03–2.01 g/L). A liver biopsy was also performed at another center, which showed features of chronic hepatitis compatible with autoimmune hepatitis. Immunohistochemistry (IHC) for IgG4 staining was performed on the same biopsy but was not contributory. Viral serology, including HBsAg, anti-HCV, and retrovirus testing, was nonreactive. Complete blood count and PT/INR were also within normal limits.

CT of the whole abdomen showed partial collapse and diffuse sclerosis of the D11 vertebra, features of chronic liver parenchymal disease, ill-defined retroperitoneal soft tissue thickening, a right perinephric nodular lesion, and bilateral retrocrural lymphadenopathy, raising suspicion of a neoplastic etiology. A PET-CT scan was recommended for further evaluation.

Positron Emission Tomography-Computed Tomography showed increased fluorodeoxyglucose (FDG) uptake in the right thyroid gland and diffuse nodular thickening in the bilateral retrocrural regions, more prominent on the right, and in the retroperitoneum, encasing the celiac axis, superior mesenteric artery, and right renal vessels, with associated compression (Figure 1A, B).

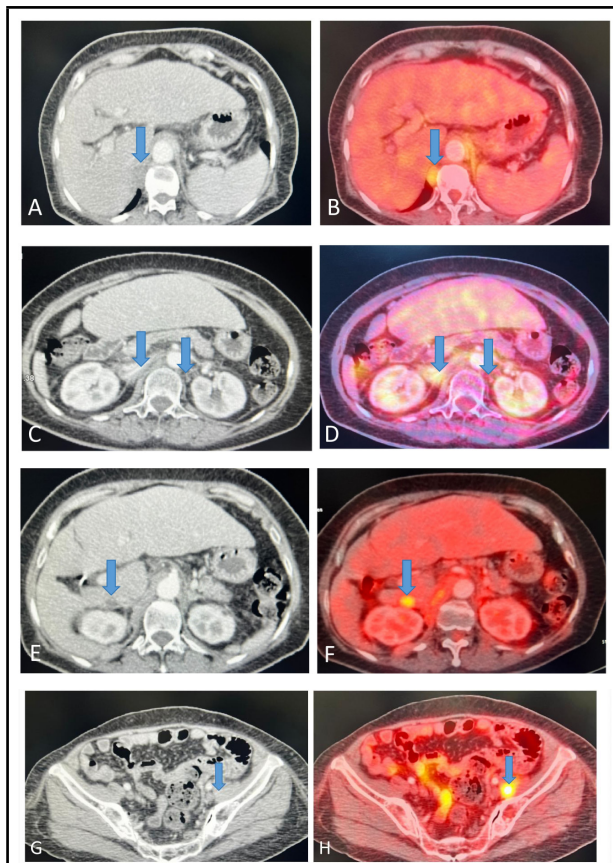


Figure 1. Blue arrows indicate (A) CT Scan showing hypodense nodule in right retrocrural region with increase FDG uptake in corresponding PET CT Scan (B), (C) CT Scan showing diffuse nodular thickening in retroperitoneum encasing right renal vessel and compressing Inferior venacava with increase FDG uptake in corresponding PET CT Scan (D), (E) CT Scan showing hypodense nodule in right perinephric region with increased FDG uptake in corresponding PET CT Scan (F), (G) CT Scan showing hypodense nodule in left external iliac lymph node with increase FDG uptake in corresponding PET CT Scan (H).

of the inferior vena cava (Figure 1C, D) and involvement of the bilateral adrenal glands were also noted. Similar nodular thickening was noted in the right perinephric region (Figure 1E, F). PET-avid nodules in the para-aortic and left external iliac lymph nodes (Figure 1G, H) were also noted. Partial collapse and diffuse sclerosis were seen in the D11 vertebra, with diffuse osteopenia but without significant FDG uptake.

For the heterogeneously enhancing nodule in the right lobe of the thyroid gland, ultrasound-guided fine-needle aspiration cytology was performed, which was reported as follicular nodular disease. CT-guided core needle biopsy (CNB) of the perinodal soft tissue adjacent to the left external iliac lymph node was performed. Multiple fragments of soft tissue revealed predominantly histiocytic infiltration along with multinucleated histiocytes,

sparse lymphocytes, and mast cells in fibrocollagenous tissue (Figure 2).

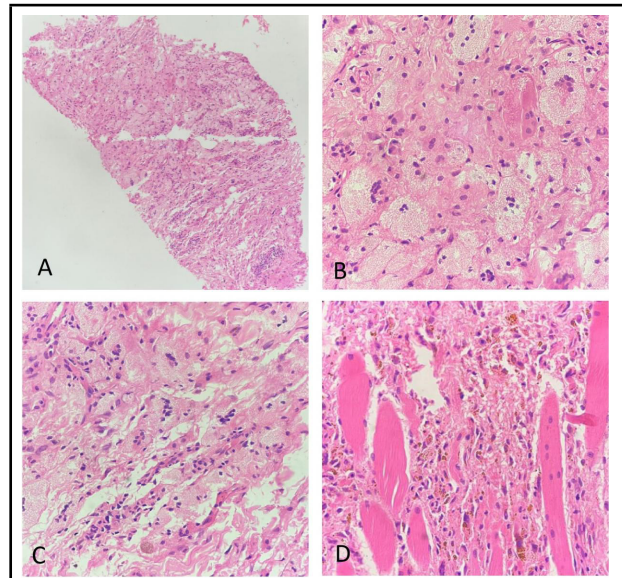


Figure 2. (A and B): Foamy histiocytic collection and multinucleated histiocytes (H&E, x100 and x400 respectively) C: Foamy histiocytes, lymphocytes and fibrosis. (H&E, x400) D: Muscle bundles and hemosiderin laden macrophages. (H&E, x400).

Focal adipocytes, muscle bundles and nerve fibers were noted. Few muscle bundles were entrapped within the fibroinflammatory tissue composed of lymphocytes and plasma cells. Few blood vessels and hemosiderin laden macrophages were also identified along with fibrinohemorrhagic material.

Immunohistochemistry showed histiocytes positive staining for CD68 (Figure 3A) and CD163, negative staining for CD34, CD1a, S100, IgG4 and BRAF V600E (Figure 3 B-F respectively).

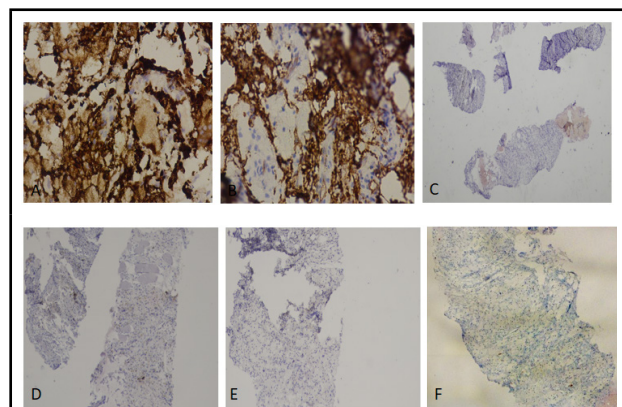


Figure 3. (A) CD68 immunoreaction highlighted foamy histiocytes. (B-F respectively) CD34, CD1a, S100, IgG4 and BRAFV600E respectively with negative immunostain.

Molecular analysis done by Somatic 161 gene panel Next Generation Sequencing including BRAF, KRAS, NRAS, ARAF, PIK3CA, MAP2K1, ALK and genes involved MAPK-

ERK pathway and in other neoplastic disease, did not show any mutations in the biopsy specimen. The immunoprofile supported a diagnosis of non-Langerhans histiocytic proliferation. Based on histomorphology, IHC along with given radiological evidence confirmed ECD.

With the diagnosis of ECD, systemic therapy of oral Cobimetinib was initiated with scheduled clinical, laboratory and radiological follow up every 3-6 months to monitor effectiveness of therapy, for disease progression, including skeletal symptoms, endocrine dysfunction, renal impairment or cardiovascular and central nervous system involvement.

DISCUSSION

ECD is a rare multisystem histiocytic disorder with heterogeneous

clinical manifestations. The diagnosis often requires integration of histopathological, clinical, and radiological findings due to its variable presentation.¹ ECD typically affects adults in the fifth to seventh decades of life and demonstrates a wide clinical spectrum ranging from asymptomatic disease to life-threatening multisystem involvement. Commonly affected sites include long bones, retroperitoneum, cardiovascular system, central nervous system, lungs, and endocrine organs.⁵ Histologically, ECD is characterized by infiltration of CD68-positive, CD1a-negative histiocytes within a fibrotic stroma. However, diagnosis may be challenging in cases lacking classic features such as foamy histiocytes or Touton giant cells, necessitating correlation with clinical and radiological findings.⁶

Only two cases of ECD have previously been reported in Nepal, along with our case (Table 1).

Table 1. Cases of ECD reported in Nepal.

Authors	Age/Sex	Clinical features	Radiological findings	Histopathology	Immunophenotyping
Singh P et al. ⁷	67 yrs/M	Right sided chest pain	CT chest showing lytic lesions in right second rib	Excision biopsy of lesion site in 2nd rib shows tumor comprised of foamy histiocytes intermixed with small lymphoid cells.	IHC: Positive: CD68 Negative: CD1a, S100, SATB2, TLE1 and BCL2 BRAFV600E: Not performed
Chhetri S et al. ⁸	64 yrs/M	Headache, ataxia and vision change	MRI Brain shows two separate extra-axial lesions in the posterior aspect with increased FDG uptake in PET-CT scan.	Bone marrow biopsy revealed lipid laden histiocytes with lymphomononuclear cells with peripheral fibrosis.	IHC: Positive: CD68 Negative: CD1a, S100 BRAFV600E Mutation detected
Present	65 yrs/F	Asymptomatic	PET-CT scan showing multiple areas of increased FDG uptake including retroperitoneal region encasing major vessels and adrenal gland.	CT guided CNB showing predominantly histiocytic infiltration along with multinucleated histiocytes, sparse lymphocytes and mast cells in fibrocollagenous tissue.	IHC: Positive: CD68 and CD163 Negative: CD34, CD1a, S100 and IgG4 BRAFV600E Wildtype
Note: ECD: Erdheim-Chester disease; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET-CT: Positron Emission Tomography-Computed Tomography; CNB: Core Needle Biopsy; IHC: Immunohistochemistry; BRAF V600E: BRAF V600E mutation; FDG: Fluorodeoxyglucose; M: Male; F: Female.					

The hallmark of ECD is infiltration of tissues by lipid laden histiocytes associated with inflammation and fibrosis which is also seen in our case emphasizing the importance of considering ECD even in asymptomatic patients.

Radiology plays a crucial role in diagnosis revealing retroperitoneal fibrosis ("hairy kidney" appearance), periaortic fibrosis ("coated aorta"), symmetrical osteosclerosis of long bones, multiorgan involvement. The presence of retroperitoneal soft tissue encasing major vessels and adrenal involvement in this patient strongly supports ECD.⁶

Erdheim Chester disease histiocytes are characteristically CD68 positive, CD163 positive, CD1a negative, S100 negative. This immunophenotype distinguishes ECD from Langerhans

cell histiocytosis (CD1a+, S100+).⁹ Similarly, CD34 negative distinguishes ECD from Deep fibrous histiocytosis and the absence of IgG4-positive plasma cells with normal serum IgG4 levels in this case argue against IgG4-related disease.

Erdheim Chester disease is now recognized as a clonal disorder driven by mutations in the MAPK pathway, most commonly BRAF V600E (50-60% cases).¹ However, a significant subset of patients are BRAF negative and may harbor other mutations such as MAP2K1, KRAS, or NRAS. The absence of BRAF V600E mutation in this case does not exclude ECD, as BRAF wildtype variants are well described.¹⁰ Tissue genotyping sometimes fails to identify a driver mutation in a small subset of patients (10% to 15%) which is also seen in our case or the test may be limited by small tissue sample.¹¹

The key differential diagnoses include: Deep fibrous histiocytosis, Langerhans cell histiocytosis and IgG4-related disease which are ruled out by their IHC and radiological findings in this case

Erdheim Chester disease is associated with significant morbidity due to organ infiltration, particularly cardiovascular and CNS involvement, which are major determinants of prognosis.¹² Early diagnosis is essential as targeted therapies, including BRAF and MEK inhibitors, have significantly improved outcomes in recent years.¹³

CONCLUSION

This case highlights a diagnostically challenging presentation of Erdheim Chester disease in 65 years old female with PET CT scan showing multisystem involvement. The absence of clinical

features and BRAF mutation underscores the importance of comprehensive clinicopathological and radiological correlation in establishing the diagnosis.

Erdheim Chester disease should be considered in patients presenting with unexplained fibroinflammatory lesions involving multiple organ systems, even in the absence of typical clinical findings. Early recognition is crucial for appropriate management and better prognosis.

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Conflict of Interest: None.

Consent: JNMA Case Report Consent Form was signed by the patient and is attached with the patient's chart.

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