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Case Report

Cardiac and pleuropulmonary involvement in Erdheim-Chester disease without bone lesions: A case report ☆

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ABSTRACT

Erdheim–Chester disease is a rare multisystemic non-Langerhans histiocytosis characterized by histiocytes that stain positive for CD68 and negative for CD1a. Skeletal involvement is reported to be present in up to 96% cases and *BRAF* mutation in about half of the cases.

Here, we report a patient with an unusual longstanding BRAF-negative Erdheim–Chester disease without bone lesions who developed pleuropulmonary and cardiac involvement.

Introduction

Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis of unknown etiology with less than 1000 cases reported in the literature [1–4]. It is a histiocytic neoplasm characterized by the presence of cells positive for CD68 and negative for CD1a [1,5,6]. Recently, V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutation was found to be present in 50% of ECD cases [5,7]. Patients with ECD may be asymptomatic; however, some may have multisystemic manifestations that may be life-threatening. Skeletal manifestations are reported to be present in up to 96% of patients [4]. Meanwhile, extra-skeletal manifestations are reported in more than half of the cases, mainly affecting the central nervous, respiratory, cardiovascular, and renal systems, including the retroperitoneum. Pleuropulmonary and cardiovascular involvement have also been reported [8–10]. Although frequently asymptomatic, cardiac involvement is present in about half the cases and is associated with a poor

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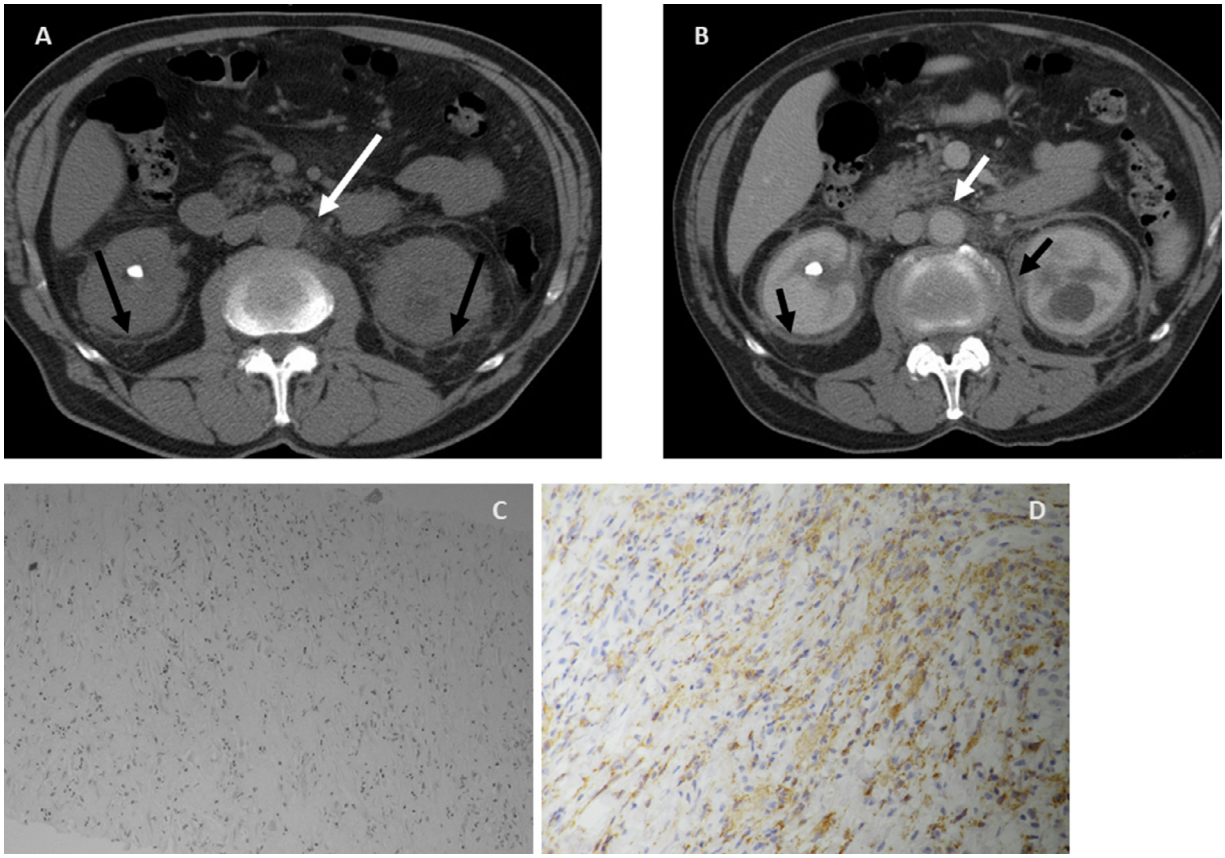

Fig. 1 – (A-D) Initial axial plain abdominal CT (A) depicting minimal retroperitoneal fat stranding in the peri-renal tissue (black arrow) and aortic areas (white arrow) associated with mild bilateral hydronephrosis. There is also evidence of non-obstructive right renal stone. A follow-up axial contrast enhanced abdominal CT taken 2 years later (B) showing evidence of "hairy" appearance of kidneys (short black arrow) and a periaortic concentric soft tissue also known as "coated" aorta.
(C) Initial peri-renal space biopsy using Hematoxylin phloxine saffron (HPS) stain x20 showing numerous hystiocytes and CD68 immunohistochemical x20 staining positive (D) .
CT, computed tomography (Color version of figure is available online)

prognosis [7,9]. Given its rarity, complex physiopathology, and varied manifestations, the diagnosis and subsequent treatment of ECD is often challenging [6,11].

Here, we present a case of long-standing ECD initially presenting as non-specific retroperitoneal fibrosis that later developed into pleuropulmonary and typical cardiac involvement in the absence of both bone lesions and *BRAF* mutation.

Case presentation

An 82-year-old man had unexplained mild anemia, bilateral flank pain, and night sweats in 2008. Initial plain abdominal computed tomography (CT) revealed non-obstructive right renal stones, which partially explained the patient's symptoms. Moreover, it showed minimal retroperitoneal fat stranding in the peri-renal and aortic areas associated with mild bilateral hydronephrosis (Fig. 1A). A follow-up contrast-enhanced abdominal CT taken 2 years later (Fig. 1B) revealed deterioration and evidence of "hairy" appearance of kidneys and a "coated" aorta. Peri-renal biopsy showing non-specific retroperitoneal fibrosis with numerous histiocytes staining positive for CD68 (Figs. 1C and D). The patient received corticosteroid therapy, which was replaced with methotrexate.

In 2015, a follow-up contrast-enhanced abdominal CT (Figs. 2A and B) showed stability/minimal deterioration of retroperitoneal fibrotic changes. Full-body positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) (Figs. 2C, D and E) revealed evidence of active inflammatory changes within the retroperitoneal fibrotic changes and increased uptake in the left pleural area without evidence of bone lesions. The patient later developed an episode of acute renal failure and pneumonia that required in-patient management.

In 2016, a chest CT showed new pleural, fissural, and some inter-lobular septal thickening as well as lung parenchymal ground-glass opacities (Figs. 3A, B and C). The biopsy specimen revealed chronic inflammatory infiltrates and numerous

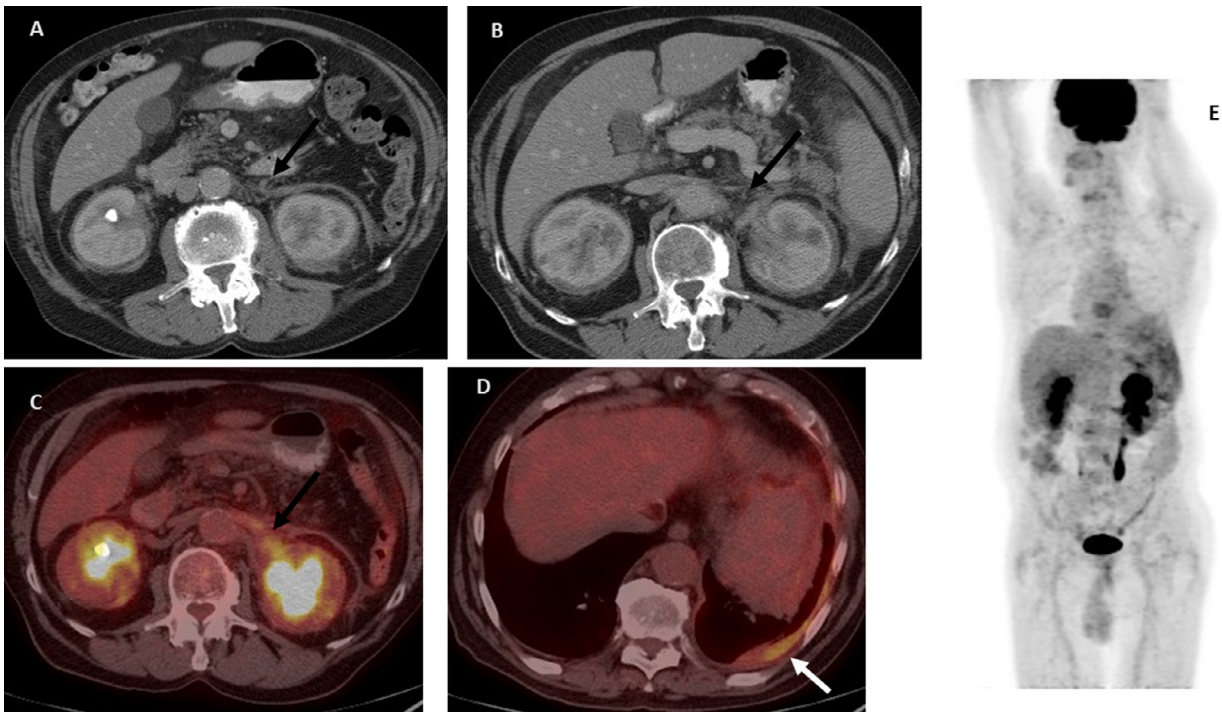

Fig. 2 – (A-E) A 7-year follow-up axial abdominal CT angiography (A-B) showing relative stability of retroperitoneal fibrotic changes (black arrow). Corresponding 18F-FDG PET/CT (B-D) revealing active inflammatory changes within the retroperitoneal fibrotic changes (black arrow) and increased uptake of the left pleura (white arrow) with no evidence of skeletal lesions (E).
CT, computed tomography
18-FDG PET: positron emission tomography with 18F-fluorodeoxyglucose (Color version of figure is available online)

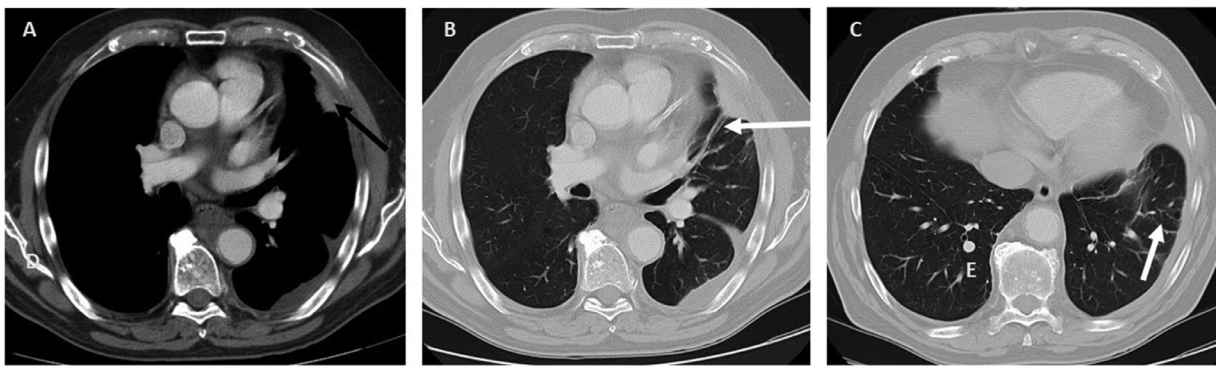

Fig. 3 – (A-C). Axial non-contrast enhanced chest CT (A-C) showing pleural (black arrow), fissural (white arrow), and some inter-lobular septal thickening (short black arrow) with lung parenchymal ground-glass opacities (short white arrow) (Color version of figure is available online)

histiocytes like those seen in the previous perirenal biopsy, staining positive for CD68 and negative for both CD1a and S-100. *BRAF* V600E mutation testing of the pleural specimen was negative.

A follow-up PET scan taken 3 years later (Fig. 4A) demonstrated no skeletal involvement and mild incidental focal abnormal uptake within the right atrium (RA) (max SUV 2.6). Transthoracic echocardiography revealed a small (1.8×3.0 cm) mass attached to the anterolateral wall of the RA (Fig. 4B). Nevertheless, the left ventricular ejection fraction was normal, and the patient had no cardiac symptoms.

In 2019, another follow-up PET scan (Fig. 5A) demonstrated increased uptake in the RA lesion (max SUV 4.6) while still being asymptomatic. It also showed progression of the uptake in the left pleural thickening, lung opacities, and bilateral perirenal lesions with no skeletal involvement. Cardiac magnetic resonance imaging (MRI) demonstrated a focal RA lesion consistent with heart involvement in ECD (Figs. 5B, C, D and E).

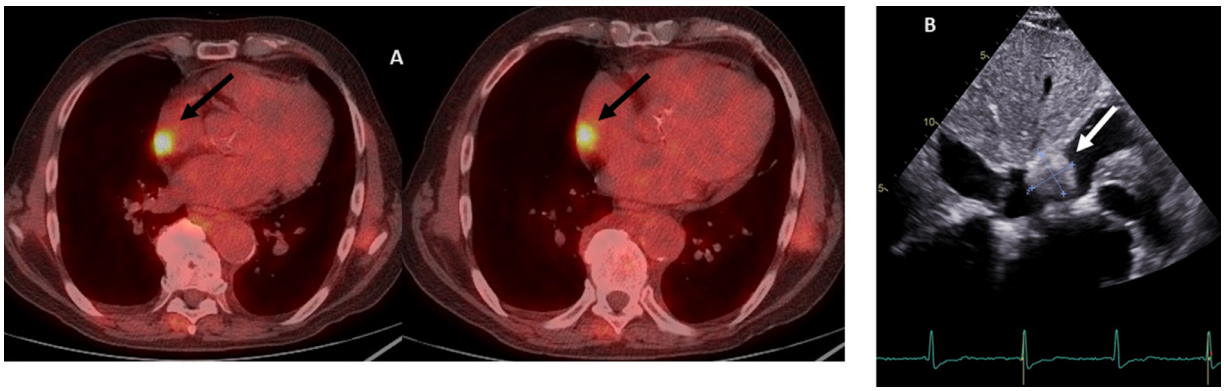

Fig. 4 – (A-B) A follow-up 18F-FDG PET/CT (A) revealing a focal uptake within the right atrial mass (black arrow). Corresponding transthoracic echocardiography (B) is shown (white arrow).
CT, computed tomography
18-FDG PET: positron emission tomography with 18F-fluorodeoxyglucose (Color version of figure is available online)

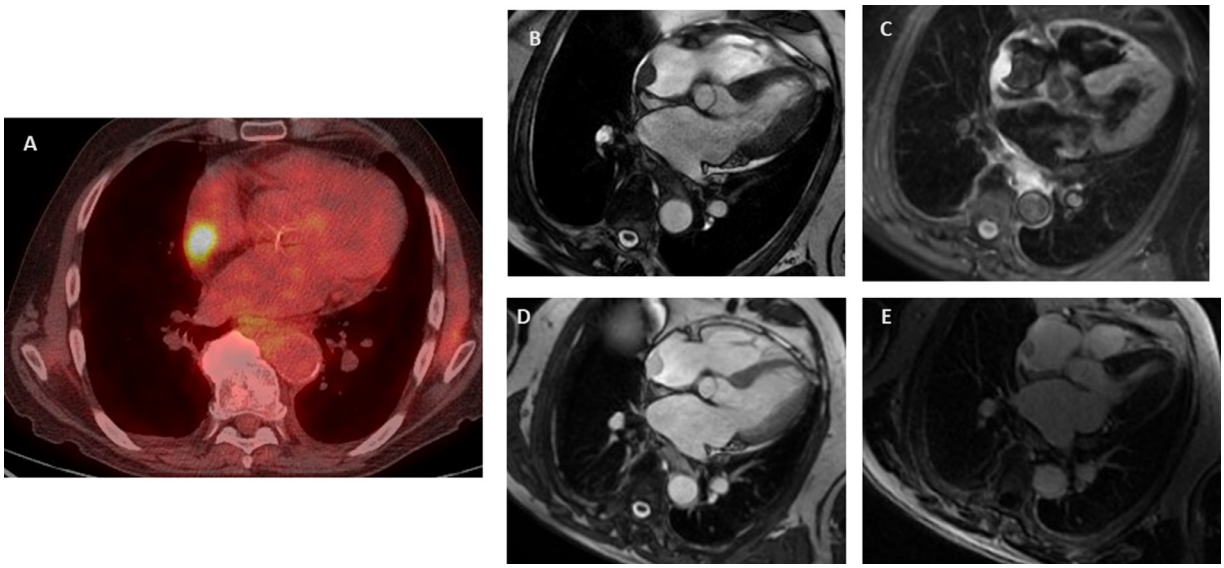

Fig. 5 – (A-E) Another follow-up 18F-FDG showing new increased uptake of the right atrial mass (A). Corresponding cardiac SSFP MRI demonstrating right atrial ECD involvement as a hypointense soft tissue mass (B). Inversion recovery T1W (C) and T2W fat saturation (not shown) sequence showing hyperintensity. Early (D) and late (E) gadolinium enhancement sequences showing slight enhancement, which reflect edema and disease activity.
18-FDG PET: positron emission tomography with 18F-fluorodeoxyglucose
SSFP, Cine Steady State Free Procession
MRI, Magnetic resonance imaging
T1W: T1-weighted
T2W: T2-weighted

Despite these radiologic changes, the patient remained clinically stable. However, given the progressive increase in uptake on the PET scan within the RA and pleuropulmonary and perirenal lesions, corticosteroid treatment was readjusted and settled in association with interferon-alpha therapy. The patient remained stable for 5 months but later developed severe elbow cellulitis with sepsis and pericarditis, which deteriorated gradually. The patient died of progressive pleuropulmonary, cardiovascular, and renal disorders after a total of more than 10 years of disease course.

Discussion

ECD is a rare multisystemic non-Langerhans histiocytosis with heterogeneous manifestations ranging from asymptomatic to limited organ or systemic involvement that may have life-threatening manifestations. The pathophysiologic mechanism of ECD is complex and remains unclear. However, it is argued to be a neoplastic disease rather than a simple inflammatory entity. The most common manifestation of ECD

involves the skeleton, which occurs in up to 96% of cases [4]. However, in the case presented here, no bone lesions were found, as reported by some previous studies [12,13].

Extra-skeletal manifestations are also common and may involve multiple organs and structures, including the kidneys, retroperitoneum, central nervous system, lungs, and skin.

Cardiovascular involvement in ECD is also common but not always clinically evident, thereby resulting in under-diagnosis. Its discovery has recently increased because of the increasing use of total-body PET/CT studies during follow-up. It often presents as non-specific mass even with advanced imaging tools such as cardiac MRI, as in the case presented here. Knowledge of the clinical setting is very helpful in establishing a correct diagnosis. The differential diagnosis is large, including cardiac lymphoma and angiosarcoma. Several studies, including the study by Haroche et al., reported that cardiac involvement is strictly linked with poor prognosis [7], as observed in the case presented here. Indeed, death is reported to be due to cardiovascular disease in more than one-third of ECD cases [9].

Pleuropulmonary involvement in ECD is also common and is observed in approximately half of the cases. Radiologic evidence of pleuropulmonary disease is also non-specific but often presents as inter-lobular septal, pleural, or fissural thickening, pulmonary nodules, ground-glass opacities, and effusion [1,8]. The differential diagnosis is wide, including lymphangitic carcinomatosis, tuberculosis, lymphoma sarcoidosis, and some interstitial pneumonias. Knowledge of the clinical context helps diagnosis if biopsy results are not available. We must emphasize that radiologic pleuropulmonary and cardiac manifestations of ECD may precede clinical manifestations [4,8], as observed in the present case.

Recent advances in ECD have shown an evident link between ECD and *BRAF* V600E mutation [1,5,7], which is observed in more than half of the cases. This is important in the clinical decision tree, given the recent development of therapies based on the inhibition of *BRAF* mutation. However, in the case presented here, *BRAF* V600E mutation testing was negative, which increased the complexity of our case.

Moreover, we have illustrated here the complexity of diagnosing ECD despite advances in technology, which may be associated with a significant delay as reported in some previous reports [1,6]. Indeed, a correct diagnosis of ECD often requires investigations involving clinical, radiologic, biochemical, immunohistochemical, and pathologic findings.

Until recently, poor knowledge of the pathophysiologic mechanisms had resulted in a lack of standardized therapy of proven efficacy. However, experts' consensus guidelines have proposed a new therapeutic strategy based on clinical experience and literature review, considering clinical, biological, radiologic, and *BRAF* mutation status [5].

Conclusion

We have reported an unusual case of long-standing ECD complicated by pleuropulmonary and cardiac involvement in the absence of both bone lesions and BRAF mutation. This report illustrates that even today with the advances in diagnostic technologies, a correct diagnosis of ECD may take years to be established given its rarity, varied manifestations, and complex pathophysiologic mechanisms. Increased awareness among radiologists, cardiologists, and other referral physicians should be encouraged.

Patient Consent

All patient identifying information has been stripped from the images. Additionally, no patient identifying information is used in this case report.

No IRB approval was required for this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2021.11.056.

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