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CASE REPORT | PATHOLOGY

A Rare Cause of Abdominal Pain: Erdheim-Chester Disease

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ABSTRACT

A 65-year-old man presented with hematuria, night sweats, nausea, intermittent nonbloody diarrhea, and abdominal pain. Computed tomography angiogram with enterography showed retroperitoneal fibrosis surrounding both kidneys and ureters without any evidence of vascular obstruction or hydronephrosis. Laparoscopic biopsy demonstrated fibroadipose tissue involved by a subtle histiocytic infiltrate in a background of marked fibrosis, scattered lymphocytes, and plasma cells. The histiocytes strongly expressed CD163, Factor XIIIa, and *BRAF V600E*. He was diagnosed with Erdheim-Chester disease, a rare histiocytic neoplasm uncommonly presenting with gastroenterological manifestations.

KEYWORDS: Erdheim-Chester disease; IgG4 pancreatitis; IgG4 disease; histiocytic neoplasms; retroperitoneal mass

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm with variable clinical presentation.[1] Some patients are asymptomatic and incidentally detected on imaging, and others may present with multiorgan dysfunction and rapidly progressive disease.

CASE REPORT

We present a 65-year-old man with hematuria and abdominal pain who underwent abdominal computed tomography (CT) scan that demonstrated a retroperitoneal mass. Additional symptoms included night sweats, nausea, and intermittent nonbloody diarrhea. His medical history was significant for coronary artery disease with previous myocardial infarction, impaired fasting glucose, and hypertension. His physical examination was unremarkable. A CT-guided biopsy of the mass showed dense fibroadipose tissue with predominant lymphocytes and plasma cells. He was evaluated by his local oncologist, and workup for lymphoma included a bone marrow biopsy that was nondiagnostic. He was subsequently referred to our gastroenterology clinic for further evaluation of his nausea, abdominal pain, diarrhea, and unexplained weight loss. Repeat abdominal and pelvic imaging with CT angiogram and enterography was performed to assess for inflammatory small bowel changes, partial small intestinal obstruction, and signs of chronic mesenteric ischemia. Imaging at our center demonstrated retroperitoneal fibrosis surrounding both kidneys, renal vessels, left ureter, proximal right ureter, portions of the aorta, common iliac arteries, and the left internal and external iliac arteries without any evidence of vascular obstruction or hydronephrosis (Figure 1). Laparoscopic retroperitoneal biopsy was performed for further diagnostic evaluation, and demonstrated fibroadipose tissue involved by a subtle histiocytic infiltrate in a background of marked fibrosis, scattered lymphocytes, and plasma cells (Figure 2). There was a focal plasma cell infiltrate comprising immuoglobulin (Ig)G-positive plasma cells, with approximately 50% of these cells staining for IgG4 raising concern for IgG4-related disease. Subsequently on immunohistochemistry (IHC), the lesional histiocytes strongly expressed CD163, Factor XIIIa, and *BRAF V600E* and were focally positive for S100 (10%–20%). These cells were negative for CD1a and langerin (Figure 2). This patient was diagnosed with ECD based on detection of the *BRAF V600E* mutation within the histiocytes.

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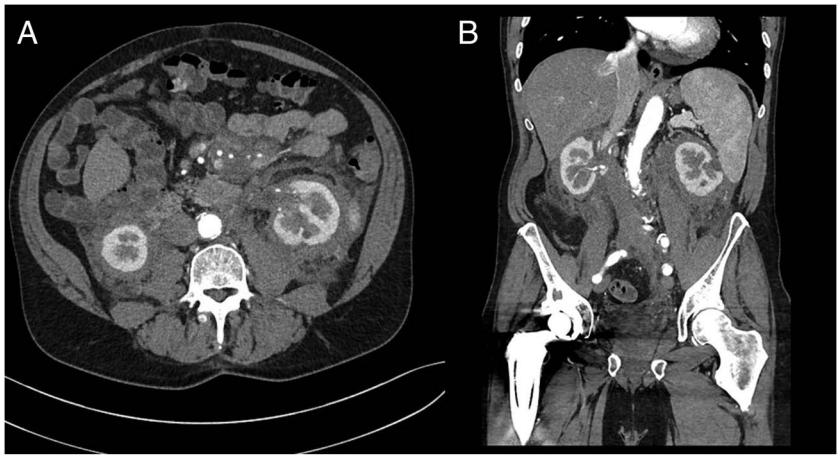

Figure 1. (A) Axial section of the abdominal and pelvic CT demonstrating bilateral kidney involvement and a normal pancreas. (B) Coronal section of the abdominal and pelvic CT demonstrating bilateral kidney involvement. CT, computed tomography.

DISCUSSION

ECD was first described by Jakob Erdheim and William Chester in 1930, and since then, less than 1,000 cases of this disease had been reported worldwide (ECD Global Alliance registry).[1,2] Most patients with ECD are diagnosed between the fourth and seventh decade of life, with a male preponderance.[3] ECD is a systemic illness that typically affects the skeletal system, but more than 50% of patients also have extraskeletal involvement.[3] Renal involvement classically presents as diffuse bilateral perirenal fat infiltration ("hairy kidneys"), which may cause ureteral narrowing and hydronephrosis. Other clinical manifestations of ECD include diabetes insipidus, mediastinal infiltration, orbital masses, and cardiac involvement.[3,4] Involvement of liver, pancreas, and gastrointestinal tract is extremely rare.[5,6] Gastrointestinal symptoms are uncommon in ECD and may include nausea, vomiting, abdominal pain, diarrhea, and hematochezia.[5–8] Liver and biliary involvement may manifest with hepatomegaly, biliary obstruction, and liver nodules, and elevated serum levels of hepatic transaminases have been reported.[9,10] Pancreatic involvement with hypodense nodular lesions has also been reported.[11] Colonic involvement has also been rarely reported, and colonoscopic findings include hyperpigmented lesions with decreased vascularity in the surrounding mucosa,[12] diffuse nodular lesions with normal intervening mucosa,[5] as well as inflammation, friability, and ulceration.[8] Endoscopic appearance of the stomach in a patient with ECD has been described as cobblestone-like raised nodular pylorus-sparing gastritis, and gastric biopsy demonstrated histiocytic infiltration.[12]

With our patient's nonspecific presentation, there was a broad differential diagnoses for retroperitoneal masses, which included neoplastic retroperitoneal masses such as lymphoma, liposarcoma, leiomyosarcoma, neurogenic tumors, germ-cell tumors, as well as benign etiologies such as previous radiation therapy, drug-induced, and IgG4-related disease (IgG4-RD).[13] Before referral to our center, a CT-guided biopsy of the mass and a bone marrow biopsy in this case ruled out most of the other neoplastic diagnoses. IgG4-RD was initially considered, given the retroperitoneal involvement and tissue IgG4 staining. Classically, pancreaticobiliary IgG4-RD presents with painless jaundice, diffusely enlarged pancreas, or a focal pancreatic mass, although renal and retroperitoneal involvement may be present. It is usually associated with a raised serum IgG4, which

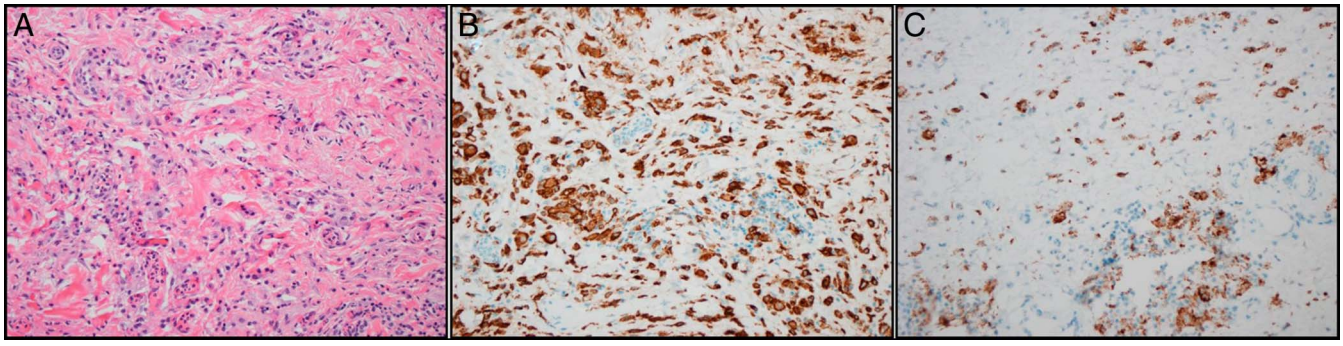

Figure 2. The retroperitoneal biopsy shows (A) fibroadipose tissue with a subtle histiocytic infiltrate in a background of marked fibrosis, lymphocytes, and plasma cells. Immunohistochemistry highlights (B) CD163-positive histiocytes that strongly express (C) *BRAF V600E* (all images 200× magnification).

was absent in this case, and although there was tissue IgG4 positivity, subsequent tissue IHC showed CD163-positive histiocytes that strongly expressed Factor XIIIa and *BRAF V600E*, which is diagnostic for ECD.[14] Langerhans cell histiocytosis was also considered as a differential diagnosis. Diagnosis of Langerhans cell histiocytosis requires demonstration of CD1a and langerin expression by IHC. These were both negative by IHC in this case. The focal expression of S100 is compatible with a diagnosis of ECD as it is seen in about 30% of cases.[3,15] Our patient presented with the classic imaging features of perinephric stranding and periaortic infiltrates, and histopathology indicated *BRAF V600E* mutation, which is sufficient for the diagnosis of ECD, despite the absence of recognizable bone lesions.[16]

Except for asymptomatic individuals who may be closely monitored, treatment is recommended for all symptomatic patients. Targeted therapy is the preferred modality of treatment. Vemurafenib selectively inhibits the kinase domain of mutant *BRAF* and is used as first-line therapy for individuals with *BRAF-V600E* ECD.[16–18] MEK inhibitors may be considered for ECD patients without *BRAF-V600E*.[16] Our patient was started on vemurafenib at diagnosis. Three months later, he underwent a follow-up positron emission tomography scan, which showed radiologic improvement. On subsequent follow-up, he was diagnosed with concomitant chronic myelomonocytic leukemia. ECD has been reported to increase the chance of developing secondary myeloid neoplasms.[4] He was initiated on cobimetinib. Both medication dosages were reduced for an appropriate side-effect profile, and he has been doing well for 2 years.

There is no known cure for ECD; historically, prognosis has been poor and varies based on treatment response and disease site, with worse outcomes in advanced age, involvement of the central nervous system, lungs, and retroperitoneum.[3,19] With the advent of targeted therapies, even severe forms of ECD have become a treatable, rather than terminal, condition, with 5-year survival rates improving from 43% in 1996 to 83% in recent literature.[20,21] However, the long-term effects of targeted agents are still not well defined.[19]

Although uncommon, physicians should consider the possibility of ECD when evaluating patients who have persistent unexplained gastrointestinal complaints and retroperitoneal perinephric mass-like infiltration on cross-sectional imaging.

DISCLOSURES

Author contributions: [as per ICMJE criteria for authorship] A. Chatterjee and J. de la Fuente: drafting the article. KL Rech and N. Takahashi: data acquisition and drafting the article. S. Majumder: drafting and final approval of manuscript and is the article guarantor.

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Informed consent was obtained for this case report.

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