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Erdheim-Chester Disease: A Rare Disease Causing Diagnostic Challenge in A 35 Year Old Male From Ethiopia

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ABSTRACT

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell tumor with histopathology features of foamy histocytes and fibrosis. The disease has varying manifestations from asymptomatic to life-threatening organ involvement including long bones, CNS, lung, heart, and kidneys. On histopathology staining, the cells exhibit CD68 positivity but CD1a and S100 negativity. The prognosis of the patients is poor. ECD poses a diagnostic and therapeutic challenge due to its resemblance to various disorders requiring a multidisciplinary approach. We report a case of a 35-year-old male patient from Ethiopia with literature review, who initially presented with massive chylous ascites and retroperitoneal manifestation but later developed pulmonary and cardiac manifestations. The diagnosis was suggested from an abdominal CT scan with subsequent image-guided biopsy which compartments a diagnosis.

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Introduction

Erdheim-Chester disease/ECD/ is a rare non-Langerhans cell histiocytosis that was recently recognized as a neoplastic disorder of unknown etiology [1,2]. To date, more than 1500 case reports describe clinical presentation and diagnosis of ECD in literature but none exist from our country Ethiopia. The incidence and prevalence of the disease are unknown due to the paucity of data related to the rare disease [2]. ECD usually affects individuals between the age of fifth and seventh decade with a male to female ratio of 3:1, but diagnoses of patients at any age have been documented in literatures [2-4]. ECD involves mainly the skeletons, retroperitoneal organs, Central nervous system, Cardiovascular system, lungs, and skin [3]. ECD is characterized by xanthogranulomatous infiltrates of foamy histocytes surrounded by fibrosis [5]. The disease is marked by BRAFV600E mutation and immune histochemistry staining with positivity for CD68 and CD1a in most patients [6-8].

Case Presentation

A.A (MRN 95060) is a 35-year-old man from Jigjiga, East Ethiopia, who was admitted at a referral hospital in Jigjiga three months ago after he presented with a one-week complaint of progressive abdominal distension associated with loss of appetite, low-grade intermittent fever, nausea, and left side abdominal pain. He was a civil servant, married, and had 5 children, who are in good health. He had no history of alcohol intake or illicit drug use. He had no chronic illness.

On physical examination at jigjiga he was acutely sick looking; tachycardic. The abdomen was distended, with periumbilical tenderness and ascites. The rest of the physical examination was unremarkable. Abdominal CT scan showed left perirenal collection and moderate hydroureteronephrosis suggesting retroperitoneal fibrosis. He then underwent exploratory laparotomy. Intraoperatively thick non-offensive chylous fluid and mesenteric lymphadenopathy, which was biopsied, and a drainage tube was left in situ. Post OP, the patient was empirically initiated on Anti – TB considering the endemicity of tuberculosis. The drainage tube continued to drain 1-2 liters of chylous ascites per day. The Lymph node biopsy revealed capsulated lymph node with germinal centers and dilated sinuses filled with histiocytes. Despite taking anti-TB for 5 weeks patient had no symptomatic improvement and the drainage tube continued to drain a chylous ascetic fluid. Subsequently, the patient was referred to Addis Ababa, for better evaluation and management.

Upon arrival to our center, he was emaciated and weak. Vital signs were normal. He had mild pallor but no icterus or

lymphadenopathy. There was dullness and decreased air entry over the left posterior basal lung field. The pericardial exam was unremarkable. The abdomen was distended with mid-line surgical scar, he had left lower quadrant and periumbilical tenderness and there was a drainage tube in situ at the right lower quadrant with 50 ml chylous fluid. Otherwise, there was no abnormality noted.

The laboratory investigations showed mild leukocytosis of 12000/uL, Hgb 15.5g/dl, Platelet 392000/uL, and ESR40 mm/hr. On urine analysis, he had proteinuria and hematuria. Serum albumin was 2.8 g/dl and had an elevated serum lipid profile with Triglyceride 292mg/dl, cholesterol 244 mg/dl, and LDL 154mg/dl,otherwise, electrolytes, liver, and renal function tests were normal. HBsAg was positiveand CA-125 was 600 U/mL.Chylous pleural fluid analysis showed transudative fluid with 1100 cells, 65% of lymphocyte, albumin 1.59 g/dl, glucose 125 mg/dl andLDH 163 U/ml. The cytology showed clusters of cells exhibiting large cells with pleomorphic hyperchromatic nuclei disposed in proteinaceous background. Gram stain and GeneXpert tests were negative from both pleural and ascitic fluid. Chest X-ray showed left minimal subpulmonic pleural effusion which later became massive (Figures 1A&B).

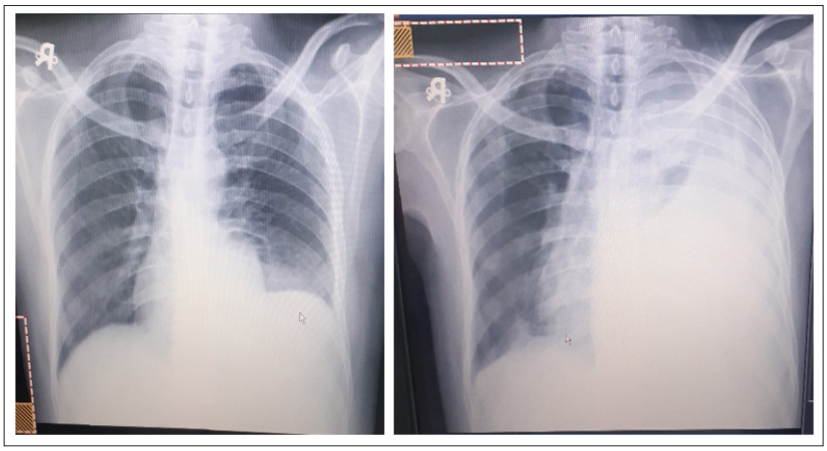
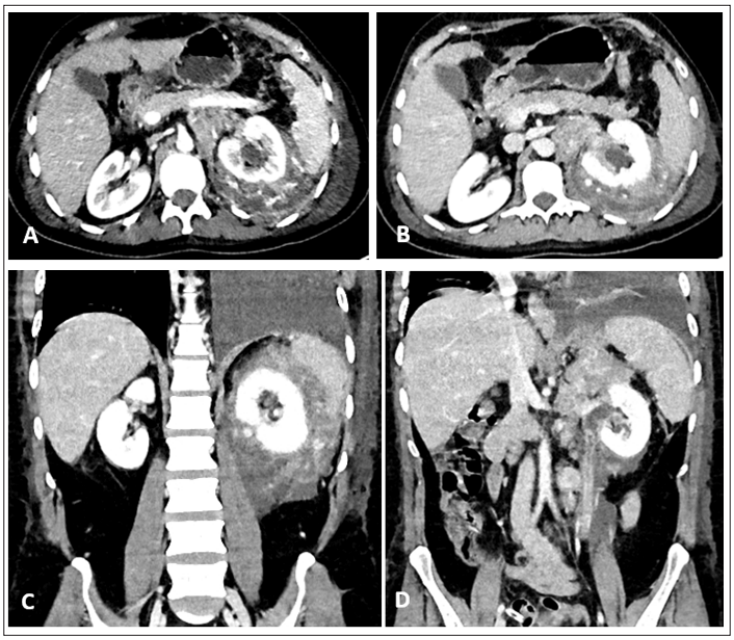


Figure 1A: initial chest x-ray finding of the patient Showing mild left subpulmonic pleural effusion

Figure 1B: after 2 months subsequent chest x-ray finding showing massive left side pleural effusion

(Figure 1A& 1B): Addis Ababa, Adera Medical Center, 2021.

Echocardiography also revealed minimal pericardial effusion. Repeated abdominal CT scan revealed, heterogeneously enhancing lesion in the left perirenal space that showed heterogeneous enhancement with contrast, demonstrating increased enhancement of the lesion into subsequent phases of the scan [figure 2A, 2B]. There was mild left hydronephrosis, enhanced and thickened urothelium, and a left pleural fluid collection [figure 2C, 2D]. Erdheim Chester Disease (ECD) was considered as a possible differential diagnosis and diagnostic CT-guided biopsy was done.



Figures 2A-3D: The above image shows a heterogeneously enhancing left perirenal lesion showed increased enhancement in the deleted phases of the scan [2A,2B and 2C]. There was also mild left hydronephrosis with thickened and enhancement in the renal pelvis and analysis of the whole length of the ureter [2D]. There was also left pleural effusion [2C and 2D]

Figure 2: Addis Ababa, Adera Medical Center, 2021.

CT-guided biopsy from the perirenal mass revealed diffuse proliferation of histiocytes with a single nucleus and compact eosinophilic cytoplasm and associated fibrosis (Figure 3A). Immunohistochemistry study showed strong positivity of the foamy histocytes for CD 68 (Figure 3B). Thus, the patient was diagnosed with severe multi-organ Erdheim-Chester disease. A skeletal survey done using X-rays didn't show the characteristics of symmetric sclerotic lesion of ECD.

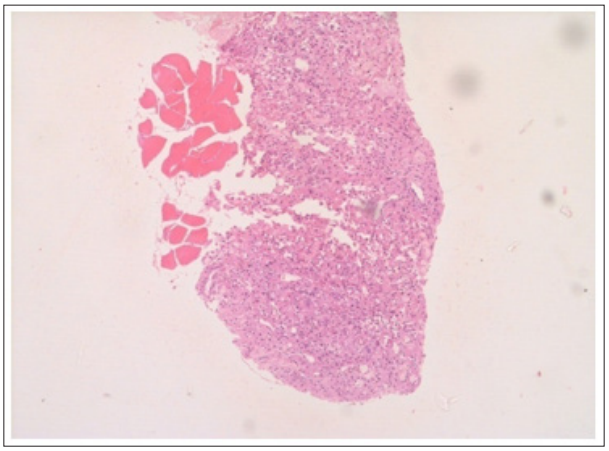


Figure 3A: Histopathology of retroperitoneal lesion: atypical histiocytic proliferation with compact eosinophilic cytoplasm and associated fibrosis

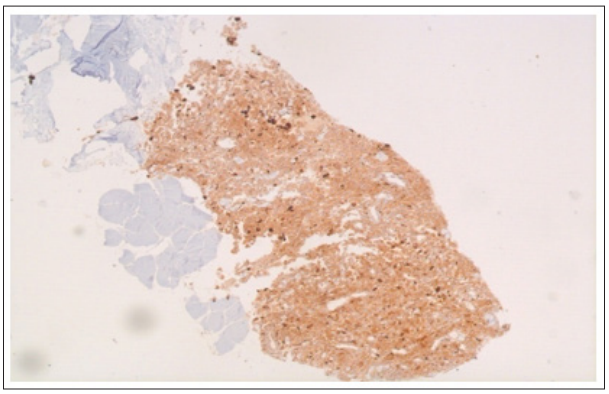


Figure 3B: Histopathology of retroperitoneal lesion, the histiocytic proliferation displays strong positivity for CD 68 [8].

Figure 3A and 3B: Addis Ababa, Adera Medical Center, 2021.

The hematologist decided to treat the patient with Cladribine considering the disease burden and the available literature evidence. Before initiation of Cladribine, he was started on tenofovir (TDF) for prevention of HBV reactivation. He then took a 05-day course of IntravenousCladribine. Meanwhile, he was on ulcer and DVT prophylaxis, antiviral and antifungal prophylaxis, and supportive care. While on Cladribine patient was having a symptomatic improvement of dyspnea and he became off oxygen just after completing the course of Cladribine. The ascetic fluid drainage also decreased. Nevertheless, two days after completing cladribine, he developed profuse watery diarrhea and became weak. He also started to experience bone pain. His BP dropped progressively and he went into shock. Stool exam revealed Trophozoite of E. histolytica. He was resuscitated with IV fluids however hypotension persisted and he was put on vasopressors, IV steroids, cefepime, vancomycin. Acyclovir and fluconazole were also continued. Despite all these, the patient was still in shock and after 12 hours of presser administration, the patient passed from multi-organ failure secondary to refractory septic shock.

Discussion

Erdheim-Chester Disease is a rare non-Langerhans histiocytosis with slight male predominance. The disease shows varying clinical manifestations and organ system involvement. The commonest manifestation is peripheral skeletal involvement in 80-95% of cases. The bone lesions are bilateral and symmetric involving the long bones of the lower limbs more than the upper limbs. Patients present with local pain and edema with orbital involvement. The bone scans show sclerotic changes mainly localized to the diaphysis-metaphysis junction [9,10].

Retroperitoneal involvement is the most frequent (50%) extra skeletal manifestation of the disease, though most patients remain asymptomatic for years. Patients present with non-specific symptoms such as lower back or abdominal pain, urinary complaints, and renal impairment. On imaging, common findings are bilateral perirenal lesions showing heterogeneous contrast enhancement. Lesion may compress the kidney of the collecting system and may cause hydronephrosis [11]. Most of the time manifestations of ECD mimic that of retroperitoneal fibrosis. Image-guided biopsy is crucial for making management decisions [12-14].

With CNS involvement patients have evidence of intracerebral and intramedullary lesions. The clinical manifestation may range from headache, blurred vision, focal neurologic deficit, and symptoms of Diabetes Insipidus to change in mentation including Comadepending on the area affected [15,16]. Pulmonary involvement was described in nearly half of the patients with ECD [10]. The imaging findings can be ground-glass opacities, centrilobular nodular opacities, interlobular septal, and fissural thickening [17]. The imaging findings are mistaken for several infectious, inflammatory and tumor infiltrates [18,19].

Patients with ECD can have cardiovascular manifestation with pericardial infiltration [20]. The patients mostly appear asymptomatic. Imaging studies may reveal pericardial effusion. Others could have circumferential soft-tissue sheathing of the thoracic and abdominal aorta and its branches. This periaortic fibrosis is also known as the "coated aorta" as a result of periaortic infiltration by histiocytes [5,21].

Most documented laboratory findings are microcytic anemia, low calcium, and albumin [22,23]. Some patients also exhibited increased ESR [3]. The histopathologic study is important to confirm the diagnosis of ECD from the biopsy of involved organs [24]. Biopsy shows non-Langerhans cells with typical foamy histiocytes, main¬ly involving bones and the retroperitoneal space. Confirmation of ECD is made on the detection of CD68 positive, and negativity for CD1a and S100 protein [3, 25]. Half of the patients with ECD have evidence of $BRAF^{V600E}$ mutation [26]. Testing the BRAF and RAS mutation will help in guiding therapy.

Regarding treatment, Cytostatic chemother¬apy, extensive surgery, and radiation therapy have been used without success [25]. Since ECD is rare, there is no evidence-based therapy suggested by literature [27]. Interferon therapy is the most extensively studied therapy in ECD and serves as the first-line treatment [25]. Other treatments included in different studies and clinical trials with no concrete evidence-based recommendation on which agent is superior, other than expert consensus are steroids, biphosphonates, imatinibmesylate, cladribine, and stem cell transplantation [2,27].

The prognosis of patients with ECD is poor. The most common cause of death is lung fibrosis followed by renal failure, secondary to

retroperitoneal involvement and heart failure [28]. Gastrointestinal manifestation of ECD is exceedingly rare. Involvement of the biliary tract, the liver, and the GIT were previously reported [29-31]. But we haven't found a case of ECD manifesting with chylous ascites and, our report may be the first one. Bone involvement which is almost universal in ECD (96% of cases), was absent in our patient [32]. However, extensive studies were not done to check for bone involvement and the patient had developed bone pain before his death which might indicate bone involvement. Other features of ECD demonstrated in our patient include retroperitoneal, respiratory and cardiovascular involvement.

Chylous ascites is known to have high mortality ranging from 40-70% depending on the underlying etiology [33]. Death results from malnutrition, hypoproteinaemia, dehydration, or sepsis. Our patient was progressively deteriorating; he was cachexic, had severe hypoalbuminemia, and unfortunately developed refractory septic shock that led to his death. Cladribine has shown promising results for ECD treatment [34]. our patient also had shown response for the cladribine evidenced by the improvement in dyspnea, hypoxia, respiratory condition, and the decrement in the chylous ascites drainage.

Conclusion

we report the first case of ECD having a GI manifestation of chylous ascites. Though, our patient presented with one of the commonest extraskeletal manifestations (retroperitoneal involvement)the rarity of the disease, absence of bone involvement, and presence of abdominal complaint all contributed to the delayed diagnosis. Establishing ECD diagnosis is challenging, due to vague and nonspecific presenting symptoms. However, it is important to recognize its unique radiographic findings and the pathognomonic infiltration of foamy histiocytes with dense fibrosis for timely diagnosis and early intervention.

Disclosure Statement

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