Erdheim-Chester Disease Presenting with Histiocytic Colitis and Cytokine Storm

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INTRODUCTION

Erdheim-Chester Disease (ECD) is a rare form of non-Langerhans cell histiocytosis. It is characterized by increased proliferation of dendritic cells/macrophages affecting middle age adults [1]. It involves the excessive production of histiocytes, cytokine production, and is often a severe systemic disease. It commonly affects the bones, with occasional involvement of the kidney, skin, brain, lung, heart, and retroperitoneum [2]. The etiology of ECD is unclear, but is thought to involve a cytokine-mediated dendritic cell proliferation of BRAF somatic mutation and may be potentially triggered by a viral infection. Gastrointestinal involvement is exceedingly rare. There are few case reports demonstrating the hepatobiliary, mesenteric, and pancreatic organ ECD involvement [3]. This report documents for the first time ECD causing isolated histiocytic colonic inflammation leading to distributive shock consistent with a potent cytokine storm.

CASE PRESENTATION

A 68-year old Caucasian female with a history of chronic obstructive pulmonary disease (COPD) and diabetes mellitus presented to an outside facility with fever, fatigue, dyspnea on exertion, and chronic diarrhea. She reported a one-year history of intermittent episodes of fever and night sweats, along with one year of progressively worsening diarrhea. Over the last two months, she experienced three watery bowel movements.
daily, occasionally mixed with red blood. Initial infectious workup, including blood, urine and tracheal cultures, was unrevealing. A CT of the chest, abdomen, and pelvis showed mucosal thickening of the sigmoid colon.

The patient was transferred to our ICU for fever of unknown origin, eight days after initial hospital admission. The physical examination revealed mild pulmonary crackles and bloody stool on rectal digital examination. The patient received vancomycin, cefepime, acyclovir, micafungin and doxycycline for two weeks. She continued to remain febrile to 41°C. Her diarrhea progressed to hematochezia up to two liters daily, requiring blood transfusions. Although *Clostridium difficile* toxin was negative, she received 14 days of empiric treatment with intravenous metronidazole and oral vancomycin.

Basic laboratory work showed a white blood cells (WBC) count of 30,000/ul, hemoglobin of 11.5g/dL, and platelets of 278,000/ul, albumin of 3g/dL, total bilirubin of 0.2 mg/dL, AST of 56 U/L, ALT of 64 U/L, and alkaline phosphatase of 100 U/L. C-reactive protein was 11mg/L. ANA, ANCA, anti-striated muscle, and anti-acetylcholine receptor were negative. The patient had a negative ova/parasites manual screen, enteric pathogen culture, and *Clostridium difficile* toxins. In addition, multiple blood and urine cultures were negative. Acid-fast bacilli (AFB) sputum stain was negative. A lumbar puncture was performed and serological tests for Cytomegalovirus, HSV, enterovirus, West Nile virus, JC virus, and rapid plasma regain (RPR) test were all negative. Blood tests for Erhlichia, Hepatitis A, B, C, Human Immunodeficiency Virus, Lyme, Coxiella burnetii, Blastomyces, fungal cultures, Aspergillus, Histoplasma, Cryptococcus were negative. In addition, a left knee arthrocentesis was performed. Synovial fluid was unrevealing. A brain MRI was normal. Transthoracic echocardiogram was negative for endocarditis.

Given her progressive hematochezia a repeat CT scan was obtained (three weeks after admission). This showed wall thickening and lack of haustration of the descending colon, sigmoid colon, and rectum along with gas and fluid distention of the ascending and transverse colon (Fig.1). In addition, Whole Body Radionuclide Imaging with Abscess Localization demonstrated nonspecific increased radiopharmaceutical uptake in the colon corresponding to a long segment of colitis as seen on CT (Fig. 1). A bone survey was conducted and no osseous skeletal radiographic findings consistent with lytic or blastic bone lesions were found.

Colonoscopy revealed a single area of ulceration, about 20cm in length at the splenic flexure (Fig. 3A). A similar area of ulceration was seen at the hepatic flexure, less than 10 cm in length, which also demonstrated inflammation, friability and granularity (Fig. 3B). The area between the ulcerations and the remaining colon showed a normal vascular pattern without any evidence of ulceration, lesions or masses. The ileum was endoscopically normal.

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**Fig. 1.** A and B: abdominal CT on admission: point to areas of mucosal thickening of the sigmoid and ascending colon. C and D: repeat CT obtained three weeks after admission. Wall thickening and lack of haustration of the descending colon, sigmoid colon and rectum along with gas and fluid distention of the ascending and transverse colon. E and F: whole body radionucleotide scan. Leukocyte scintigraphy at 4 hours (E) and at 24 hours showing increased uptake at the descending colon.
Biopsies from the ileum demonstrated Paneth cell hyperplasia and mild architectural disarray with features suggestive of chronic mucosal injury. The hepatic and splenic flexure biopsies showed atypical lymphohistiocytic process and colonic mucosa with architectural disarray and ulceration. In addition, complete effacement of the colonic crypts with lymphohistiocytic proliferation in H&E staining. The histiocytic cells demonstrated a foamy cytoplasm and were admixed with multinucleated giant cells, lymphocytes, plasma cells, and scattered eosinophils. Touton type giant cells within this infiltrate. The CD68 positive immunohistochemical staining depicts tissue macrophages, consistent with a histiocytic process. D: PASD staining negative for bacterial organisms; PASD positive finely granular material within the cytoplasm of the foamy cells.

Fig. 2. A and B: Colonoscopy revealing an area of ulceration, about 20 cm in length at the splenic flexure. C and D: Similar area of ulceration at the hepatic flexure, < 10 cm in length, also demonstrating inflammation, friability and granularity.

Fig. 3. A: the hepatic and splenic flexure biopsies showed atypical lymphohistiocytic process and colonic mucosa with architectural disarray and ulceration. Complete effacement of the colonic crypts with lymphohistiocytic proliferation in H&E staining. B: the histiocytic cells demonstrated a foamy cytoplasm and were admixed with multinucleated giant cells, lymphocytes, plasma cells, and scattered eosinophils. Touton type giant cells within this infiltrate. C: the CD68 positive immunohistochemical staining depicts tissue macrophages, consistent with a histiocytic process. D: PASD staining negative for bacterial organisms; PASD positive finely granular material within the cytoplasm of the foamy cells.
crypts with lymphohistiocytic proliferation was noted. The histiocytic cells demonstrated a foamy cytoplasm and were admixed with multinucleated giant cells, lymphocytes, plasma cells, and scattered eosinophils. Touton type giant cells were noted within this infiltrate, which are representative of areas with high fat content. No polarizable foreign body or nuclear grooves was noted. There was no evidence of hemophagocytosis or phagocytosis of platelets, lymphocytes, neutrophils, or debris in the sections to suggest evidence of hemophagocytosis or phagocytosis of platelets, foreign body or nuclear grooves was noted. There was no representative of areas with high fat content. No polarizable giant cells were noted within this infiltrate, which are plasma cells, and scattered eosinophils. Touton type admixed with multinucleated giant cells, lymphocytes, histiocytic cells demonstrated a foamy cytoplasm and were crypts with lymphohistiocytic proliferation was noted. The histiocytic cells demonstrated a foamy cytoplasm and were admixed with multinucleated giant cells, lymphocytes, plasma cells, and scattered eosinophils. Touton type giant cells were noted within this infiltrate, which are representative of areas with high fat content. No polarizable foreign body or nuclear grooves was noted. There was no evidence of hemophagocytosis or phagocytosis of platelets, lymphocytes, neutrophils, or debris in the sections to suggest hemophagocytic lymphohistiocytosis.

Immunohistochemical staining was positive for CD68 in the foamy cells (Fig. 3) consistent with macrophages. Periodic acid-Schiff with diastase (PASD) was negative for bacteria but did reveal finely positive granular material within the cytoplasm of the atypical, foamy cells. Cells were also CD163 positive, but negative for S100 protein and CD1a consistent with non-Langerhans histiocytosis. These foamy cells were also negative for cytokeratin 7, cytokeratin 20, and Melan A. AFB, GMS and PASD stains were negative making this unlikely infectious. The CD3 and CD20 stains showed scattered small T and B-cells. CD21 was negative. Kappa and lambda in-situ hybridization showed polytypic light chain expression.

The patient was empirically treated with steroids but continued to have fever, hematochezia and developed progressive distributive shock.

**DISCUSSION**

This case report described a 68-year old female who presented with intermittent fevers and progressive bloody diarrhea for one year. Infectious workup was negative with imaging revealing segmental colitis. Pathology from the colon revealed infiltration of large foamy histiocytes CD3-/CD20-/CD68+/CD163+/S100- consistent with non-Langerhans histiocytosis and ECD [4].

A broad differential for segmental colitis and persistent fever includes infection, ischemia, inflammatory, immunologic, drug induced, radiation and malignancy, or colitis associated with systemic diseases such as vasculitis, Behcet's disease, and sarcoidosis [5].

Infectious causes of colitis include bacterial, tuberculosis (TB), and fungal infections. Common sites of gastrointestinal TB include ileocecum, jejunum and colon. Colonoscopy usually demonstrates presence of linear/fissured, transverse or circumferential ulcers covered with dull white or yellow exudate [6]. Aeromonas infection demonstrates hemorrhagic colitis on colonoscopy. Pathology shows inflammation without epithelioid granulomas [7]. Histoplasma causes multiple deep and large patchy exudative ulcers with pathology stains revealing acute infectious colitis with multiple granulomas, rich in epithelioid and oval budding yeast cells [8]. Isolated involvement of aspergillus in the colon is extremely rare but can present with mucosal ulceration, segmental lesions, polypoid masses and necrosis. Pathology demonstrates transmural necrosis and angioinvasion [9].

Inflammatory and rheumatologic diseases can have an unusual presentation of segmental colitis, synovitis, and persistently high fever [10]. Inflammatory bowel disease has recognizable histopathology findings that show crypt disarray, Paneth cell hyperplasia, and neutrophil infiltration but it is not associated with histiocytic inflammation [11]. Sarcoïd involvement of the gastrointestinal tract is extremely rare. Findings during colonoscopy usually show scattered ulcerations and erosions, nodules, polyps, obstructive lesions, stenosis and small punctate bleeding sites. Pathology reveals the presence of intramucosal non-caseating granulomas and the presence of calcium and protein inclusion within the cryptoplasm of Langerhans multinucleate giant cells (Schaumann bodies) [12, 13]. Vasculitis involvement of the GI tract is commonly seen in small vessel and medium vessel vasculitis. The endoscopic and histopathologic appearance can vary from eosinophilic infiltration seen in Churg-Strauss to hemorrhagic ulcers, erosions seen in Henoch-Schonlein purpura due to the deposition of IgA immune complexes [14]. Bechet's is a systemic vasculitis and intestinal lesions include large round shaped deep ulcers usually involving the ileocolonic area. Pathology reveals non-specific inflammation without granulomas, and blood vessels with hyaline degeneration, lymphocyte infiltration and thickened vessel walls along with the involvement of submucosal venules [15].

Non-Langerhans histiocytosis can be categorized into ECD or Rosai-Dorfman disease, which predominantly involves extracutaneous sites [2, 16]. Rosai-Dorfman disease is usually seen in children and young adults of African descent and usually presents with massive painless lymphadenopathy [16]. Endoscopically, most case reports demonstrate a hypoechoic submucosal mass with lymph node swelling. Pathology demonstrates emperiploisis by the histiocytes with staining positive for S100 and CD68 [4].

Erdheim-Chester disease is a rare form of non-Langerhans cell histiocytosis showing increased proliferation of macrophages and commonly affects the bones. Most commonly, histiocyte staining is positive for CD163 and negative for CD1a and S100 protein. Despite attempts to treat ECD with steroids, vinblastine, vincristine, doxorubicine, cyclophosphamide, radiotherapy, anakinra, or bone marrow transplant, response to treatment has been very poor [9]. Prognosis and response to treatment is dictated by the extent of the invasion of the various organ systems, highlighting the importance of early recognition and treatment. In this patient, once the diagnosis of non-Langerhans histiocytosis was made, she was treated with corticosteroids. Despite steroids, she continued to have fever, hematochezia, and distributive shock, likely to have been a secondary cytokine storm [17, 18].

**CONCLUSION**

Erdheim-Chester disease involves the excessive production of histiocytes, cytokine production, and is often a severe systemic disease. For prompt diagnosis and appropriate treatment, it is imperative to consider immunoproliferative and histiocytic processes in unusual clinical and endoscopic presentations of colitis. Gastrointestinal ECD might exhibit poor response to steroid treatment and other potential treatments including chemotherapy, and biologic treatments targeting IL-1 and TNF-alpha signaling should be considered.
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