

A 37-Year-Old Female With Abdominal Pain and Diarrhea: A Case of Idiopathic Hypereosinophilic Syndrome

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Abstract

We report a case of a 37-year-old female who presented with diffuse abdominal pain associated with dysphagia, weight loss, and history of chronic non-bloody diarrhea. Labs showed severe eosinophilia and esophagogastroduodenoscopy (EGD) showed patchy erythema in antrum and body of the stomach. The pathological exam showed lymphoplasmacytic inflammation of lamina propria with increased eosinophil count and eosinophilic abscesses. The immunophenotypic analysis did not show evidence of clonality. There was no evidence of allergic reaction or infection. In view of the absence of causes to explain severe eosinophilia, the diagnosis of hypereosinophilic syndrome (HES) was made and she was started on steroids with improvement in her symptoms and eosinophils counts in subsequent evaluations.

Keywords: Hypereosinophilic syndrome; Eosinophilia; *Strongyloides*; FIP1L1-PDGFR α ; Eosinophilic gastroenteritis; Bowel thickness

Introduction

Hypereosinophilic syndrome (HES) is characterized by sustained overproduction of eosinophils, leading to multi-organ damage by eosinophilic infiltration. HES is defined as the absolute count of eosinophils $> 1,500$ cells/ μ L on two separate occasions or pathologic confirmation of tissue hypereosinophilia in the absence of alternative etiologies. It is a rare disorder with estimated prevalence of 0.36 - 6.3 per 100,000 [1], and approximately one-third of these present with gastrointestinal (GI) symptoms [2]. We report a rare case of idiopathic HES associated with GI symptoms.

Case Report

A 37-year-old female presented to the emergency depart-

ment with 3 weeks of diffuse abdominal pain. The patient reported 2 weeks of vomiting and 1 week of diarrhea 2 - 3 times per day. She also complained of difficulty swallowing and sensation of food stuck in her throat along with decreased appetite and weight loss of 10 pounds since illness started.

The patient's medical history was remarkable for hypothyroidism and eosinophilia first noticed 8 years ago, for which she underwent multiple diagnostic tests including bone marrow examination, positive for marked eosinophilia, negative for granulomas or tumor, evaluation for FIP1L1-PDGFR α mutation, and a thorough infectious workup. She was found positive for *Strongyloides* IgG and received a course of ivermectin with transient symptomatic improvement. She was re-admitted for the same symptoms 1 year ago, at which point she was negative for *Strongyloides* antibodies, but showed temporary improvement after a second course of ivermectin.

On the present admission, her vital signs showed BP of 118/70 mm Hg, RR of 18, HR of 83 bpm, and O₂ of 98%. The physical exam was significant for mild abdominal tenderness to palpation diffusely and was otherwise unremarkable. Initial laboratory work was significant for WBC of 24,800 cells/ μ L with absolute eosinophil count of 13,144 cells/ μ L, Hgb of 14.8 g/dL, and Plt of 269,000/ μ L. TSH, free T4, and basic metabolic panel including phosphate, magnesium and liver enzymes were all within normal limits. Additional laboratory tests for stool O&P, *Strongyloides* ab, *Toxocara* ab, C. Diff, HIV, UA, ANA, lipase, ANCA-C, ANCA-P, dsDNA, SCL-70, anti-centromere, tryptase, C-reactive protein, and sedimentation rate were normal. Because she had responded to ivermectin in the past, she was treated with a third empiric course of ivermectin without improvement.

CT scan of the abdomen showed findings consistent with a long segment of small bowel wall thickening, greatest in the jejunum, consistent with enteritis. There was diffuse mild small bowel ileus with mild circumferential wall thickening in the visualized distal esophagus and a small volume of abdominal and pelvic ascites (Figs. 1 and 2). A small to moderate left pleural effusion was also seen (Fig. 1).

Esophagogastroduodenoscopy (EGD) was performed showing white plaques throughout the esophagus that washed off with water. A diffuse erythematous mucosa with mosaic pattern was found in the body of the stomach. Pathological examination reported esophageal mucosa with acute neutrophilic and eosinophilic esophagitis, eosinophils were focally too numerous to count and focal basal eosinophilic abscess

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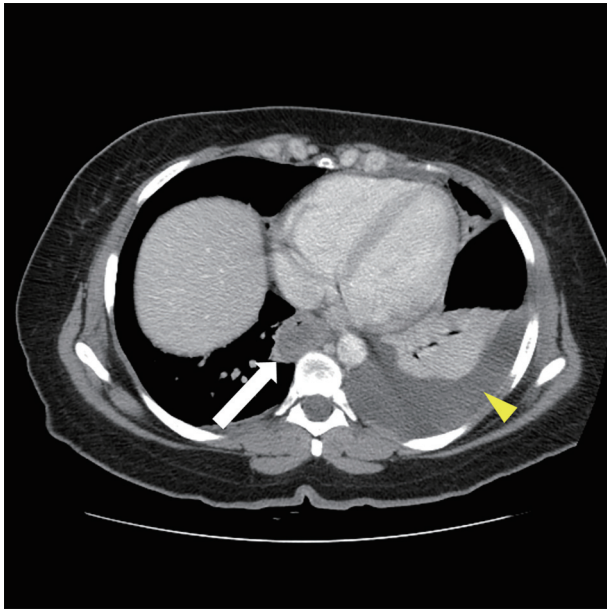


Figure 1. Abdominal CT, thickening of distal esophagus (white arrow) is evident. A left-sided pleural effusion is also seen (yellow arrow head).

was noted (Fig. 3). Gastric antrum and body-type mucosa showed evidence of chronic gastritis with mild lamina propria eosinophils (0 - 5 per high power field (HPF)) and focal stromal fibrosis with > 40 eosinophils per HPF. Duodenal mucosa revealed eosinophilic duodenitis with diffuse lamina propria eosinophils (Fig. 4).

An immunophenotypic analysis of peripheral blood showed eosinophilia and no evidence of a B-cell or T-cell lymphoma or signs of acute leukemia. In view of the absence of causes to explain the degree of eosinophilia, the diagnosis of HES was made. The patient was started on prednisone 60 mg daily and budesonide BID by nebulization with improvement in diarrhea and abdominal pain. On the 10th day of her hospital course, the patient was discharged home. A complete blood count on discharge showed a significant decrease in WBC with return of eosinophils to normal proportions.

The patient was seen in the clinic 7 days after discharge. She reported being well with minor abdominal pain. On physical examination, there was still mild abdominal tenderness to palpation. Prednisone was tapered to 50 mg daily. Complete blood count the day before the visit showed sustained suppression of eosinophils with a WBC of 11.4 cells/ μ L, absolute eosinophilic count of 0.9 cell/ μ L, Hgb of 12.7 g/dL, and Plt of 381,000/ μ L.

Discussion

The differential diagnosis of eosinophilia (defined as an absolute eosinophil count (AEC) > 500 cells/ μ L [3]) is broad and includes a wide range of conditions, from allergic to autoimmune disease (Table 1) [2, 4, 5]. The first step in the approach of eosinophilia is distinguishing between primary (where the main defect is affecting the regulation of eosinophils production) and secondary (or reactive) eosinophilia.

To identify the etiology of the eosinophilia, a complete and thorough history is required. Some essential aspects include different signs and symptoms that are suggestive of end-organ compromise by eosinophilia (skin, pulmonary, cardiac, GI, skin, and neurologic), a complete medications and natural supplements list, past medical history including neoplastic conditions, allergic/atopic symptoms, travel and social history, and a complete physical examination to identify features suggestive of a specific disorder or etiology [5]. Medications are a frequent cause of eosinophilia, and the development of eosinophilia may not coincide with the introduction of the medications. Therefore, all medications taken by the patient should be evaluated as possible causes of eosinophilia. Allergy is also a common cause of eosinophilia; however, as a rule of thumb, it should not cause an AEC of > 1,500 cells/ μ L [2]. Other important etiologies are infections, most of which are parasitic. *Strongyloides spp* infection is common in patients from endemic regions (tropical/warm regions) or exposed to soil or waters contaminated with feces. Identification of *Strongyloides spp* is essential given the risk of hy-

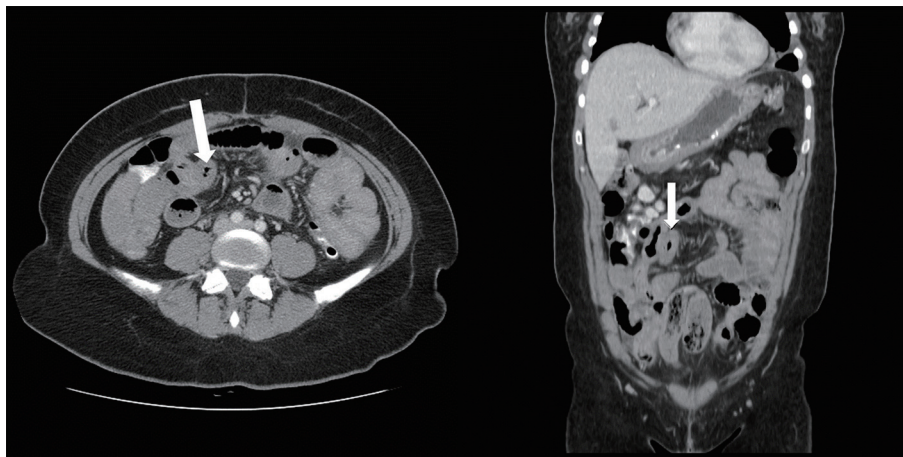


Figure 2. Abdominal CT, small bowel thickening (arrow) is evident in both axial (right) and coronal images.

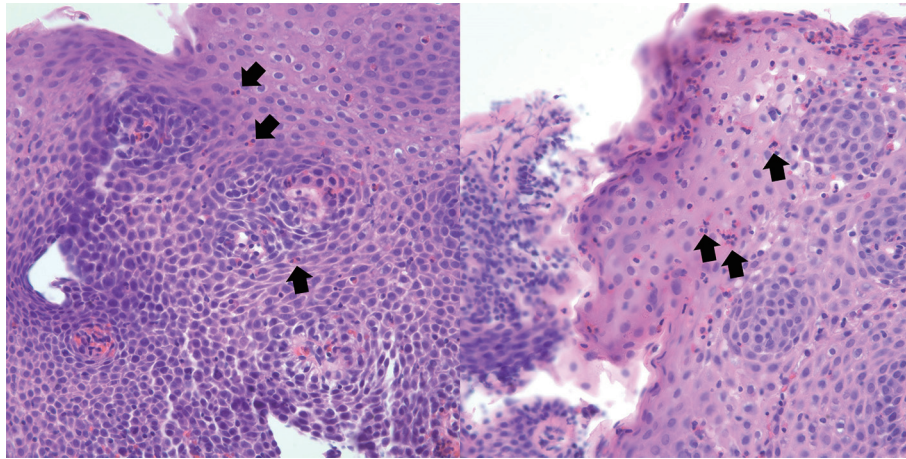


Figure 3. Hematoxylin and eosin stains of proximal (right) and distal (left) esophagus. Abundant eosinophils present (arrow), with the formation of eosinophilic abscess.

perinfestation syndrome if the patient is started on immunosuppressive therapy for presumed immune-related causes of eosinophilia. Other causes of infectious eosinophilia include helminth infections such as *Sarcocystis hominis*, *Toxocara spp*, *Schistosoma spp* and viral infections including EBV and HIV infection [5].

In cases where no secondary cause of eosinophilia is identified, a diagnosis of HES should be considered. HES is a heterogeneous syndrome described by Chusid et al in 1975 [6] after a cohort of patients with unexplained eosinophilia and end-organ damage. After multiple classifications and diagnostic criteria, the definition was refined by Simon et al [7] in 2010 to include some variation of this syndrome and provide a functional approach (as opposed to World Health Organization classification, where a merely descriptive ap-

proach is used [3]). Currently, HES is defined as peripheral eosinophilia $> 1,500$ cells/ μL in two different occasions or evidence of tissue hypereosinophilia with symptoms and peripheral eosinophilia after excluding secondary causes [7]. HES is divided into six sub-types [7]: 1) myeloproliferative HES (M-HES), where patients have features that resemble myeloproliferative neoplasm (such as cytopenia, spleno/hepatomegaly, elevated B12, and with a higher incidence in male population) often with monoclonal eosinophilia with distinct mutations or fusion proteins such as fusion gene PDGFRA-FIP1L1; 2) lymphocytic HES (L-HES) where a monoclonal T-cell population is often identified, and leads to eosinophilia through cytokine (usually IL-5) production, presenting with frequent skin compromise; 3) idiopathic HES, with no clear triggers found; 4) overlap HES, where only one system is affected and peripheral eosinophilia is present (eosinophilic GI disease, chronic eosinophilic pneumonia, among others); 5) associated HES, where a disorder known to have eosinophilia is found (such as HyperIgE syndrome, sarcoidosis and inflammatory bowel disease; and 6) familial HES, where multiple generations are affected and usually present after birth [8]. This subdivision not only has a functional purpose, but also represents different phenotypes, different prognosis, and different therapeutic implications [9].

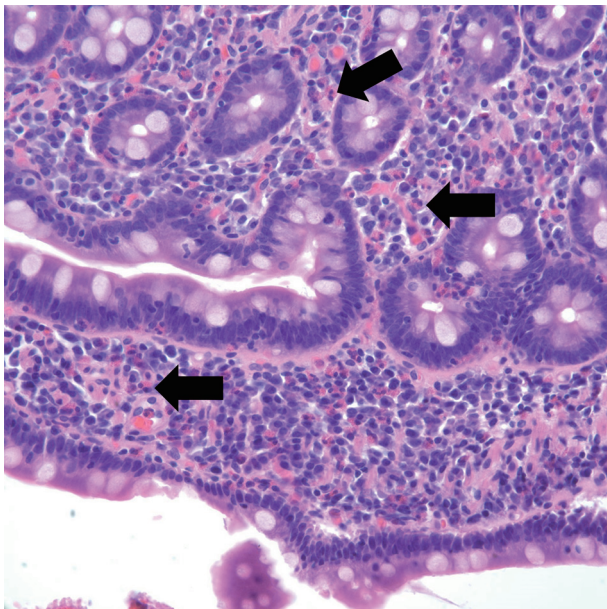


Figure 4. Hematoxylin and eosin stain of duodenal mucosa. Eosinophilic duodenitis with diffuse lamina propria eosinophils (arrow).

Conclusion

The present case represents a young woman with long-standing severe hypereosinophilia and multiple GI complains including vomiting, diarrhea and abdominal pain. Although this was initially thought to represent *Strongyloides spp* infection, the patient was seronegative at the time of presentation and did not respond to treatment. Peripheral blood flow cytometry did not identify any clonal subset of T cells or immature precursors, and other myeloproliferative features were absent. The patient responded well to initial systemic steroid management and was later tapered with no recurrence of symptoms or eosinophilia. The patient's presentation and

Table 1. Etiology of Eosinophilia

Infectious	Viral (HIV, HTLV1, EBV)
	Parasitic (<i>Strongyloides spp</i> , <i>Sarcocystis hominis</i> , <i>Isospora belli</i> , <i>Schistosoma spp.</i> , filariasis)
	Fungal (<i>Coccidioides spp</i>)
Allergic	Bacterial (tuberculosis)
	Asthma
	Atopic dermatitis
Malignancies	Allergic rhinitis
	Solid tumors
	Systemic mastocytosis
Medications	Hematologic malignancies (Hodgkin lymphoma, chronic eosinophilic leukemia, chronic myeloid leukemia)
	Anticonvulsivants (carbamazepine, valproic acid)
	Antidepressives (IRSS, amitriptyline)
	Allopurinol
Hypereosinophilic syndrome (HES)	Antibiotics (beta-lactam antibiotics, trimethoprim-sulfamethoxazole, quinolones)
	Antiretrovirals (efavirenz, abacavir)
	Myeloid HES
	Lymphocytic HES
	Idiopathic HES
Immune deregulation	Associated HES
	Overlap HES
	Familiar HES
	Allergic bronchopulmonar Aspergiliosis
Others	HyperIgE syndrome (Job syndrome)
	Eosinophilic granulomatosis with polyangiitis
	Gleich syndrome
	IgG4 disease
	Inflammatory bowel disease
Others	Adrenal insufficiency
	Sarcoidosis
	Radiation exposure
	Cholesterol emboli

Modified from [2, 5].

response to corticosteroids were consistent with idiopathic HES.

Conflict of Interest

No conflict of interest exists from any of the authors.

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