

Hypereosinophilic syndrome presenting with gastrointestinal manifestations

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SUMMARY

Hypereosinophilic syndrome (HES) is a spectrum of diseases characterised by an elevated eosinophilic count causing end-organ damage. Differential diagnoses of hypereosinophilia are vast and include drug hypersensitivities, allergies, infections, cancers, autoimmune disorders and rare eosinophilic syndromes. Herein, we describe a case of a patient presenting with gastrointestinal (GI) symptoms including progressive dysphagia, abdominal distension, vomiting, diarrhoea and abdominal pain with significant peripheral eosinophilia who was found to have an overlap HES involving the GI tract. This patient's eosinophilia was rapidly corrected with intravenous methylprednisolone, and the patient experienced gradual resolution of clinical symptoms with maintenance oral prednisone. Due to the rarity and diverse presentation of HES, there are few large, longitudinal studies that describe disease progression and inform treatment guidelines. This case demonstrates the difficulty in designing a treatment regimen for these patients and emphasises the clinical need for improved understanding of HES.

BACKGROUND

Hypereosinophilic syndrome (HES) was first termed by Hardy and Anderson to describe several patients with cardiopulmonary symptoms and hepatosplenomegaly in the context of absolute eosinophilia.¹ Later, the WHO as well as the 2011 Working Conference on Eosinophil Disorders and Syndromes provided criteria for the classification of eosinophilic disorders.^{2,3} Hypereosinophilia (HE) can be broadly defined as blood HE (>1500 eosinophils/ μL) and/or overabundance of eosinophils in tissue. HES describes blood HE accompanied by organ damage or dysfunction that is attributable to eosinophilia burden. Gastrointestinal (GI) symptoms are a common presentation in HES and can either be present as a single organ manifestation of HES or as a part of multisystem HES.⁴ However, it is unclear whether isolated GI HES commonly progresses to multisystem HES. Additionally, it is unclear if patients commonly become refractory to glucocorticoid therapy. Here, we describe a patient with isolated GI symptoms attributable to eosinophilic burden who experienced a dramatic reduction in eosinophil count and resolution of clinical symptoms following glucocorticoid therapy.

CASE PRESENTATION

A man in his 60s with a history of hypertension presented to the emergency department (ED) with a 3-week history of nausea/vomiting, progressive

dysphagia, abdominal distension and pain, and diarrhoea with incontinence. His symptoms started 1 day after eating shrimp at a restaurant. His symptoms progressed to significant abdominal pain, solid-food dysphagia, diarrhoea with incontinence, abdominal distension and 5 kg weight loss. He visited an ED 3 days after his initial symptoms, where he had a slightly elevated absolute eosinophil count at 725 K/ μL . At that visit, he was prescribed pantoprazole, metoclopramide and a 7-day course of levofloxacin. After 17 days without improvement, he presented to our ED and was found to have leucocytosis due to significant HE (absolute eosinophil count: 13 683 K/ μL). Other pertinent laboratory findings are shown in [table 1](#). CT of the chest, abdomen and pelvis with intravenous contrast on the following morning showed extensive circumferential wall thickening throughout the oesophagus, mild gastric wall thickening suggesting gastritis, diffuse small bowel wall thickening with extensive enteritis, no colon involvement, hepatic cysts and hypodensities, and a small amount of ascites.

The initial concern was for an infectious aetiology or hypersensitivity reaction, given the patient's significantly lower eosinophil count just 17 days previously. A GI pathogen PCR panel showed no evidence of common viral, bacterial or parasitic infections. Additionally, stool ova and parasite gross and trichrome evaluations were negative, and *Strongyloides* serologies were done, which were negative. Peripheral smear revealed hypervacuolated absolute eosinophilia with no abnormalities noted in the red blood cells or platelets ([figure 1](#)). Flow cytometry of the peripheral blood showed no monoclonal B-cell population or aberrant T-cell antigen expression or increase in circulating myeloblasts. Fluorescence in situ hybridisation (FISH) studies revealed no rearrangement for the PDGFRB, FGFR1 and other mutations commonly present in myeloproliferative HES. IgA, IgG and IgM were within normal limits (70–400 mg/dL, 700–1600 mg/dL and 33–255 mg/dL, respectively). B_{12} and tryptase were also within normal limits (211–946 pg/mL and <10.9 $\mu\text{g/mL}$, respectively). IgE level was 457 IU/mL (normal range 0–100 IU/mL). Immunoglobulin G subclass 4 was slightly elevated (normal range 1–123 mg/dL). The patient did not have a history of allergic rhinitis or asthma. Their only reported drug allergy was famotidine, which the patient had not taken recently. The patient's symptoms did not improve, and no aetiology was found, so the gastroenterology service was consulted for further investigations.



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Table 1 Initial laboratory findings

Laboratory investigations	Results	Reference ranges
Sodium	136 mEq/L	135–148 mEq/L
Chloride	100 mEq/L	98–112 mEq/L
CO ₂	24 mEq/L	24–31 mEq/L
Blood urea nitrogen	9 mg/dL	8–23 mg/dL
Creatinine	1.16 mg/dL	0.70–1.20 mg/dL
Albumin	3.4 g/dL	3.5–5.0 g/dL
Alkaline phosphatase	94 U/L	40–129 U/L
Aspartate aminotransferase	16 U/L	10–50 U/L
Alanine transaminase	16 U/L	5–50 U/L
Total bilirubin	0.6 mg/dL	0.0–1.2 mg/dL
White blood cells	19.83 K/ μ L	4.50–11.00 K/ μ L
Haemoglobin	14.3 g/dL	14.0–18.0 g/dL
Platelets	309 K/ μ L	150–400 K/ μ L
Lipase	25 U/L	13–60 U/L
Amylase	88 U/L	28–100 U/L
Lactic acid	1.1 mmol/L	0.5–2.2 mmol/L
C reactive protein	0.58 mg/dL	0.00–0.58 mg/dL
Erythrocyte sedimentation rate	5 mm/hour	0–10 mm/hour

INVESTIGATIONS

The gastroenterology service conducted esophagogastroduodenoscopy (EGD) and colonoscopy with biopsies. EGD showed irregular Z-line and abnormal motility in the lower oesophageal sphincter that raised concerns for achalasia. The oesophagus exam was otherwise normal (figure 2A). The stomach showed striped mildly erythematous mucosa (figure 2B). Duodenal exam revealed one localised erosion without bleeding in the duodenal bulb and two medium-sized semipedunculated polyps without bleeding in the second portion of the duodenum; the remainder of the duodenum exam was normal. No abnormalities were found in the colon. Oesophagus biopsies showed superficial squamous mucosa with variable degrees of basal cell hyperplasia, basal reactive epithelial changes, and markedly increased intraepithelial eosinophils with small eosinophilic microabscesses and eosinophil degranulation. Focally, there were more than 100 eosinophils per high-power field (figure 3). Gastric biopsies showed histological features of moderate chronic active gastritis with scattered eosinophils along with positive *Helicobacter pylori*

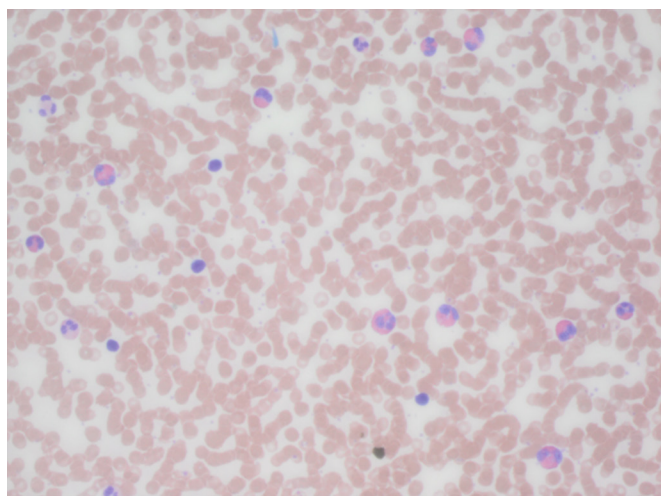


Figure 1 Peripheral smear showing the increasing number of circulating eosinophils.

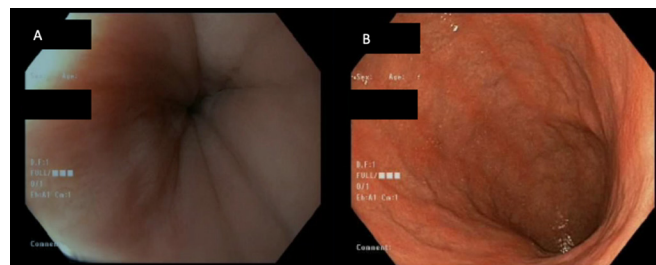


Figure 2 (A) Normal-appearing mucosa (oesophagus). (B) Slightly erythematous-appearing mucosa (stomach).

immunostain. Duodenum and colon biopsies were negative for significantly increased eosinophils. The haematology service was consulted, and bone marrow biopsy was not performed due to low suspicion of primary myeloproliferative HE following the normal flow cytometry study and quick rise in eosinophils over several weeks.

DIFFERENTIAL DIAGNOSIS

The initial concern for an infectious aetiology was ruled out by a negative GI panel and normal *Strongyloides* serologies. In addition, the patient did not have typical risk factors for *Strongyloides* such as recent travel or an immunocompromised state. Hypersensitivity to the three new medications (pantoprazole, metoclopramide and levofloxacin) was also ruled out: these medications have not previously been associated with drug hypersensitivity, and the patient began experiencing GI symptoms prior to using them. The quick rise in eosinophils made immunological disorders, such as hyper-IgE syndrome, sarcoidosis and IgG4-related disease, unlikely. A negative antinuclear antibody test, normal inflammatory markers and normal-appearing mucosa on endoscopy made inflammatory bowel disease unlikely. Given the patient's symptoms, the involvement of multiple parts of the GI tract and the relative sparing of other organs including heart, lungs and kidneys, the patient was diagnosed with overlap HES involving the GI tract.

TREATMENT

Because *Strongyloides* serologies take several days, we empirically treated for *Strongyloides* with two doses of ivermectin 200 μ g/kg, which decreased absolute eosinophil count slightly but did not improve symptoms. We subsequently treated him with methylprednisolone 1 g intravenously, which dramatically decreased his absolute eosinophil count (figure 4). Afterwards, his symptoms improved significantly, with reduced dysphagia, no regurgitation with meals, no bowel incontinence, less frequent episodes of diarrhoea, no abdominal pain and slight improvement in abdominal distension. On discharge, the patient was started on prednisone 40 mg/day with plans to follow up with haematology. To address the *H. pylori*, the patient was discharged with triple therapy clarithromycin, amoxicillin and pantoprazole 40 for 14 days.

OUTCOME AND FOLLOW-UP

The patient was seen in clinic 2 weeks after discharge, and his symptoms had improved significantly. There were no further episodes of diarrhoea or vomiting, his abdominal bloating had resolved, and his weight had stabilised. His appetite had returned, and his weight was back to his previous baseline. His eosinophil count on laboratory findings had remained less than

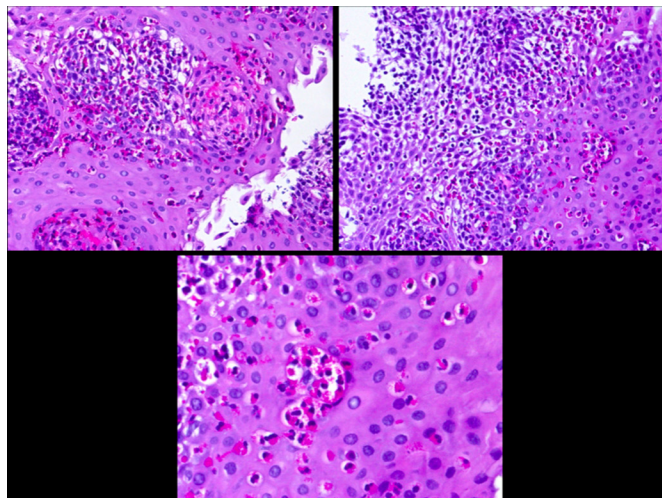


Figure 3 Oesophageal biopsies showing markedly increased intraepithelial eosinophils with small eosinophilic microabscesses and eosinophil degranulation.

50. His prednisone dose has been tapered to 15 mg with plans to taper further after repeating blood counts in 2–3 weeks.

DISCUSSION

In the case presented here, a patient with isolated GI symptoms attributable to high eosinophil burden responded to glucocorticoid treatment with a dramatic reduction in eosinophil count and a progressive reduction in symptoms. Glucocorticoids' effectiveness in treating eosinophilic disorders was recognised in the early 20th century, and they remain a first-line therapeutic for HES today.^{5–7} While not fully understood, the mechanism underlying glucocorticoid-induced eosinopenia appears to be multifactorial, in that glucocorticoids lead to eosinophil bone marrow sequestration, apoptosis and gene transcription changes.^{8,9} Glucocorticoids are not effective for all patients with HES, but improvements in the classification and understanding of HES have helped to identify disease characteristics that predict response to glucocorticoids. Patients with clinical features

suggestive of myeloproliferative HES—including elevated B_{12} , hepatosplenomegaly or known chromosomal abnormalities that lead to clonal eosinophilia—do not respond well to glucocorticoids.⁶ Similarly, patients with lymphocytic subset HES are poor responders.¹⁰ On the other hand, patients with high IgE and no hepatosplenomegaly respond well to glucocorticoids; those who initially respond profoundly to glucocorticoids continue to respond well.¹⁰ The patient presented in this case exhibited high IgE levels, dramatic and persistent reduction of eosinophils following initial glucocorticoid treatment, and lack of myeloproliferative features, which suggest a good prognosis with early glucocorticoid intervention. However, the lack of large, prospective studies or studies with long-term outcomes of organ-specific HES yields uncertainty regarding clinical decisions for these patients.

A particularly unclear aspect of HES is disease progression. Cardiac dysfunction is a major cause of mortality in patients with HES and presents in 40%–50% of them.^{11,12} HES can be classified as single-organ, but whether isolated HES commonly progresses to multisystem involvement and cardiac dysfunction has not been systematically addressed. One retrospective study of 22 patients with multisystem HES noted that 8 of them initially presented with isolated GI symptoms.⁴ Another retrospective study that examined echocardiograms of patients with idiopathic HES noted that 12 out of 85 had no echogenic abnormalities at initial presentation, but only 5 of those 12 had normal echocardiograms 2 months–11 years later.¹³ These studies are limited by their low patient numbers and retrospective design, so they likely overestimate the proportion of patients who progress to multisystem and cardiac symptoms. However, these studies highlight the need to clinically follow up patients with HES and monitor for symptom progression.

In summary, we present a case of HES with isolated GI symptoms that responded to high-dose methylprednisolone followed by prednisone taper. The patient's dysphagia, abdominal pain and distension, and diarrhoea with incontinence improved following glucocorticoid intervention. FISH panel ruled out common chromosomal abnormalities related to clonal eosinophilia; flow cytometry showed no evidence of abnormal B-cell or T-cell clones, and extensive, infectious workup was negative,

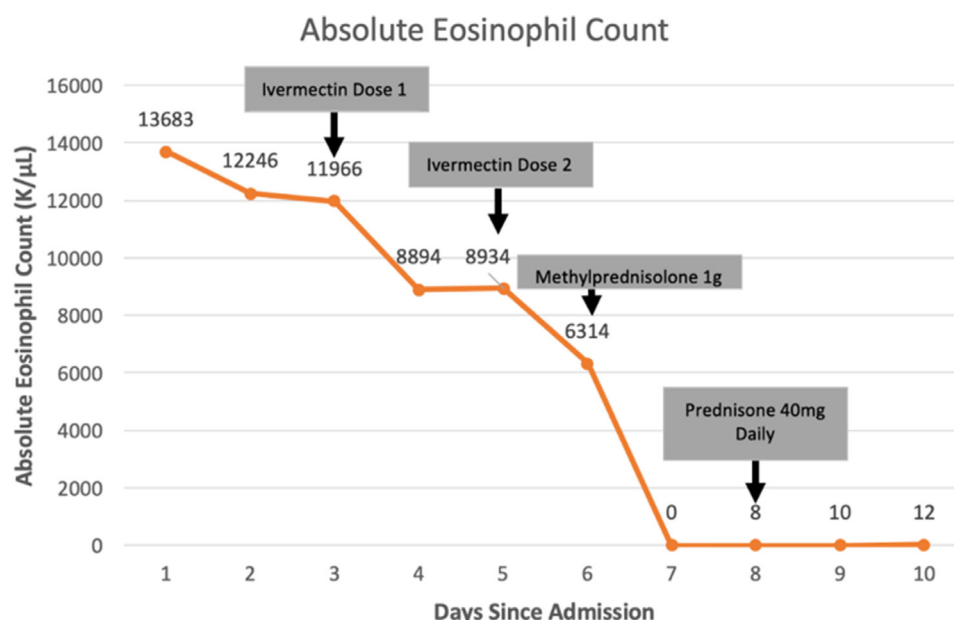


Figure 4 Line graph showing changes in absolute eosinophil count over time with treatments administered.

resulting in a diagnosis of single-organ HES. Echocardiogram at initial presentation showed no evidence of cardiac dysfunction, and the patient has plans for continued outpatient follow-up to evaluate for progression of symptoms. The rarity of HES has prevented comprehensive study of disease progression and long-term treatment response in large patient cohorts. This case highlights the clinical need to better understand HES clinical manifestations and disease progression, as well as predictors of long-term glucocorticoid response.

Learning points

- ▶ Thorough patient history and diagnostic workup are needed to rule out common causes of eosinophilia, including drug/food hypersensitivity reactions and parasitic infections.
- ▶ Clinical follow-up is essential for early detection of disease progression or steroid refractory hypereosinophilic syndrome (HES).
- ▶ Evaluation for myeloproliferative or lymphocytic subsets of HES will inform treatment options, as these are less responsive to glucocorticoids.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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