

Hyper-eosinophilic syndrome: An uncommon cause of chronic abdominal pain in an elderly male

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Abstract

Hypereosinophilia is defined as an absolute eosinophil count of $\geq 1.5 \times 10^9/L$, and its presence with involvement of at least one organ system defines the hypereosinophilic syndrome. It may occur with parasitic infestation, connective tissue disorder or rarely in clonal disorders such as eosinophilic leukaemia. Organ systems that may be involved include the cardiovascular, central nervous, respiratory and gastrointestinal systems. In the latter, a wide spectrum of clinical presentation may be seen from trivial, to debilitating or rarely fatal. We report an elderly male with a history of bronchial asthma, obstructive sleep apnoea and food allergy who presented with chronic abdominal pain and weight loss. Abdominal examination and routine evaluation were essentially normal other than a peripheral hyper-eosinophilia. We witnessed a brisk and lasting response to an elimination diet and corticosteroids.

Keywords

Hypereosinophilic syndrome, eosinophilic gastroenteritis, corticosteroids

Introduction

Eosinophils, basophils and neutrophils are subpopulations of granulocytes. Eosinophils were named by Paul Ehrlich in 1879 as they can be stained by the acidophilic dye, eosin.¹ In healthy individuals, eosinophils in peripheral blood constitute 1–5% of the total number of leucocytes. The absolute eosinophil count (AEC) in normal healthy individuals ranges from 50 to $500 \times 10^9/L$; there occurs a diurnal variation in blood eosinophil levels. The count is usually lowest in morning and highest in evening, owing to variation in level of stress hormones.² Normally, stress, fever and both bacterial and viral infections reduce blood eosinophil levels, while parasitic infestations increase them.² In contrast to the peripheral blood, eosinophils are present only in a few body tissues which include the gastrointestinal tract (GIT), breast, uterus, thymus and spleen.³

Raised blood eosinophils is typically seen in bronchial asthma, urticaria, food or drug allergy, eosinophilic oesophagitis, atopic dermatitis, helminthic infestations, eosinophilic leukaemia and the hyper-eosinophilic syndromes (HESs).⁴ In tropical countries, infections, especially parasitic infestations, contribute to c.33% of all cases of eosinophilia.⁵ With significant

recent improvement in laboratory techniques, the aetiology of hypereosinophilia can now be determined in up to 50% of cases previously classified as idiopathic.⁵ There is also significant progress in classification of hypereosinophilia. A classification system proposed by the World Health Organization (WHO)⁶ purely deals with clonal causes, but the definitions and classification system proposed by the International Cooperative Working Group on Eosinophil Disorders² are comprehensive.

HES is diagnosed on the basis of hypereosinophilia of at least one month's duration checked at least twice, together with eosinophil-mediated organ dysfunction.

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All other potential causes of hypereosinophilia must be excluded to establish a diagnosis of HES. A patient with HES may present with single or multiple organ involvement. Involvement of the GI system is seen in c.25% of cases of HES either in isolation or with involvement of other organ systems. Patients with isolated GI involvement at initial presentation may later have involvement of other organ systems.⁷ Common clinical features in patients with GI involvement include diarrhoea, vomiting and abdominal pain.⁸

Case report

A 65-year-old male with a history of bronchial asthma, obstructive sleep apnoea, urticaria and allergy to dust, pollen and penicillin and fruits, including bananas and sugar apple, presented with history of epigastric pain and postprandial fullness for six months. The pain was dull, aching and intermittent without any specific aggravating or relieving factors. On evaluation, he had hypereosinophilia with AEC of $1 \times 10^9/\text{L}$. Erythrocyte sedimentation rate (ESR) was elevated at 36 mm/1st h. Gastro-duodenoscopy and colonoscopy were normal.

Contrast-enhanced CT abdominal scan revealed sub-centimetric mesenteric lymphadenopathy and minimal ascites. On the basis of these investigations, he was commenced on anti-tubercular therapy, which, however, worsened his symptoms.

On examination at our centre, the patient was conscious, co-operative and well-oriented. There was no pallor, jaundice, clubbing, cyanosis or lymphadenopathy. However, pitting pedal oedema was present. There was mild epigastric tenderness on deep palpation, but no hepatosplenomegaly or ascites. Examination of the ear, nose and throat was normal.

Laboratory tests showed anaemia (Hb 125 g/L), leucocytosis ($16.1 \times 10^9/\text{L}$). The AEC was $9.6 \times 10^9/\text{L}$. A peripheral blood smear showed normocytic normochromic red blood cells with eosinophilic leucocytosis. Liver function showed hypoalbuminaemia with serum albumin of 28 g/L. Renal function was within normal limits. Serological markers for hepatitis B, C and HIV were negative. Serological tests for parasites including IgM and IgG antibodies for toxoplasma, toxocara, trichinella and microfilaria were all negative. Routine and microscopic examination of the stools was negative for

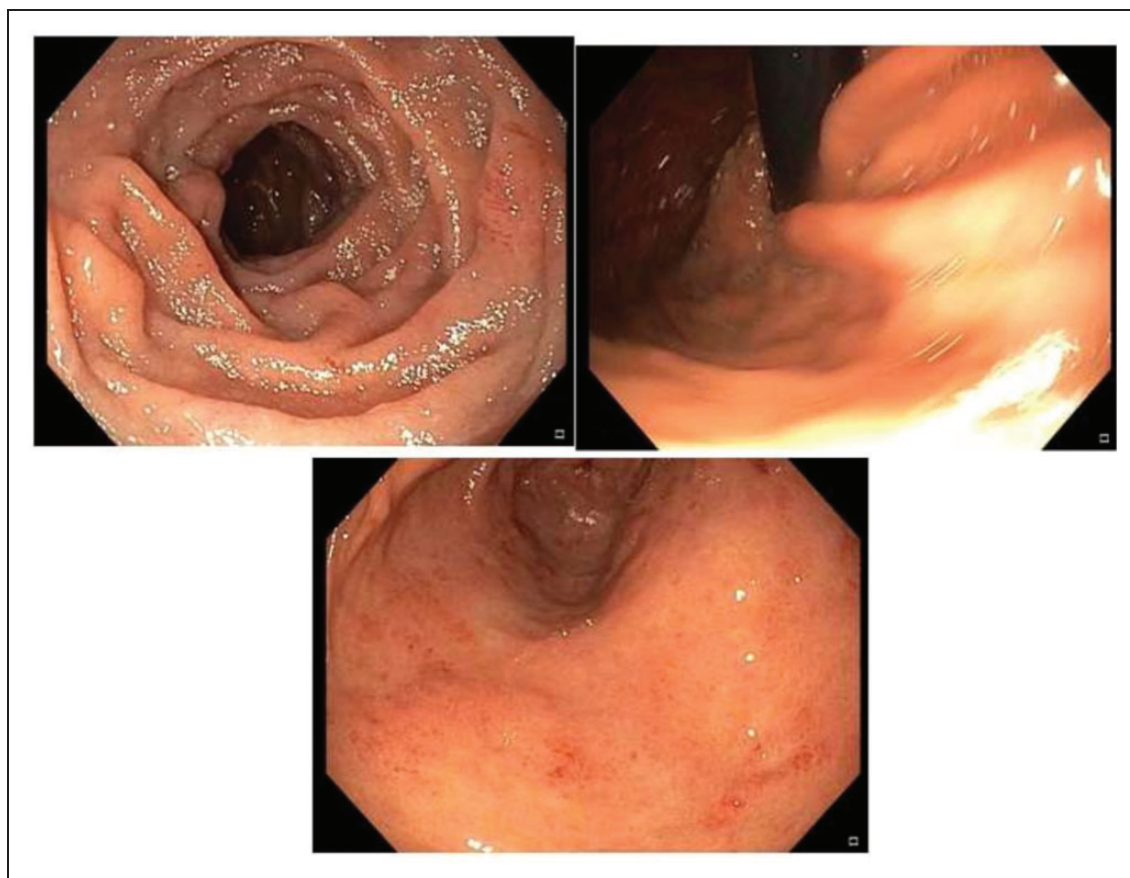


Figure 1. Gastroduodenoscopy showing erosions in fundus/body/antrum of stomach and second part of duodenum.

ova and cysts. ESR was elevated (78 mm/1st h). Serum IgE was elevated, while anti-nuclear antibody and anti-neutrophilic cytoplasmic antibody were negative.

Gastro-duodenoscopy showed erosions in the stomach and second part of the duodenum (Figure 1). Biopsies taken from esophagus, stomach and duodenum (Figure 2) revealed eosinophilic infiltrate in the lamina propria with eosinophil count of more than 50/HPF in the duodenum. Colonoscopy was normal apart from a small caecal sessile polyp, which, on histopathological examination, turned out to be a simple hyperplastic polyp.

Bone marrow aspiration (Figure 3) revealed a predominance of eosinophil precursors without atypical cells or dysplasia, while biopsy showed mature and immature eosinophils. Clonal HESs, *FIP1L1-PDGFR* (F/P)⁵ mutation analysis was negative. Immunophenotyping of mature T cells was likewise normal. Abdominal CT scan was normal other than finding a few enlarged mesenteric lymph nodes and panniculitis with minimal ascites. The electrocardiogram, echocardiogram and pulmonary function tests were all normal.

Thus, a diagnosis of eosinophilic duodenitis was made. Treatment with oral prednisolone 40 mg/day

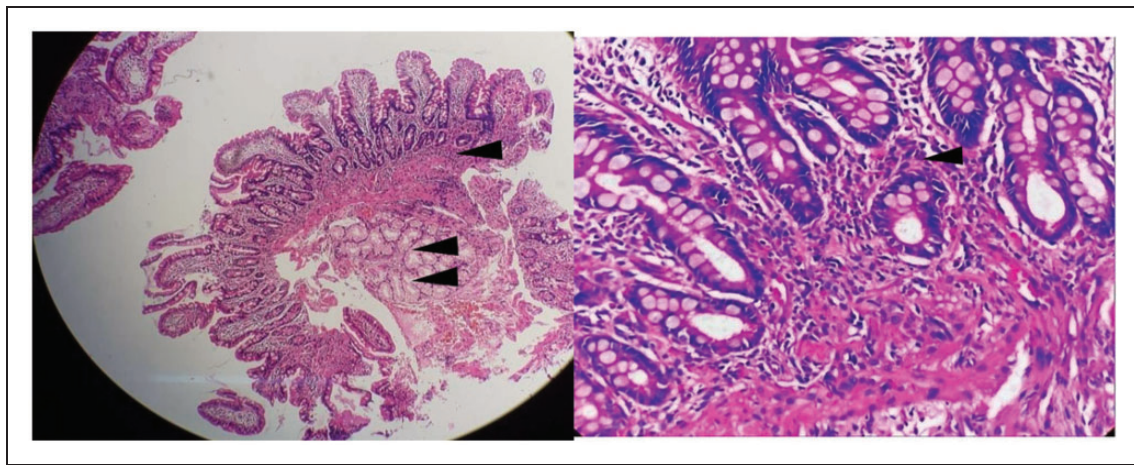


Figure 2. Left panel, duodenal biopsy: HE (40×), arrow head showing inflammation of lamina propria while double arrow head showing Brunner's gland characteristics of duodenal mucosa. Right panel, duodenal biopsy: HE (400×), Arrow head showing lamina propria reveals inflammation predominant eosinophils > 50/HPF.

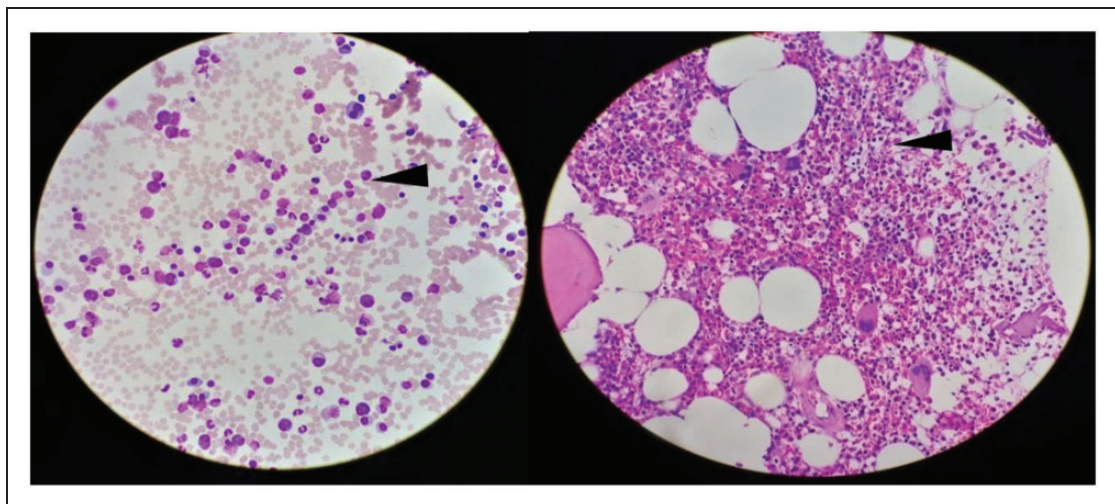


Figure 3. Left panel, bone marrow aspiration cytology: HE (400×), arrow head showing mildly predominance of eosinophil precursors without any atypical cells and dysplasia. Right panel, bone marrow biopsy: H and E (400×), arrow head showing mature and immature eosinophils.

Table 1. Case reports describing HES with GI involvement.¹⁶⁻¹⁸

Author/year	Clinical features	Examination	Investigations	Histopathology	Final diagnosis	Treatment
Jeon et al. ¹⁶	56-year-old, male alternating constipation/diarrhoea: three months Abdominal pain: five days Bloody diarrhoea: five days Chronic cough	Tenderness over lower abdomen	AEC: 12,000/ μ L CT chest: Nodular opacity CT abdomen: liver abscess Gastroduodenoscopy: erythematous duodenum and stomach Colonoscopy: Multifocal erythematous and oedematous mucosa	Duodenal biopsy: eosinophilic infiltrates Colonoscopic biopsy: eosinophilic infiltrates	IHES with involvement of lungs, liver and gastrointestinal system	Corticosteroids for six weeks followed by tapering
Iyanat and Hurairah ¹⁷	20-year-old male Progressive jaundice: seven months	Signs of malnutrition	AEC: 15,000/ μ L TSB-9.7, AST-1204 IU/mL ALT-721 IU/mL ALP-153 IU/mL CT abdomen: loss of colonic haustrations Colonoscopy: oedematous/erythematous/ulcerated mucosa	Eosinophilic infiltrates Liver biopsy: eosinophilic infiltrates in portal triad No interface: hepatitis/rosetting	IHES with involvement of liver and colon	Corticosteroids for six weeks followed by tapering
Vui et al. ¹⁸	80-year-old, Male Non pruritic rashes upper limb: two months Melaena: two days	Annular lesion on left forearm with erythematous oedematous margins and clear centre	AEC: 8300/ μ L ECG: AF with variable AV block CT thorax: Bilateral upper lobe alveolitis and peripherally located patchy consolidation	–	IHES with GI, cardiac, pulmonary and dermatological involvement	Corticosteroids for 10 months

AEC: absolute eosinophil count; CT: computerized tomography; HP: histopathology; IHES: idiopathic hypereosinophilic syndrome; TSB: total serum bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ECG: electrocardiography; AF: atrial flutter; AV: atrioventricular; GI: gastrointestinal.

was commenced. Elimination diet was also introduced. After three days, the intensity of his abdominal pain reduced, and by 10 days, he was pain-free.

AEC reduced to $1.3 \times 10^9/L$. He was discharged on oral prednisolone, elimination diet and advised to continue for six weeks. By then, he was asymptomatic; the AEC remained within normal limits, and his serum albumin came back to normal levels, with disappearance of pedal oedema. Abdominal ultrasonography showed complete resolution of ascites. The dose of prednisolone was therefore reduced and was tapered off. A repeat endoscopic duodenal biopsy to confirm histologic resolution is planned.

Discussion

A quarter of patients with HES have involvement of the GI system, with a third having a history of atopy, allergic rhinitis and bronchial asthma. Half of these have elevated IgE levels.⁹ Patients may present with ascites, diarrhoea, gastritis, colitis or even pancreatitis. Clinical features depend on the site and the depth of involvement of GIT. Patients with eosinophilic esophagitis commonly present with dysphagia, while eosinophilic gastritis, enteritis and colitis commonly present with bloating and abdominal pain. HES confined to the mucosa can present with abdominal pain, nausea, vomiting, diarrhoea, rectal bleeding, anaemia, protein-losing enteropathy, malabsorption and weight loss, and rarely, involvement of muscular layer may cause intestinal obstruction. Eosinophilic ascites denotes involvement of serosal layer.⁸ Rarely, there may be eosinophilic vasculitis which may cause intestinal perforation.¹⁰

Cardiac involvement is seen in c.60% of cases, and its most common feature is endomyocardial fibrosis which carries a poor prognosis.¹¹ Cardiac involvement is the most common cause of mortality in HES. Those with initial GI symptoms may later have involvement of cardiac or other systems.⁷ Pulmonary manifestations are seen in c.44%, and cough is present in a quarter of these.¹²

The diagnosis is confirmed by endoscopic biopsy of an involved GI segment. In healthy individuals, the oesophageal mucosa lacks eosinophilic infiltration, but the mucosa of stomach, small and large intestines may have infiltration of eosinophils in the lamina propria of mucosal. The threshold of diagnosis of eosinophilic esophagitis, gastritis and enteritis is 15, 30 and 50/HPF, respectively.¹³

Elimination diet and corticosteroids produce a clinical response in c.85%.⁹ The elimination diet involves exclusion of six highly allergenic substances: dairy products, wheat, nuts, eggs, soy and sea foods. Its use, along with corticosteroids, helps to produce an

early clinical remission in eosinophilic gastrointestinal disorders. This diet is also useful in maintaining remission after withdrawal of corticosteroids.^{9,14} In patients with F-P mutation positivity, imatinib mesylate is used as a first line agent. For patients with idiopathic HES not responding to corticosteroids, immunosuppressive agents including azathioprine, methotrexate, 6-mercaptopurine and cytarabine have been used with success.¹⁵ Other agents useful in steroid refractory HES include interferon- α and interleukin-5 antagonists including mepolizumab and reslizumab.¹⁵ Published case reports describing HES with GI involvement are elaborated in Table 1.¹⁶⁻¹⁸ Close follow-up, particularly in relation to development of other organ system involvement is essential.

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