A case of hypereosinophilic syndrome presenting with intractable gastric ulcers

Tae Young Park, Chang Hwan Choi, Suh Yoon Yang, In Soo Oh, In-Do Song, Hyun Woong Lee, Hyung Joon Kim, Jae Hyuk Do, Sae Kyung Chang, Ah Ra Cho, Young Joo Cha

Abstract
We report a rare case of hypereosinophilic syndrome (HES) presenting with intractable gastric ulcers. A 71-year-old man was admitted with epigastric pain. Initial endoscopic findings revealed multiple, active gastric ulcers in the gastric antrum. He underwent Helicobacter pylori (H pylori) eradication therapy followed by proton pump inhibitor (PPI) therapy. However, follow-up endoscopy at 4, 6, 10 and 14 mo revealed persistent multiple gastric ulcers with a review of the literature.

INTRODUCTION
Hypereosinophilic syndrome (HES) is a rare disorder characterized by the overproduction of eosinophils in the bone marrow with persistent peripheral eosinophilia, tissue infiltration, and end-organ damage by eosinophil infiltration and the secretion of mediators. The diagnosis of HES is based on marked eosinophilia exceeding 1500/mm³, a chronic course longer than 6 consecutive months, exclusion of parasitic infestations, allergic diseases and other etiologies for eosinophilia, and signs and symptoms of eosinophil-mediated tissue injury. While HES can involve multiple organ systems, including bone marrow, heart, lung, liver, lymph node, muscle, and nerve tissue, gastrointestinal tract involvement is rare. To date, only a handful of cases of HES presenting with gastritis or enteritis have been reported worldwide, and HES presenting with intractable gastric ulcers has not been reported. We report our case of a 71-year-old male patient with HES presenting with multiple intractable gastric ulcers with a review of the literature.

CASE REPORT
A 71-year-old man presented with epigastric pain. He underwent cholecystectomy 20 years previously due to acute cholecystitis with gallstones, and has intermittently taken nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids on account of degenerative arthritis.
for 15 years. Other symptoms, as well as his past medical and family history, were otherwise unremarkable. The initial physical examination showed a flat, soft abdomen with normoactive bowel sounds with no sign of direct or rebound tenderness and no hepatosplenomegaly. Thoracic auscultation revealed no remarkable results. Routine complete blood count reported a leukocyte count of 7790/mm$^3$ with 5.3% eosinophils, hemoglobin level of 12.1 g/dL, and a platelet count of 19 8000/μL. There were no noteworthy findings on simple chest and abdominal radiography. No specific cardiac abnormalities on standard 12-lead electrocardiogram (ECG) or Doppler echocardiogram were detected. ECG revealed normal sinus rhythm and the echocardiogram showed normal global left ventricular systolic function (estimated ejection fraction 70%).

Esophagogastroduodenoscopy (EGD) findings revealed several active gastric ulcers in the antrum of the stomach (Figure 1A). Biopsy findings showed an ulcer with Helicobacter pylori ($H$ pylori). He underwent $H$ pylori eradication therapy (lansoprazole 30 mg twice a day, clarithromycin 500 mg twice a day and amoxicillin 1000 mg twice a day for 7 d) followed by a proton pump inhibitor (PPI) and gastroprotective agent therapy for 2 mo. Follow-up EGD and biopsy performed after 2 mo showed that $H$ pylori was eradicated, whereas multiple gastric ulcers were still noticeable with only slight improvement (Figure 1B). Follow-up endoscopy at 4, 6, and 10 mo showed persistent multiple gastric ulcers in the antrum despite continuous PPI treatment. Therefore, he was readmitted after 14 mo for etiological evaluation of the intractable gastric ulcers.

In the follow-up laboratory data, routine complete blood count showed a leukocyte count of 18 380/mm$^3$ with 43% eosinophils, and an absolute eosinophil count of 7903/mm$^3$. Serum chemistry showed: Aspartate aminotransferase/alanine aminotransferase (AST/ALT), 39/97 IU/L; total bilirubin/direct bilirubin, 0.3/0.1 mg/dL; alkaline phosphatase, 235 IU/L; total protein/albumin, 7.3/3.2 g/dL; and BUN/Cr, 14/1.1 mg/dL. Serum immunoglobulin E level was elevated to 2147 kU/L. In pulmonary function tests, pre-bronchodilator FEV1 was 2090 mL (95% of predicted value) and the bronchodilator response was negative. The allergen skin test was negative. There were no parasites or ova in stool specimens. ELISA of paragonimiasis westermani, Clonorchis sinensis, cysticercus, and sparganum were negative. Anti-HIV antibody and anti-nuclear antibody were negative.

In the EGD findings, multiple gastric ulcers were still found in the antrum of stomach (Figure 1C). The endoscopic biopsy specimen revealed prominent eosinophilic infiltrations of > 20 cells/HPF (Figure 1D). A retrospective review of the previous endoscopic biopsy specimens disclosed eosinophilic infiltration at the antrum which was overlooked at the initial evaluation.

The chest computed tomography (CT) scan showed very tiny nodules in both lungs and approximately 15-mm-sized nodular lesions in the posterior basal segment of the right lower lobe (Figure 2A and B). In the abdominal-pelvic CT scan, multiple, small, and ill-defined low density lesions were found in both lobes of the liver (Figure 3A and B). The liver biopsy showed eosinophilic infiltration in the portal tract and sinusoid (Figure 3C and D).

The peripheral blood smear report showed that there were no immature or dysplastic cells or morphologically abnormal eosinophils. The bone marrow aspiration smear showed an M:E ratio of 3:81 and an elevated eosinophil count of 22.2% (Figure 4A). Bone marrow biopsy findings also indicated eosinophilic hyperplasia, with increased cellularity of 70% and normal distribution of erythroid, myeloid, and megakaryocytic cell lineages (Figure 4B). The Fip1-like 1-platelet-derived growth factor receptor A
fusion gene (FIP1L1-PDGFR-A) rearrangement was not detected and there were no cytogenetic abnormalities. This patient was finally diagnosed with HES involving the stomach, liver, lung, and bone marrow. He was treated with oral prednisolone 60 mg/d and PPI. After two weeks of therapy, clinical manifestations rapidly improved and peripheral blood eosinophilia had subsided.

DISCUSSION

HES is a rare disease characterized by unexplained persistent eosinophilia associated with multiple organ dysfunction[1,2]. In 1968, Hardy and Anderson[10] reported three patients with hypereosinophilia, hepatosplenomegaly, and cardiopulmonary symptoms, and first suggested that they had a nonmalignant disorder that belonged within the spectrum of disease termed hypereosinophilic syndrome. In HES, the degree of end-organ damage is heterogeneous, and there is often no correlation between the level or duration of eosinophilia and the severity of organ damage[1,3]. Also, the clinical manifestations are variable from one patient to another, depending on target-organ infiltration by eosinophils[11,12]. Virtually any tissue or organ can be affected, but cardiac involvement is the major cause of the morbidity and mortality associated with HES[1,3,13]. We did not find cardiac involvement in our patient.

Since Chusid et al[13] reported the analysis of fourteen cases of HES in 1975, some cases of HES involving the gastrointestinal (GI) tract have been reported. Ichikawa et al[4] reported a case of probable HES with a gastric lesion, López Navidad et al[5] reported a case of HES presenting as a form of epithelioid leiomyosarcoma of gastric origin, and Levesque et al[6] reported two cases of HES with predominant digestive manifestations. In Korea, Jung et al[8] reported a case of HES presenting as colitis and You et al[9] reported a case of HES presenting with various GI symptoms. However, HES presenting with intractable gastric ulcers has not been reported. Our patient suffered from HES presenting with multiple intractable gastric ulcers as well as liver, lung, and bone marrow involvement. The exact mechanism of
The idiopathic hypereosinophilic syndrome (IHS) is characterized by persistent peripheral eosinophilia and tissue infiltration by eosinophils, often associated with multiple organ involvement. The diagnosis of IHS is challenging due to the overlap with other eosinophilic disorders and the lack of specific diagnostic criteria. The differential diagnosis of IHS includes eosinophilic gastroenteritis (EG), other forms of eosinophilic enteritis, eosinophilic pneumonia, and eosinophilic meningoencephalitis. The diagnosis of IHS is based on a combination of clinical, laboratory, and histopathological findings. In our patient, a bone marrow biopsy showed eosinophilic hyperplasia, and histopathological examination of multiple organs revealed eosinophilic infiltration. The patient also had clinical symptoms of eosinophilic gastroenteritis, such as abdominal pain and gastrointestinal bleeding. The diagnosis of IHS was confirmed by the presence of characteristic radiologic findings, including characteristic radiologic findings, and the absence of other causes of eosinophilia.

In conclusion, we report a case of IHS presenting with multiple organ involvement. The diagnosis of IHS is challenging due to the overlap with other eosinophilic disorders and the lack of specific diagnostic criteria. The differential diagnosis of IHS includes eosinophilic gastroenteritis (EG), other forms of eosinophilic enteritis, eosinophilic pneumonia, and eosinophilic meningoencephalitis. The diagnosis of IHS is based on a combination of clinical, laboratory, and histopathological findings. In our patient, a bone marrow biopsy showed eosinophilic hyperplasia, and histopathological examination of multiple organs revealed eosinophilic infiltration. The patient also had clinical symptoms of eosinophilic gastroenteritis, such as abdominal pain and gastrointestinal bleeding. The diagnosis of IHS was confirmed by the presence of characteristic radiologic findings, including characteristic radiologic findings, and the absence of other causes of eosinophilia.

REFERENCES
1. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood 1994; 83: 2759-2779
2. Fauci AS, Harleb JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med 1992; 97: 78-92
3. Wilkins HJ, Crane MM, Copeland K, Williams WV. Hypereosinophilic syndrome: an update. Am J Hematol 2005; 80: 148-157
4. Ichikawa K, Kasanuki J, Suseishi M, Imaizumi T, Koseki H, Kaneko R, Tomioka H, Tokumasa Y, Yoshida S. [A case of probable hypereosinophilic syndrome with a gastric lesion] Nippon Naika Gakkai Zasshi 1984; 73: 1697-1702
5. López Navidad A, Roca-Cusachs Coll A, Olázabal Zudaire A, Andreu Soriano J. Hypereosinophilic syndrome. [Hypereosinophilic syndrome. Presenting form of an epithelioid leiomyosarcoma of gastric origin] Med Clin (Barc) 1986; 86: 565-566
6 Levesque H, Elie-Legrand MC, Thorel JM, Touchais O, Gancel A, Hecketsweiller P, Courtois H. [Idiopathic hypereosinophilic syndrome with predominant digestive manifestations or eosinophilic gastroenteritis? Apropos of 2 cases] Gastroenterol Clin Biol 1990; 14: 586-588

7 Hwang KE, Sung KC, Lee HM, Cho YK, Keum JS, Kim BI, Kim H, Chung ES, Lee SJ. A case with idiopathic hypereosinophilic syndrome involving the liver and GI tract. Korean J Gastroenterol 1997; 30: 397-403

8 Jung HK, Jung SA, Lee HC, Yi SY. A case of eosinophilic colitis as a complication of the hypereosinophilic syndrome. Korean J Gastrointest Endosc 1998; 18: 417-425

9 You IY, Kim MO, Chai JY, Hong ES, Chae HB, Park SM, Kim MK, Youn SJ, Jang LC, Sung RH. Two cases of eosinophilic gastroenteritis and one case of hypereosinophilic syndrome presenting with various gastrointestinal symptoms. Korean J Gastrointest Endosc 2003; 27: 31-37

10 Hardy WR, Anderson RE. The hypereosinophilic syndromes. Ann Intern Med 1968; 68: 1220-1229

11 Roufosse F, Cogan E, Goldman M. The hypereosinophilic syndrome revisited. Am J Med 2003; 54: 169-184

12 Harley JR, Fauci AS, Gralnick HR. Noncardiovascular findings associated with heart disease in the idiopathic hypereosinophilic syndrome. Am J Cardiol 1983; 52: 321-324

13 Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore) 1975; 54: 1-27

14 Gleich GJ. Mechanisms of eosinophil-associated inflammation. J Allergy Clin Immunol 2000; 105: 651-663

15 Kobayashi S, Inokuma S, Setoguchi K, Kono H, Abe K. Incidence of peripheral blood eosinophilia and the threshold eosinophile count for indicating hypereosinophilia-associated diseases. Allergy 2002; 57: 950-956

16 Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut 1990; 31: 54-58

17 Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon HU, Wechsler ME, Weller PF, The Hypereosinophilic Syndromes Working Group. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. J Allergy Clin Immunol 2006; 117: 1292-1302

18 Freeman HJ. Adult eosinophilic gastroenteritis and hypereosinophilic syndromes. World J Gastroenterol 2008; 14: 6771-6773

S-Editor Wang YR  L-Editor Webster JR  E-Editor Tian L