

CASE REPORT

A case of a teenage boy with eosinophilic gastroenteritis with esophageal involvement developing a hemorrhagic duodenal ulcer

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Abstract A boy in his early teens visited our hospital with chief complaints of hematemesis and tarry stools. Upper gastrointestinal endoscopy identified a hemorrhagic duodenal ulcer, for which hemostasis was performed using a clip. Proton pump inhibitor (PPI) administration diminished the ulcer but relapse occurred after PPI discontinuation. The esophagus showed concentric rings and longitudinal linear furrows considered to be characteristic of eosinophilic esophagitis. Biopsies of the duodenal ulcer and the esophagus revealed marked infiltration of eosinophils, leading to a diagnosis of eosinophilic gastroenteritis with esophageal involvement. Steroid treatment was initiated, and the duodenal ulcer and esophagitis resolved. Endoscopic findings characteristic of eosinophilic esophagitis were key to the diagnosis of eosinophilic gastroenteritis.

Keywords Eosinophilic gastroenteritis · Hemorrhagic duodenal ulcer · Esophageal involvement

Introduction

Eosinophilic gastrointestinal disorders are classified in three categories: eosinophilic esophagitis that presents with abnormal infiltration of eosinophils only in the esophagus, eosinophilic gastroenteritis that manifests as infiltration of eosinophils in the gastrointestinal tract, and eosinophilic colitis that manifests as infiltration of eosinophils only in the large bowel. All three disease types are considered to be allergic in origin and caused by an excessive Th2 immune response due to allergens such as food, but their etiologies are not fully understood [1]. The prevalence of eosinophilic gastroenteritis is estimated at 1 in 100,000 [2], with abnormal eosinophilic infiltration occurring throughout the body from the esophagus to the large bowel. In a survey on Japanese patients, eosinophilic infiltration of the small bowel accounted for the majority of cases, 72 %, and eosinophilic gastroenteritis characterized by eosinophilic infiltration in the esophagus represented only a small proportion, at 9 % [3]. We recently experienced a patient who was hospitalized for a hemorrhagic duodenal ulcer, which was difficult to diagnose. Eventually, however, we confirmed that this teenage boy had eosinophilic gastroenteritis based on findings of esophageal involvement.

Case report

The patient, a boy in his early teens, had been suffering from repeated episodes of abdominal pain and diarrhea since approximately June 2012. Starting around May 2013, the abdominal pain became persistent. In June 2013, the patient visited our pediatric department with chief complaints of hematemesis and tarry stools, and was subsequently hospitalized.

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He had a history of bronchial asthma from 3 to 8 years of age. There was no previous history of food allergy. Family history was unremarkable.

Physical findings on admission: height 135 cm, weight 27 kg, blood pressure 120/70 mmHg, pulse 120 bpm, and temperature 37.5 °C. The conjunctiva showed anemia. Mild tenderness was noted in the epigastric region.

The results of laboratory tests on admission (Table 1) indicated marked anemia, with a hemoglobin level of 4.8 g/dL. The eosinophil count was not elevated. Albumin concentration was low, at 3.0 g/dL. The nonspecific IgE concentration was elevated to 1451 IU/mL. Although IgE test results specific to wheat, peanut, soybean, and egg white were positive, the patient had no history of food allergy.

There were no findings indicative of parasitic disease.

Upper gastrointestinal endoscopy identified an ulcer with a thickened, white, moss-like appearance in the duodenal wall at the superior duodenal angulus. Marked edema was apparent in the duodenal bulb (Fig. 1). The patient was placed under observation with proton pump inhibitor (PPI) treatment, but tarry stools persisted. Approximately 1 week after the initial endoscopy, a second endoscopy (Fig. 2) revealed limited epithelial regeneration around the ulcer as

well as bleeding from an exposed vessel at the ulcer floor, for which hemostasis was performed using a clip (Fig. 2).

Abdominal computed tomography identified marked thickening of the duodenal wall. No ascites was present. *Helicobacter pylori* infection was ruled out after negative results were obtained on the rapid urease test performed before the administration of PPI, the serum *H. pylori* antibody test, and the stool *H. pylori* antigen test, as well as on the basis of the absence of gastric mucosal atrophy. Serum cytomegalovirus antigen was negative, and the gastrin level was within the normal range. The patient was placed on a fasting regimen and began receiving PPI along with blood transfusions. Thereafter, his anemia showed resolution. Approximately 10 days after the initial endoscopy, another endoscopic examination revealed limited epithelial regeneration at the ulcer floor (Fig. 3). At this time, the patient resumed eating and was discharged on the 17th hospital day. In July 2013, approximately 1 month after the initial endoscopic examination, abdominal endoscopic ultrasonography showed persistent thickening of the duodenal wall, although the abdominal pain had resolved. After the absence of tarry stools was confirmed, PPI administration was discontinued in September 2013. At that time, the cause of duodenal ulcer development was

Table 1 Results of laboratory tests on admission

WBC	6900	/μL	Fe	7	μg/dl
Neut.	60	%	Ferritin	2.7	ng/ml
Lymph.	33	%	Reticulocytes	53	%
Mono.	4	%	Serum cytomegalovirus antigen	negative	
Eosino.	3	%	Serum <i>Helicobacter pylori</i> antibody	negative	
Baso.	0	%	Stool <i>H. pylori</i> antigen	negative	
RBC	175	×10 ⁴ /μL	Rapid urease test	negative	
Hb	4.8	g/dL	Gastrin	176	pg/ml
Ht	13.9	%	Nonspecific IgE	1451	IU/ml
Plt	287	×10 ⁴ /μL	Specific IgE		
CRP	0.15	mg/dL	Wheat	2	LC
PT	82	%	Nuts	3	LC
TP	5.1	g/dL	Soy	2	LC
Alb	3	g/dL	Egg	3	LC
BUN	16	mg/dL			
Cr	0.38	mg/dL			
T-Bil	0.19	mg/dL			
AST	21	IU/L			
ALT	9	IU/L			
LDH	138	IU/L			
ALP	497	IU/L			
γGTP	6	IU/L			
Na	136	mEq/L			
K	3.8	mEq/L			
Cl	105	mEq/L			

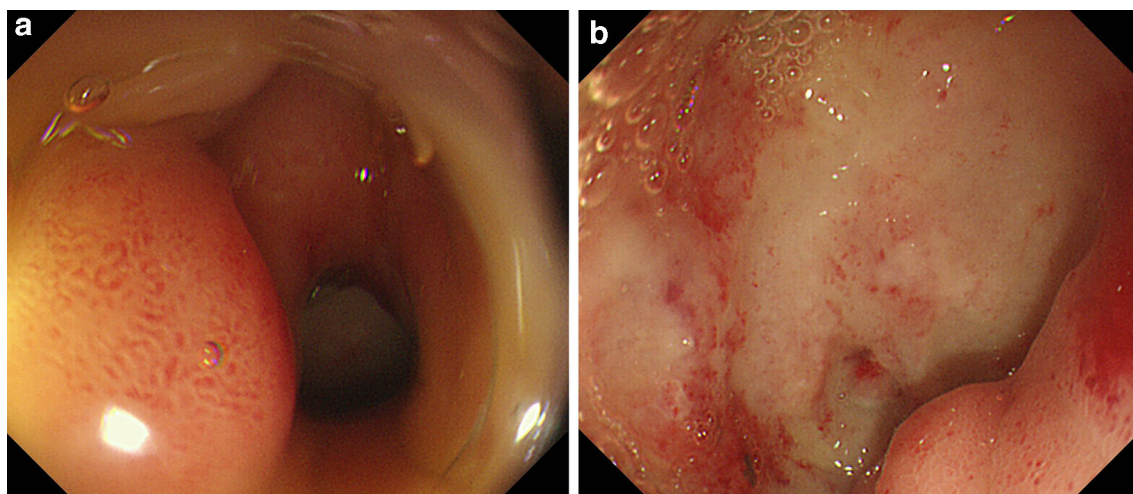


Fig. 1 Upper gastrointestinal endoscopic findings (at a visit in June 2013). **a** Marked mucosal edema was observed in the duodenal bulb. **b** An ulcer with a thickened, deep, white, moss-like appearance and marked edema at its edge was present at the superior duodenal angulus

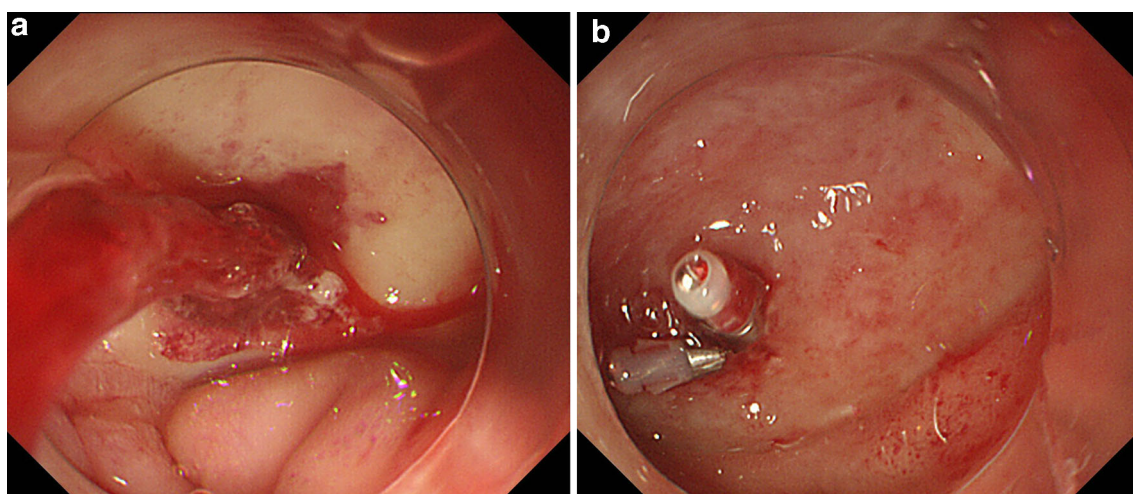


Fig. 2 Upper gastrointestinal endoscopic findings (approximately 1 week after the initial endoscopy). **a** Bleeding from an exposed vessel was noted. **b** Hemostasis was performed using a clip

recorded as unknown. No biopsy was performed during any of the endoscopic examinations.

Thereafter, the patient regularly visited his pediatrician; in December 2013, mild progression of anemia was noted, along with duodenal wall thickening on abdominal ultrasound, which led to the performance of an upper gastrointestinal endoscopy. This endoscopic examination confirmed an ulcer in the duodenal wall at the superior duodenal angulus similar to the previous findings. No bleeding was seen (Fig. 4). The esophagus showed concentric rings and longitudinal linear furrows that were considered characteristic of eosinophilic esophagitis (Fig. 5). Various examinations supported the negative diagnosis of *H. pylori* infection, and gastric findings indicative of *H. pylori* infection or other abnormal findings, including erosion,

erythema and ulceration, were absent. The patient was suspected of having eosinophilic gastroenteritis with esophageal involvement, and underwent biopsies of the esophagus, stomach, and duodenal ulcer edge.

Biopsy of the duodenal ulcer edge revealed inflammatory cell infiltration in the lamina propria, with marked infiltration of eosinophils (at least 20 eosinophils per high-power field [HPF]) (Fig. 6). There were no findings indicative of cytomegalovirus infection, such as inclusion bodies.

Esophageal biopsy revealed marked infiltration of eosinophils in the epithelium (at least 20 eosinophils per HPF) (Fig. 7). Gastric biopsy was performed in two regions, one in the pyloric and the other in the fundic gland, but did not identify significant eosinophil infiltration.

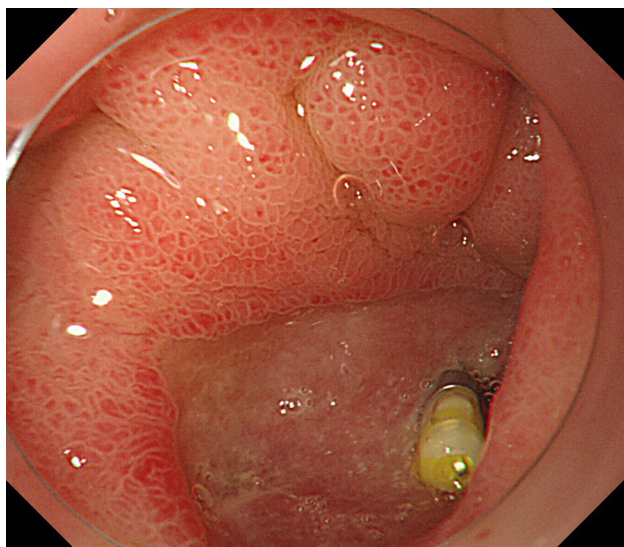


Fig. 3 Upper gastrointestinal endoscopic findings (approximately 10 days after the initial endoscopy). Epithelial regeneration was observed at the ulcer floor. Edema was seen in the surrounding mucosa

Based on these biopsy findings, the patient was diagnosed as having eosinophilic gastroenteritis with esophageal involvement, which was complicated by a duodenal ulcer. PPI administration was resumed in combination with prednisolone (PSL) at 15 mg/day (0.5 mg/kg/day). PSL was subsequently tapered and finally discontinued. In March 2014, cure of the duodenal ulcer was confirmed by endoscopy. The previously observed concentric rings and longitudinal linear furrows were no longer detectable in the esophagus. Biopsies of the duodenal and esophageal

mucosa were repeated, and the histopathological findings also demonstrated eosinophil infiltration to be reduced. The patient is currently under observation receiving PPI administration alone. The abdominal pain and diarrhea also resolved. Colonoscopy has not been performed because neither the patient nor his family have given consent.

Discussion

Eosinophilic gastroenteritis and eosinophil esophagitis are diseases that both show marked infiltration of eosinophils in the gastrointestinal tract. Eosinophilic gastroenteritis was first reported by Kaijser in 1937 [4]; reports on this disease in Japan have since accumulated, and it is now relatively well known in this country. In contrast, eosinophilic esophagitis was first reported in 1977 by Dobbins et al., who managed a case complicated by eosinophilic gastroenteritis [5]. This disease has been regarded as relatively rare in Japan, but has recently attracted attention for its non-negligible prevalence, which has reached 17.1 per 100,000 persons [6].

The diagnostic criteria for eosinophilic gastroenteritis proposed by Talley et al. [2] are still in use today. Eosinophilic gastroenteritis is diagnosed if all of the following criteria are met: (1) relapsed or chronic gastrointestinal symptoms, (2) infiltration of at least one eosinophil in a single gastrointestinal biopsy or X-ray findings characteristic of eosinophilic gastroenteritis with eosinophilia, and (3) exclusion of other diseases, such as parasitic disease, that cause eosinophilia. Our present case met all of these criteria. While Talley's criteria do not include an

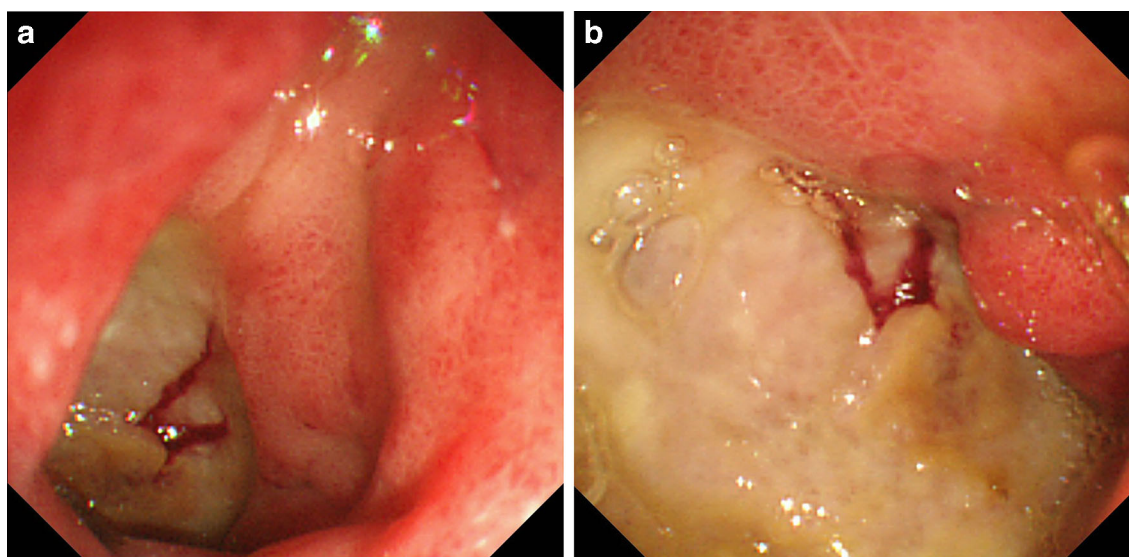


Fig. 4 Upper gastrointestinal endoscopic findings (December 2013). **a, b** Endoscopic findings at relapse showed an ulcer with a thickened, white, moss-like appearance and mucosal edema at its edge at the superior duodenal angulus

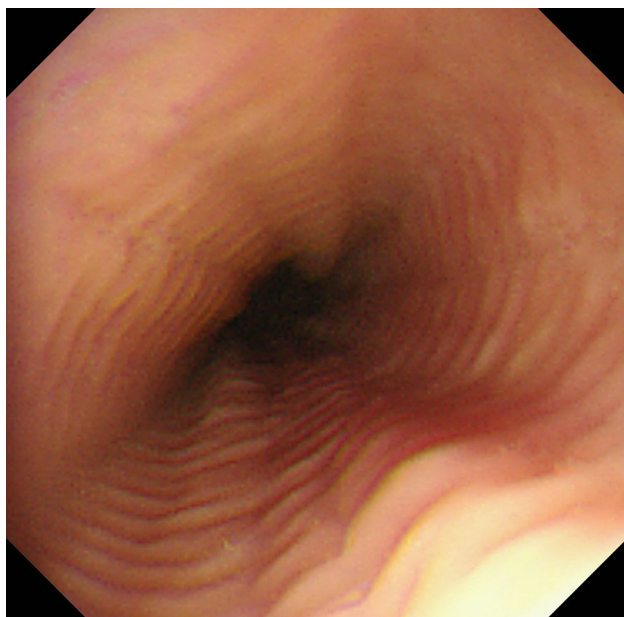


Fig. 5 Upper gastrointestinal endoscopic findings (December 2013). Endoscopic findings at relapse. Concentric rings and longitudinal linear furrows considered characteristic of eosinophilic esophagitis were observed in the esophagus

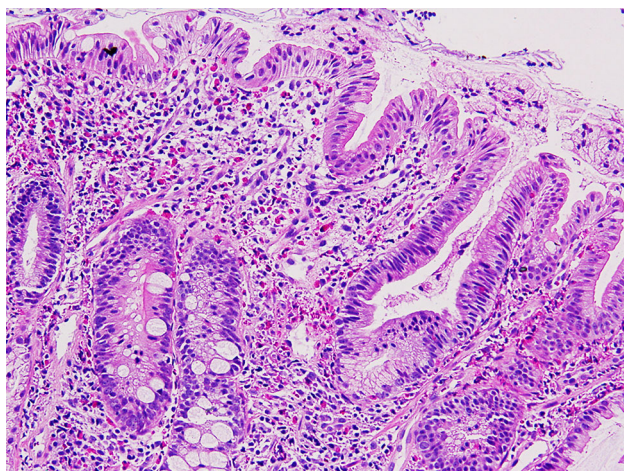


Fig. 6 Histopathological findings (H&E stain, $\times 100$ December 2013). Duodenal biopsy findings. Marked inflammatory cell infiltration in the lamina propria of the duodenum was observed, with marked infiltration of eosinophils

eosinophil infiltration criterion, the Japanese draft proposal for diagnostic criteria [5] includes infiltration of at least 20 eosinophils per HPF. Diagnostic criteria for eosinophilic gastroenteritis in Japan (draft 2011 revision) [7] are as follows: (1) presence of symptoms (abdominal pain, diarrhea, vomiting), (2) gastric, small bowel, and large bowel biopsy findings demonstrating inflammatory cell infiltration dominated by eosinophils in the mucosa (infiltration of at least 20 eosinophils per HPF, biopsies of multiple sites,

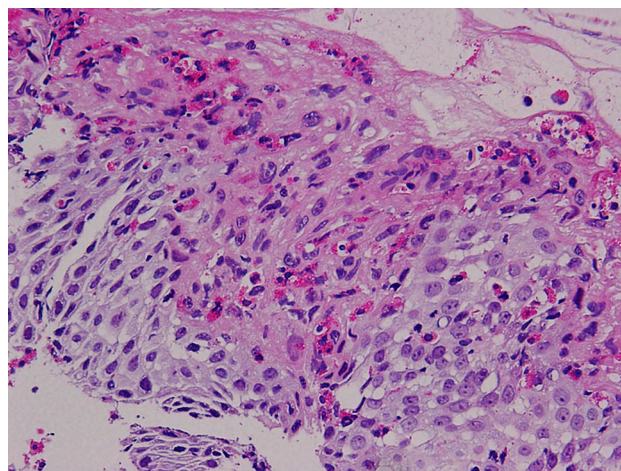


Fig. 7 Histopathological findings (H&E stain, $\times 200$ December 2013). Esophageal biopsy findings. Marked infiltration of eosinophils was observed in the lamina propria of the esophagus

and exclusion of inflammatory intestinal diseases required), (3) the presence of ascites including many eosinophils, (4) prior history of allergic disease such as asthma, (5) eosinophilia in peripheral blood, (6) CT scan findings of gastric and intestinal wall thickening, (7) endoscopic findings of edema, erythema, and erosion in the stomach and in both the small and large bowels, and (8) responsiveness to glucocorticoid administration. Criteria 1 and 2 or 3 are absolutely required, while meeting the other criteria increases the likelihood of diagnosis of eosinophilic gastroenteritis. Our present case met all criteria except 3 and 5.

Klein et al. [8] proposed classification of the disease into three types: (1) predominant mucosal disease, manifesting predominantly as mucosal lesions along with vomiting, diarrhea, and malabsorption; (2) predominant muscle layer disease, manifesting predominantly as muscle layer lesions, along with stenosis and occlusive symptoms; and (3) predominant subserosal disease, manifesting predominantly as subserosal lesions, along with serosal thickening and eosinophilic ascites. The present case showed marked eosinophil infiltration in the mucosal layer on biopsy and marked duodenal wall thickening on abdominal ultrasound and abdominal CT scan. Based on these findings, the patient was diagnosed as having a mixed form of predominant mucosal and predominant muscle layer disease.

This patient was initially diagnosed as having a duodenal ulcer of unknown cause and treated with PPI. Biopsy was not performed during endoscopic examination until the disease relapsed. Abdominal ultrasonography at 1 month after the initial endoscopy showed thickening of the duodenal wall, suggesting the presence of the disease despite disappearance of the symptoms of abdominal pain and tarry stools. The ulcer was initially resolving, but after PPI

discontinuation, abdominal symptoms recurred, and ulcer recurrence was confirmed by endoscopy. At reexamination, concentric rings and longitudinal linear furrows characteristic of eosinophilic esophagitis were noted during esophageal observation, and biopsy was performed, allowing the diagnosis of eosinophilic gastroenteritis with esophageal involvement. Until this time, the esophageal lesion had not been detected in upper gastrointestinal endoscopic examinations performed by different examiners, and we determined that the esophageal lesion had been overlooked. Mucosal edema, erythema, and erosion are readily identifiable as endoscopic findings of eosinophilic gastroenteritis, but there are no endoscopic findings specific to eosinophilic gastroenteritis; therefore, endoscopic findings alone are insufficient for a making definitive diagnosis of eosinophilic gastroenteritis [9–11]. It is well known that eosinophilic gastroenteritis is often complicated by ulcerative findings, but duodenal ulcer is a rare endoscopic finding [12]. On the other hand, endoscopic features of eosinophilic esophagitis are becoming more established [1, 13], and characteristic endoscopic findings include concentric rings and longitudinal linear furrows, with white exudates. However, to date, there are few reports of eosinophilic gastroenteritis with esophageal involvement, and the prevalence of esophageal lesions in eosinophilic gastroenteritis is relatively low (9 %) [3]. Eosinophilic gastroenteritis and eosinophilic esophagitis are thought to share a common mechanism of eosinophil infiltration. IL5/13 production from Th2 cells and infiltrating eosinophils and associated Eotaxin-3 expression in the affected tissues have been proposed [14, 15]. It is possible that these two diseases share overlapping mechanisms of onset, and it is likely that they have similar endoscopic features of esophageal involvement. Additional case reports and further investigation are required to clarify these issues.

Suspicion of eosinophilic gastroenteritis requires not only diagnosis by aggressive biopsy, but also confirmation of the presence or absence of esophageal endoscopic findings similar to those of eosinophilic esophagitis, which are considered relatively characteristic, as a clue to the diagnosis of eosinophilic gastroenteritis. In the present case, the initial endoscopy failed to identify esophageal involvement, and although eosinophilic esophagitis is reported to be rare in cases with eosinophilic gastroenteritis, as described earlier, a detailed examination of the esophagus should have been performed. In addition, diagnosis was delayed because endoscopy identified only a duodenal ulcer, which is relatively rare for eosinophilic gastroenteritis, and the initial differential diagnosis did not include possible eosinophilic gastroenteritis. Furthermore, the patient had been diagnosed with irritable bowel syndrome based on repeated episodes of abdominal pain and diarrhea prior to the first visit, but he may have also had

involvement of the small and large bowels. The patient was a boy in his early teens, and he refused to undergo colonoscopy, which might have provided more details, but improvement of abdominal pain and diarrhea after steroid treatment did suggest possible small and large bowel involvement.

There have been no randomized controlled studies on the treatment of eosinophilic gastroenteritis, and there is no proven therapy with sufficient evidence [1]. The disease is generally treated by systemic oral steroid administration, which is reported to be effective in relieving symptoms, at least temporarily [3]. In the present case, the cause of the duodenal ulcer was initially not identifiable, and PPI treatment alone temporarily relieved subjective symptoms and endoscopic findings, but apparently did not achieve a complete cure of the ulcer. At the subsequent relapse, PPI in combination with steroid administration promoted healing of the ulcer. Studies have determined that only 40 % of cases in which subjective symptoms are resolved by steroid treatment will remain free of further relapse. In the other cases, the disease reportedly becomes chronic, thus requiring long-term treatment with steroids and other immunosuppressants to avoid repeated recurrence [16]. Because our patient showed symptom resolution once after PPI monotherapy prior to steroid treatment, we will keep him under observation with PPI alone for a reasonable period of time after terminating steroid treatment. We hypothesized that the disappearance of abdominal pain and tarry stools after the administration of PPI was at least partly attributable to a slight improvement of the ulcer caused by the inhibition of gastric acid secretion; however, the condition of eosinophilic gastroenteritis persisted and the ulcer was then aggravated with the discontinuation of PPI. If the treatment with PPI had been continued without administration of steroids, the duodenal ulcer would not have been cured. In the present case, we continued PPI treatment even after improvement of the ulcer with steroid treatment in order to prevent relapse during steroid tapering. The question of whether continuous PPI administration is needed requires further investigation.

For eosinophilic gastroenteritis, causal therapy is not feasible because the etiology and pathology are not fully understood. Our patient had no subjective symptoms of food allergy. Various approaches have been used to eliminate food allergens, including (1) an elimination diet that does not contain typical food allergens such as wheat, milk, egg, soy, nuts, and seafood, (2) an elimination diet based on skin tests, (3) an elemental diet, and (4) a low-calorie/low-fat and gluten-free diet. The first of these is reported to be particularly effective against eosinophil esophagitis in the US and Europe [17, 18], and is expected to be applicable to the treatment of eosinophilic gastroenteritis as well. Approaches 3 and 4 are not feasible for school

children in the real-world setting. We did not offer dietary instructions in this case.

As of December 2014, 8 months had passed since steroid administration was terminated, and the patient had no signs of relapse. We will continue to carefully observe his clinical course.

In summary, we treated a teenage boy with eosinophilic gastroenteritis with esophageal involvement who developed a hemorrhagic duodenal ulcer. When a gastrointestinal ulcerous lesion of unknown cause relapses repeatedly, the differential diagnosis should include possible eosinophilic gastrointestinal disorders. Histopathological evaluation by aggressive biopsy can facilitate an accurate diagnosis. Eosinophilic gastroenteritis may be difficult to diagnose due to nonspecific endoscopic features, but esophageal involvement may present endoscopic findings characteristic of eosinophilic esophagitis. Therefore, accumulation of case reports and further investigation are required.

Disclosures

Conflict of Interest: Kenji Yamazaki, et al. declare that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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