Eosinophilic gastroenteritis as a cause of gastrointestinal tract bleeding and protein-losing enteropathy

Gastrointestinal sistem kanaması ve protein kaybettiren enteropati nedeni olarak eozinofilik gastroenterit

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Abstract

Eosinophilic gastroenteritis is an inflammatory disease characterized by pathologic eosinophilic infiltration of any portion of the gastrointestinal tract. Depending on the involved site and layer of eosinophilic infiltration, symptoms and signs are heterogeneous. This manuscript reports two patients who presented with acute upper gastrointestinal tract bleeding and protein-losing enteropathy signs, and were diagnosed as having eosinophilic gastroenteritis. Upper endoscopy revealed an appearance of mucosal pseudomasses in both patients. Both patients achieved satisfactory clinical improvement with an elimination diet and proton pump inhibitor treatment.

Keywords: Endoscopy, eosinophilic enteropathy, hemorrhage, hypoproteinemia

Introduction

Eosinophilic gastroenteritis (EoG) is a rare inflammatory disease characterized by pathologic eosinophilic infiltration of any portion of the gastrointestinal tract, which is difficult to diagnose. Generally, there is a triggering factor such as food or parasitic infestation. Irregular immune response developing against these factors predominates in the pathogenesis (1). The symptoms vary by the region affected and the layer of involvement in this region. The disease leads to a wide spectrum of clinical manifestations including nausea, vomiting, regurgitation, abdomi-
inal pain, diarrhea, dyspepsia, dysphagia, protein losing enteropathy, gastrointestinal bleeding, ascites, and intestinal obstruction (2). The gold standard for diagnosis is endoscopy and observation of 20 or more eosinophils in one high-power field (HPF) on histopathologic evaluation of biopsies obtained during endoscopy (3). Endoscopy may reveal normal mucosal appearance or hyperemia, granularity, ulceration, polyp and pseudopolyp or nodular lesions, which display an appearance of mass (4). In this article, we present two patients who had acute gastrointestinal bleeding with pseudomass appearance on endoscopic examination and were diagnosed as having eosinophilic gastroenteritis. Consent was obtained from both patients.

Case 1
A nine-year-old male patient with a diagnosis of cerebral palsy who had percutaneous endoscopic gastrostomy and a tracheostomy tube was consulted because of symptoms of fever, melena, and hematemesis. In his history, it was learned that he was receiving multiple antiepileptic drugs, underwent endoscopy 20 days previously because of recurrent vomiting and hematemesis, was found to have esophagitis and polypoid lesions in the conjunction of the first and third duodenal parts, and biopsy results were being awaited. On physical examination, his vital signs and anthropometric measurements were found to be normal. There was no sign of peristomal blood leakage or wound site infection. The laboratory test results revealed that white blood cells (WBC) (30 600 μL), procalcitonin (0.87 ng/mL), D-dimer (6.8 mg/L), and gamma-glutamyl transferase (148 U/L) levels were increased, total protein (5.7 g/dL) and albumin (2.5 g/dL) levels were decreased, and platelet count (363 000 μL), international normalised ratio (INR) (1.3), partial thromboplastin time (PTT) (15 s), fibrinogen (240 mg/dL), and other routine biochemical values were normal. Streptococcus pneumonia was grown in blood culture and ertapenem (IV) treatment was initiated. Continuing laboratory assessment revealed that the hemoglobin value, which was found as 10.2 g/dL at the time of presentation, was reduced to 6.9 g/dL on the third day of follow-up. No protein loss was detected in urine (spot urine protein/creatinine ratio: 0.39). Endoscopy and colonoscopy were performed to elucidate the etiology of protein-losing enteropathy and bleeding. Colonoscopic findings were found to be normal. Upper endoscopy revealed esophagitis, exuda plaques and lesions which were thought to be enlarged lactitol in the third part of the duodenum, and papillary structures with hyperemic surface protruded into the lumen in the conjunction of the bulbus and second duodenal part. On histologic examination of biopsies, chronic duodenitis with 80 eosinophils per HPF and chronic inflammation with 20 eosinophils per HPF in the ascending and descending colon were observed, in addition to chronic esophagitis findings. It was found that duodenal biopsies obtained during the prior endoscopy similarly revealed 90 eosinophils per HPF, enlarged lymphatics, and chronic active duodenitis. The total immunoglobulin (Ig)-E level and eosinophil count measured to elucidate the etiology in the patient, who was diagnosed as having eosinophilic gastroenteritis, were found to be normal (58.34 IU/ml and (100 μL), respectively). Food-specific IgEs and skin prick tests were found to be negative. The enteral product given to the patient was switched to a peptide-based enteral solution (Pediasure Peptide, Abbot), which contained high protein and medium-chain fatty acids. The present lansoprazole and Gaviscon treatment were continued. Gastrointestinal tract bleeding did not recur during the follow-up. An endoscopic examination performed six months later showed that the appearance of mass that was priorly observed in the duodenum had disappeared, histopathologic chronic esophagitis findings improved, eosinophilic infiltration in the duodenum disappeared, and inflammation regressed.

Case 2
A 17-year-old male patient presented to the emergency department with nausea and melena lasting for 3–4 days and hematemesis that started on the day of presentation. In his history, it was learned that iron treatment was initiated three months ago because of anemia, and he had pollen, mite, and cat allergy. On physical examination, his vital signs, anthropometric measurements and system findings were found to be normal. The hemoglobin value was found as 6.1 g/dL on the primary hemogram test and decreased to 4.9 g/dL during the follow-up. The other hemogram parameters (WBC: 7200 μL, platelets: 201 000 μL, absolute eosinophil count: 200 μL) were found to be normal. His laboratory test results were as follows: serum iron: 24 μg/dL, transferrin saturation: 6.9%, total iron-binding capacity: 347 μg/dL, ferritin: 6.1 ng/mL, vitamin B12: 174 pg/mL, and folate: 3.4 ng/mL. The other biochemical values and hemostasis findings were found as normal except for hypoproteinemia-hypoalbuminemia [total protein: 5.1 g/dL (normal range: 6–8.5 g/dL); albumin: 3.1 g/dL (normal range: 3.8–5.4 g/dL)]. Analyses of stool for parasites and abdominal ultrasonography was found to be normal.

Upper endoscopy and colonoscopy were performed following appropriate fluid replacement, erythrocyte transfusion, and intravenous omeprazole (2 mg/kg/day IV, bid) treatment. It was observed that there were diffuse nodular structures in the gastric corpus and antral mucosae and these nodular structures appeared as masses with distinct borders covered with normal mucosa in some
areas (Fig. 1a, b). The duodenum was found to be normal and the terminal ileum was nodular. On histopathologic evaluation of the biopsies obtained from the regions with and without lesion, gastritis rich in eosinophils (30–50 eosinophils/HPF) with mild activity and moderate chronicity was observed in the fundus, corpus, and antrum, and lymphocyte aggregates were observed in the fundus. Reactive lymphoid hyperplasia, 40–45 eosinophils/HPF, and eosinophilic cryptitis were observed in the terminal ileum. Chronic inflammatory process rich in eosinophilic infiltrates (40–60 eosinophils/HPF) showing focal activation in some areas and reactive lymphoid hyperplasia was observed in all segments in the colon. A diagnosis of EoG was made in the patient whose stool parasite tests were found to be negative. Cow’s milk elimination diet was initiated for the patient whose food allergen skin prick test was found as normal, but whose milk-specific IgE level was found to be positive. In the third month of the diet, the hemoglobin value increased to 15.5 g/dL. Follow-up endoscopic examination revealed gastric fold thickening and marked regression in the lesions observed on the prior endoscopic examination (Fig. 1c). However, no marked regression in eosinophilic infiltration was observed histopathologically (30–60 eosinophils/HPF).

Discussion

Although eosinophilic gastroenteritis is mostly a disease of childhood, it may occur in all age groups. Here, two patients aged 17 and 9 years who presented with upper gastrointestinal tract bleeding, have been presented. The gastric antrum (100%), esophagus (60%), proximal small intestine (79%), and gastric corpus (52%) have been reported as the regions where eosinophilic infiltration is observed most commonly (5). Only small intestinal and colonic infiltration was observed in one of our patients, and infiltration in the gastric corpus and antrum was found in addition to these regions in the other patient. There is a personal or familial history of atopy in 45–65% of patients (5, 6). IgE-dependent or IgE-independent TH2 cell-mediated delayed allergic mechanisms are observed in the pathogenesis. Eotaxin, integrin, interleukin (IL)-5, IL-3, IL-4, IL-13, leukotrienes, and tumor necrosis factor (TNF) alpha are the mediators that are involved in this reaction (1).

The symptoms vary by the region involved in the gastrointestinal tract and the depth of eosinophilic infiltration. Three types have been identified (7). Mucosal involvement is the most common type (25–100%), which may be associated with iron-deficiency anemia, malabsorption, and protein-losing enteropathy. Both of our patients had mucosal involvement and developed protein-losing enteropathy. Muscular involvement is the second most common type (13–70%), which leads to symptoms of intestinal wall thickening and intestinal obstruction. Subserosal involvement is the least common type (12–40%); this may lead to pleural effusion, peritonitis, and perforation. Chronic anemia has been reported in 54% of cases (2). One of our patients had chronic anemia. Hematochezia has been reported with a rate of 25% and acute gastrointestinal tract bleeding has been reported with a rate of 14% (2, 6). One of
our patients presented with symptoms of acute bleeding from the duodenum and the other presented with symptoms of acute bleeding from the stomach.

In the differential diagnosis, other causes leading to eosinophilic infiltration in the gastrointestinal tract should be excluded. Peripheral eosinophilia has been reported with a rate of 20–80% (more prominent in serosal involvement), increased erythrocyte sedimentation rate has been reported with a rate of 25%, and increased IgE levels have been reported with a rate of 75% (5). Paracentesis may reveal eosinophilia in ascites fluid. Peripheral eosinophilia was not found in either of our patients. IgE level was measured in one patient and observed to be normal. In addition, barium radiography and abdominal ultrasonography may be helpful in the diagnosis. Endoscopic evaluation and histopathologic examination are considerably important. Obtaining multiple biopsy samples (at least 5–6 samples) from normal and abnormal mucosa is recommended because there may be patchy involvement. In both of our patients, colonic mucosa appeared normal on endoscopic examination, but there was pathology on histopathologic examination. Biopsies provide an opportunity for diagnosis with a rate of at least 70% in patients with mucosal disease (5). In patients who have only muscular or serosal involvement without mucosal involvement, endoscopic findings and biopsy findings may be normal. In this case, laparotomy and full-thickness biopsy may be needed. More than 20/HPF eosinophils in lamina propria on histopathologic examination is significant in terms of the diagnosis. Localized eosinophilic infiltrations, crypt hyperplasia, eosinophilic cryptitis, epithelial cell necrosis, and villous atrophy are other pathologies that may be observed. Also, other causes of eosinophilia such as parasitic infestations, hypereosinophilic syndrome, inflammatory bowel disease, Churg-Straus syndrome, polyarteritis nodosa, and H. Pylori infection should be considered in the differential diagnosis (5).

The disease has been classified as “chronic-mucosal, muscular-relapsing and serosal-nonrelapsing” by illness behavior (1). Spontaneous remission has been reported with a rate of 30–40% (5). In treatment, proton pump inhibitors are recommended because they inhibit IL-4 and IL-13 (8). We administered proton pump inhibitor treatment in both patients. If the allergy-causing food is known, a specific elimination diet is given. If the allergy-causing food is not known, an empirical elimination diet or elemental diet is given. Diet is not always correlated with clinical and histopathologic response. Clinical response has been reported with rates up to 80% (5, 9). A 50% reduction in symptoms, histopathologic eosinophilia and peripheral eosinophilia, if present, is considered as a response to diet treatment. In our first patient, a triggering allergen could not be shown. However, both clinical and histopathologic response were obtained after the present enteral product of the patient, who was being fed by gastrostomy, was switched to a less allergen product that contained hydrolyzed protein. In the second patient, the allergen was found to be milk protein. A clinical and histopathologic response was observed with milk elimination that lasted for an appropriate period, but the desired histopathologic response could not be obtained. The reason for this may be that the diet period was short. The mean period of elimination to be applied has been reported as 12 weeks. However, this period was not sufficient in our patient (5). Another reason may be the other inhaler allergens that were detected in the patient. It is known that inhaled allergens may also lead to eosinophilic infiltration in the gastrointestinal tract (10).

Generally, a good response will be obtained with diet. However, 21% of patients with mucosal involvement show a course of chronic persistent disease characterized by increasing and decreasing symptoms. Systemic steroids such as budesonide or prednisolone are recommended for patients who are unresponsive to diet. Clinical response has been reported with a rate of 90% with these treatment methods. There are publications related to different treatment methods such as mepolizumab (anti-IL-5) and omalizumab (anti-Ig E) in resistant cases (5).

Relapse is observed most commonly in the muscular type (37%), it is rarer in the serosal type (1). In addition, the rate of relapse has been reported 60–80% in young patients or patients with an absolute eosinophil count of >1500 μL. Therefore, these patients may need long-term treatment with budesonide or montelukast (selective leukotriene antagonist). Azathioprine may be used to reduce steroid use in case of relapse or in patients who are resistant to treatment (5).

In conclusion, albeit rare, EoG should be considered in patients of any age group who present with gastrointestinal tract bleeding, have an appearance of pseudomass on endoscopic examination or have findings of protein-losing enteropathy. Endoscopy is the gold standard for the diagnosis, and multiple biopsy samples should be obtained from mucosa that appear normal and abnormal. Proton pump inhibitor and diet elimination for an appropriate period constitute the primary treatment and provide clinical remission with a high rate.

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