

## Educational Series

# Educational clinical case series in pediatric allergy and immunology

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Eosinophilic inflammation may occur in any part of the intestinal tract from the esophagus to the rectum. Despite 70 yr having passed since the first reference to a case of eosinophilic gastroenteritis, the epidemiology and natural history of eosinophilic gastrointestinal disorders are still poorly known. Insights into their etiology and pathogenesis have revealed an important role for allergens; interleukins 4, 5, and 13; the eotaxin family of chemokines; and eosinophil-derived proteins. Diagnosis is confirmed by typical histologic features in a patient with a suggestive clinical phenotype. Treatment involves eliminating triggering allergens, making dietary restrictions the first choice of therapy in a compliant patient; corticosteroids [topical in eosinophilic esophagitis (EE)], despite the potential for serious side effects, are used with success in refractory and non-compliant patients. In this study we discuss EE and gastroduodenitis against the backdrop of clinical case presentations.

**Seema Khan<sup>1,2</sup>, Leena Kandula<sup>3</sup> and Susan R. Orenstein<sup>4</sup>**

<sup>1</sup>Thomas Jefferson University Medical College, Philadelphia, PA, USA, <sup>2</sup>Division of Gastroenterology and Nutrition, Alfred I DuPont Hospital for Children, Wilmington, DE, USA, <sup>3</sup>Division of Pediatric Gastroenterology, Chapel Hill, NC, USA, <sup>4</sup>Pediatric Gastroenterology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

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Seema Khan, Division of Gastroenterology and Nutrition, Alfred I DuPont Hospital for Children, Wilmington, DE 19803, USA

Tel.: 001 302 615 5928

Fax: 001 302 651 5838

E-mail: sekhan@nemours.org

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## Case 1

A 14-yr-old male arrived in the emergency room of a local hospital with the chief complaint of a 'lump in my throat' shortly after he ate a piece of steak. He reported normal swallowing with the first few bites but subsequently swallowing became difficult and painful. He could not clear the lump despite drinking water, and due to growing discomfort and anxiety was brought into the emergency room for an evaluation. He had no significant past medical gastrointestinal history but did have hay fever. He was well nourished, with stable vital signs, and had an unremarkable physical examination.

In consultation with the gastroenterologist on call, the emergency room team obtained a barium upper gastrointestinal series, which appeared to show a foreign body in the mid esophagus. Subsequently, further evaluation was carried out by means of an upper endoscopy with biopsies. At the time of the endoscopic evaluation, food was visualized impacted in the mid

esophagus. The mucosal surface in the proximal third appeared normal. The food was removed using a basket. Residual pieces of food in the esophageal lumen were small enough to be easily washed down into the stomach. The mid and distal esophageal mucosa appeared furrowed and edematous, and the lumen was non-stenotic but could only be poorly distended with insufflation. The stomach and duodenum appeared unremarkable, as were the biopsies taken from both these areas. Distal esophageal biopsies showed a peak of 50 eosinophils per high power field (eos/hpf), basal cell hyperplasia, papillary elongation, and superficial aggregation of eosinophils; biopsies from the mid esophagus revealed a peak of 15 eos/hpf and proliferative changes much like the distal esophagus.

The patient experienced satisfactory relief of symptoms and later underwent a food allergy evaluation consisting of negative CAP-radioallergosorbent tests (RAST) and skin prick tests to eight common food antigens. The patient was discharged taking swallowed fluticasone 220 µg

per actuation, two puffs twice daily without a spacer and was symptom-free at an outpatient visit 2 months later. A follow-up endoscopy was recommended by his gastroenterologist, but was not accepted by the family. The patient was lost to follow-up.

## Case 2

An 8-yr-old boy presented for evaluation of long-standing heartburn and regurgitation. He was breast-fed as an infant, and diagnosed and treated for gastroesophageal reflux disease (GERD). He outgrew the need for anti-reflux pharmacotherapy around 1 yr of age, but since the age of 6 yr had vague complaints of heartburn and regurgitation. His symptoms worsened, prompting a trial of anti-reflux dietary precautions and use of a proton pump inhibitor for almost 4 months prior to presentation, but without adequate control. He denied anorexia and dysphagia, and had no weight loss. A review of systems disclosed well-controlled asthma and hay fever. He had had eczema as an infant. Family history was positive for asthma and allergies to aeroallergens. His physical examination was normal.

A complete blood count with differential obtained 3 months earlier had shown peripheral eosinophilia. His medications had included montelukast and inhaled budesonide for 2 yr. An upper endoscopy with biopsies and a pH-impedance study off anti-reflux medications were performed. The entire esophagus appeared furrowed and edematous. The proximal and distal esophageal biopsies showed a dense eosinophilic infiltrate with a maximum of 30 and 25 eos/hpf, respectively, as well as features of basal cell hyperplasia and eosinophil layering in the superficial epithelium. The pH-impedance study was normal. Further evaluation demonstrated positive prick and atopy patch tests to multiple foods.

The patient was placed on a restricted diet directed by the results of his allergy tests; a follow-up endoscopy with biopsies 2 months later revealed a maximum eosinophil density of 5 at both esophageal levels and no other inflammatory features. A gradual reintroduction of foods and close follow-up of symptoms was discussed with the patient and his parents.

## Discussion

The diagnosis of eosinophilic esophagitis (EE) is now discussed in the context of the above two cases with particular attention to its epidemiol-

Table 1. Eosinophilic gastrointestinal disorders (EGID) classification

|                             | Primary EGID                                                            | Secondary EGID                                                                                                                                                                                                   |
|-----------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Esophagus                   | Eosinophilic esophagitis<br>Atopic<br>Non-atopic/idiopathic             | Gastroesophageal reflux disease<br>Eosinophilic gastroenteritis<br>Hypereosinophilia syndrome<br>Connective tissue disorders<br>Autoimmune disorders<br>Medications<br>Leiomyomatosis<br>Transplantation         |
| Stomach and small intestine | Eosinophilic gastroenteritis<br>Mucosal<br>Muscular<br>Serosal          | Infections<br>Hypereosinophilia syndrome<br>Inflammatory bowel disease<br>Celiac disease<br>Connective tissue disorders<br>Autoimmune disorders<br>Medications<br>Transplantation<br>Inflammatory fibroid polyps |
| Large intestine             | Eosinophilic colitis<br>Proctitis<br>Food protein-induced enterocolitis | Infections<br>Inflammatory bowel disease<br>Connective tissue disorders<br>Autoimmune disorders<br>Medications<br>Transplantation<br>Juvenile polyps/polypoidosis/adenomas                                       |

ogy, clinical presentation, evaluation, treatment, and natural history.

Eosinophilic esophagitis is characterized histologically by a prominent eosinophilic infiltrate in the esophageal squamous epithelium in a patient with typical upper gastrointestinal symptoms (1, 2). Recently, an additional feature in support of the diagnosis has been suggested: a failed response to a trial of proton pump inhibitor therapy (3, 4).

The disorder is referred to as primary atopic EE if diagnosed in the context of allergies to differentiate from primary idiopathic EE. Secondary EE occurs in association with other disorders (Table 1). These include hypereosinophilia syndrome, eosinophilic gastroenteritis (EGE), autoimmune and collagen vascular disorders, parasitic infections, inflammatory bowel disease, drug hypersensitivity, and following solid organ transplantation (5–7).

## Epidemiology

Eosinophilic esophagitis is an important esophageal disorder with a worldwide distribution (4, 8–11). The last 10 yr have seen a dramatic increase in new diagnoses of EE, a phenomenon thought to be due to either a truly increased incidence, or greater recognition, or both. A fourfold increase in disease prevalence is

observed in the US Midwest (12) and the incidence of EE at Children's Hospital of Philadelphia is reported to have doubled in 4 yr (4). A retrospective survey in Western Australia found the incidence of pediatric EE to increase from 0.05 to 0.89 per 10,000 children in the period 1995–2004 (9).

Until a few years ago, EE was viewed as a uniquely pediatric disorder, but now it is widely accepted as a discrete diagnostic entity in adults as well, perhaps as a result of a shift in diagnostic approach to include performance of biopsies from endoscopically normal or near-normal esophageal mucosa (13–17). A Swiss-based population study reported a 14-fold increase in the prevalence of EE in adults during a 16-yr period (16). While EE is known to affect all ethnic groups and all ages; most reported affected individuals are children and adolescents, and the great majority are males (2, 18).

#### Clinical presentation

Patients with EE characteristically present either with GERD-like symptoms or with obstructive esophageal symptoms; these two presentations are exemplified by the above cases (4, 13). Younger children with EE typically present with GERD-like symptoms of regurgitation, feeding difficulties, chest pain, and heartburn; are usually unresponsive to acid blockade; and have normal esophageal pH studies. Older children and adults with EE commonly present with chronic vomiting and dysphagia, but recall few or no prior GERD-like symptoms. A food impaction may be the initial presentation of some EE patients. This observation currently provides the main suggestion that the natural history of untreated EE may lead to complications of esophageal dysmotility and stricture formation related to an indolent but chronically progressive inflammatory process (19).

#### Pathogenesis

The reason that food allergies are popularly proposed in the pathogenesis of EE is the common observation of a personal (53–70%) or family (43%) history of asthma, eczema, and allergic rhinitis (1, 4). The success of treatment approaches using elimination of allergens and administration of anti-inflammatory agents lend further support to this theory.

Animal studies have shown that EE is induced in mice exposed to food and aeroallergens. Investigations in animal models have elucidated an association with Th-2 type cytokines, IL-4,

IL-5, and IL-13 (20–22). Acute exacerbations of symptoms and esophageal eosinophilia have been described in the case of a patient with pollen allergy (23). Food allergies in patients with EE may be mediated by either IgE or non-IgE (delayed hypersensitivity) pathways, as evident clinically by IgE sensitization (RAST and skin prick tests) and non-IgE-mediated skin patch tests (24, 25). The inflammatory process is exerted via preformed eosinophil-derived granular proteins, cytokines, arachidonic acid mediators, and lipid products. Other studies have supported a critical role for an eosinophil-selective family of chemokines known as eotaxins, suggesting a genetic predisposition for a subtype of EE patients. In this regard the gene encoding eotaxin-3 has been observed to be highly induced in EE patients compared with healthy controls (26–28).

#### Diagnostic evaluation

As alluded to in the section on clinical presentation, children previously diagnosed with GERD but refractory to anti-GERD therapies, and those presenting with dysphagia or food impactions, warrant an evaluation for EE. In addition, virtually all symptoms attributed to esophageal disease as well as extra-esophageal otolaryngologic presentations have been reported in patients with EE (28).

An upper endoscopy with biopsies must be performed for definitive diagnosis. The variable endoscopic esophageal mucosal findings include linear furrowing (Fig. 1a), rings (Fig. 1b), crepe paper appearance, whitish specks, and granularity. The esophagus has been reported normal in up to a third of cases (29, 30). The lumen may be stenotic or non-distensible upon insufflation in the absence of a fixed obstruction (14, 31).

The diagnosis rests on the pathologic features of esophageal eosinophilia, usually a maximum count of not less than 15 eos/hpf, luminal aggregation, and eosinophilic abscesses. The morphologic features of basal cell hyperplasia and papillary elongation are frequently identified, but do not allow differentiation from peptic esophagitis (3, 29, 32–34). There is growing emphasis on sampling esophageal biopsies from at least two different levels to enhance diagnostic precision, particularly as the concentration of damage in the distal esophagus found in GERD is not found in EE.

Peripheral eosinophilia, albeit nonspecific, is a frequently observed supportive finding. An upper gastrointestinal series must be considered in patients with chronic vomiting, dysphagia, or

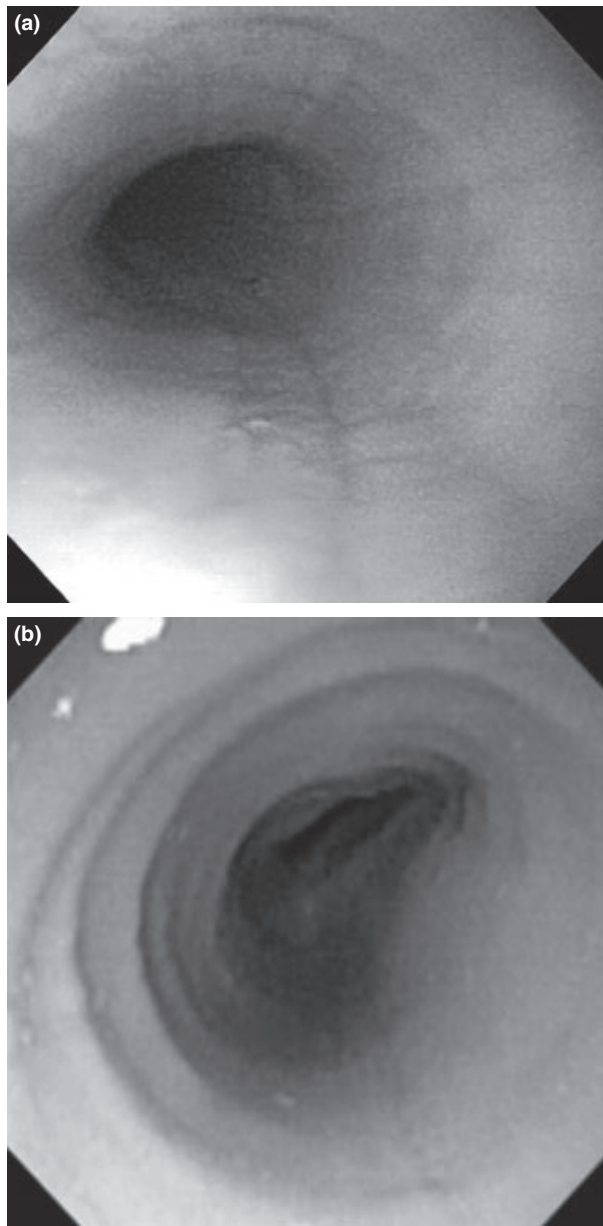


Fig. 1. Endoscopy photographs depicting distinctive findings of esophageal mucosal furrowing (a) and rings (b) in eosinophilic esophagitis.

food impactions, to evaluate other differential diagnoses, such as achalasia or esophageal webs, and EE complications, such as strictures.

An allergy evaluation is warranted in all patients with EE, as it may predict response to pharmacotherapy and guide dietary therapy. Commonly employed allergy tests shown to be useful in identifying allergens are food-specific IgE and skin prick tests. Skin patch tests in combination with prick tests have been shown to improve allergen identification and dietary plan formulation (24, 25). However, the lack of standardization of techniques and interpretation

does not currently support a role for skin patch tests in routine allergy evaluation for EE.

#### Treatment

Emergent treatment is necessary in those patients with EE who present with food impaction, severe dysphagia precluding oral nutrition, or with malnutrition. Most patients, however, despite chronic recurring symptoms, are well nourished and able to receive a stable treatment regimen for several months.

The two main treatments found effective in EE are corticosteroids and dietary restrictions (4, 32, 35–40). Choosing one over the other is complex and must take into consideration the natural history of the disorder combined with the treatment's anticipated efficacy, rapidity of effect, needed duration of use, cost-effectiveness, safety, and impact on the patient's and family's quality of life.

**Dilation.** Esophageal stricture dilation is a useful procedure, particularly as an adjunct to medical management to alleviate dysphagia due to esophageal stricture and esophageal dysmotility. Several publications report linear esophageal mucosal tears and perforation complicating dilation in EE, or even occurring spontaneously or simply during passage of the endoscope. (41–43). Hence, caution must be exercised in performing esophageal dilation in patients who have, or are suspected to have, EE. It has also been suggested, though unsupported by scientific data, that confirming the diagnosis by biopsies and pre-treatment with anti-inflammatory drugs (e.g., corticosteroids) may help minimize complications during dilation.

**Anti-reflux therapy.** Acid suppression is an important treatment for those EE patients who have a GERD-predominant phenotype and objective findings of abnormal esophageal pH studies. It is controversial whether acid suppression should be undertaken in all patients empirically as an initial treatment approach, thereby eliminating the confounding effect of GERD in producing esophageal eosinophilia. Some experts use the persistence of esophageal eosinophilia despite an adequate trial of a proton pump inhibitor as a means of validating the diagnosis of EE. Dense esophageal eosinophilia is rarely reported to resolve in response to proton pump inhibitors (44).

**Corticosteroids.** Corticosteroids are potent anti-inflammatory agents whose proposed anti-eosinophil actions include apoptosis, down-regulation

of chemotactic factors, and inhibition of pro-inflammatory cytokines. They are usually successful in inducing both symptomatic and histologic remission in EE. Since demonstration of success with topical steroids, systemic steroid use has been limited to those EE patients who have significant or acute onset of esophageal obstructive symptoms, and in patients refractory to topical steroids and dietary therapy.

Systemic corticosteroids are dosed at 1–2 mg/kg/day to induce remission and then tapered over several months, as in inflammatory bowel disease (37). Serious side effects associated with long-term use, including growth suppression, bone demineralization, and adrenocortical insufficiency, do not allow safe long-term use of systemic steroids for maintenance therapy of chronic or relapsing EE.

Topical steroids, also referred to as swallowed steroids, are used successfully for both the initial and maintenance phases of EE treatment. Using the metered dose inhaler without a spacer allows effective delivery for topical action. Patients are instructed to defer eating and drinking for 30 min after administration of the medicine. Symptomatic and histologic relapses frequently occur following treatment cessation (4, 38, 40, 45, 46). Topical steroids are not free of side effects, but are safer and better tolerated than systemic steroids. A viscous preparation of oral budesonide mixed in a sucralose suspension is another method to facilitate drug administration, especially in neurologically impaired children (47).

**Montelukast.** Montelukast, a leukotriene receptor antagonist, induced a symptomatic response in adults with EE at a daily dose of 100 mg orally, and was beneficial in maintenance doses of 20–40 mg daily for several months. However, it does not improve esophageal eosinophilia, and hence the postulated primary mechanism of action is inhibition of eosinophil activation (48).

**Mast cell stabilizers.** Despite the proposed role for mast cells as mediators in the inflammatory process, a clear benefit of mast cell stabilizers, such as disodium cromoglycate and ketotifen, has not been shown in patients with EE (3, 49).

**Anti-IL5 antibody.** An uncontrolled trial investigating mepolizumab, an anti-IL5 monoclonal antibody, found clinical and histologic remission in a small number of patients with hypereosinophilia syndrome, including an adolescent with EE (7). However, further safety and efficacy data are awaited before mepolizumab can be recommended as standard therapy for EE.

**Dietary therapy.** Dietary therapy attempts to eliminate foods either established or circumstantially suspected as allergens. Some experts recommend an elimination diet formulated on the basis of results of an allergy evaluation. Other proponents of dietary therapy in EE attempt more aggressive elimination of antigens regardless of allergy results by instituting an elemental diet composed of an amino acid-based formula; studies report elemental diets to be effective in 92–98% of patients. Clinical status improves in 7–10 days and normal histology is usually seen within 4–5 wk (4, 32, 35).

Recently, a selective diet referred to as a six-food elimination diet—removing milk, soy, wheat, egg, nuts, and seafood—was shown to produce a clinico-pathologic response in 26 out of 35 (74%) children with EE, compared to a response in 22 of 25 (88%) children treated with an elemental diet (an amino acid-based formula) (36).

The main limitations of severely restricted and elimination diets are poor palatability, cost, and potential nutrient deficiencies, impacting quality of life and compliance. The optimal duration and follow-up of dietary therapy have not yet been established. A registered dietician should be involved in the initial and follow-up care of a patient with EE undergoing dietary therapy.

#### Natural history

A noteworthy relapse rate of ~80% was found following initial response in a retrospective review of 89 children with EE followed for 8 yr, supporting the notion that EE is a chronic relapsing esophageal disorder (34). Although the natural history of EE has not been studied prospectively, concern has been raised by the initial presentation of esophageal stricture in patients without prior complaints, and by theoretical potential for other complications, such as Barrett esophagus and esophageal cancer (17). These observations have led some to advocate strongly for treatment for all EE patients irrespective of symptoms and for vigilant follow-up, including serial endoscopies with biopsies. Indeed, such considerations are compelling for researchers to investigate the natural history of treated vs. untreated EE, and to establish noninvasive and yet reliable biomarkers for disease follow-up.

#### Case 3

A 14-month-old Caucasian girl was admitted with a 5-wk history of progressively worsening projectile and non-bilious emesis. Her symptoms started 2 wk after she was switched from soy-

based formula to cow's milk. Her past history included eczema, vomiting on consumption of cow's milk-based formula, and hives on exposure to eggs. Family history was positive for asthma and food allergies. On admission, she was afebrile and irritable. Her height and weight were 50th percentile for age. She had an erythematous rash on her cheeks and extremities. The abdominal and anorectal examinations, including a stool guaiac test, were unremarkable.

Pertinent laboratory findings were: WBC of 12 K/ $\mu$ l (6–16 K/ $\mu$ l) with 11% eosinophils (absolute eosinophil count 1320/ $\mu$ l [normal <450/ $\mu$ l]). Upper gastrointestinal series revealed a narrow pyloric channel, delayed gastric emptying, and normal ligament of Trietz. Because of the clinical suggestion of allergies and peripheral eosinophilia, an esophagogastroduodenoscopy with biopsies was performed for further evaluation. The endoscopy revealed normal appearing esophagus, fundus, and gastric body. A smaller endoscope, Olympus GIF-XP 160 (outer diameter [OD] 5.9 mm) was advanced into the duodenum after an endoscope with an OD of 8.6 mm could not pass the pylorus. The pyloric and duodenal bulb mucosae appeared edematous. Small ulcers were seen in the second and third portion of the duodenum. Antral mucosal histology showed marked eosinophilic infiltration of the epithelium, deep lamina propria around the glands, and muscularis mucosa duodenal histology revealed prominent eosinophil and plasma cell infiltration in the lamina propria. She had an IgE level of 169 IU/ml (normal <60 IU/ml) and positive specific IgE to food allergens—egg white, barley, wheat, rice, milk, and corn. Stool studies did not suggest parasitic infection. The patient was diagnosed to have eosinophilic gastroenteritis with a clinical presentation of gastric outlet obstruction. All sources of complex dietary proteins were eliminated by providing an amino acid-based formula orally for 6 wk, producing a satisfactorily improved clinical status. Subsequently, she was introduced to RAST-negative foods at 2-wk intervals, and was symptom free at a 6-month follow-up visit.

## Discussion

Eosinophilic gastroenteritis was first reported by Kaijser in 1937 to describe eosinophilic infiltration of the stomach and small bowel (50). Since then, many cases have been described from around the world (51–55), and the disorder is now recognized to affect any area of the digestive system from the esophagus to the rectum.

## Epidemiology

Eosinophilic gastroenteritis affects all races and ages, and peaks during the second and sixth decades of life. Due to the lack of large population-based studies, the incidence of EGE has been difficult to determine, but currently it is much less common than EE (53, 55, 56). Similar to EE, however, the incidence is higher in males, with a ratio of 3:2 (57, 58), and personal or family history of allergic disorders such as asthma, hay fever, and eczema is present in 60–70% (5).

## Pathogenesis

Eosinophilic gastroenteritis can be idiopathic or develop in association with food allergies or any of the disorders that may provoke secondary EE (Table 1). Eosinophils, the hallmark of the pathology of EGE, normally reside in the gastrointestinal tract lining beyond the esophagus, and are believed to have a role in host defense (e.g., against parasitic infections). Reported normal densities of eosinophils vary throughout the length and depth of the gastrointestinal tract (see below). Several studies provide evidence that eosinophils function as antigen presenting cells and mediate inflammatory effects by releasing their granular proteins, such as major basic proteins, eosinophil peroxidase, and eosinophilic cationic protein. Eosinophils also secrete pro-inflammatory cytokines, such as IL-3, IL-4, IL-5, IL-18, and transforming growth factor, and lipid mediators which are cytotoxic to human intestinal epithelium (59, 60).

## Clinical presentation

Clinical manifestations depend on the site (both rostral-caudal and the gut layer) and degree of involvement, and range from abdominal pain to intestinal obstruction and ascites (51–55, 57). Clinical manifestations of EGE are discussed in depth in many reviews (56, 61–65). Stomach (25–80%) and small intestine (28–100%) are reported to be the commonly involved areas, but large intestine and rectum can also be affected (56, 66, 67) (Table 1). Pathophysiological and clinical classification of EGE has been proposed according to the intestinal layer most affected—mucosa, muscle, or subserosa (56). Mucosal disease is considered the most common subtype (25–100%); it is possible that the greater feasibility of diagnosis via mucosal biopsies contributes to this preponderance. Typical symptoms are abdominal pain, vomiting, diarrhea, and weight

loss, but iron-deficiency anemia, malabsorption, and protein-losing enteropathy may also occur (55). Due to nonspecific presenting symptoms, mucosal EGE can be confused with other conditions such as appendicitis, pancreatitis, and inflammatory bowel disease. Muscular EGE, the second most common subtype (13–70%), typically presents with gastric outlet or intestinal obstruction. Muscular subtype of EGE involving the gastric outlet mimics the presentation of hypertrophic pyloric stenosis. Reports describe this association in all ages from infancy to adulthood (51, 52, 68). Acquired gastric outlet obstruction may also occur in other conditions, such as inflammatory bowel disease, infections, peptic ulcer disease, chronic granulomatous disease, tumors, and Menetrier's disease. Differentiation from these conditions is prudent and can be made by a combination of history, physical examination, radiologic studies, blood tests, allergy testing, and endoscopy with biopsies. Serosal disease, the least common form (12–40%), may present with eosinophilic ascites and is associated with more bloating, higher levels of peripheral eosinophilia, and better response to steroids than the other two types (54, 56).

#### Diagnostic evaluation

Diagnosis of EGE requires a high index of clinical suspicion and should be considered in those with acute or recurrent gastrointestinal symptoms and peripheral eosinophilia. A detailed history and examination should hunt for eczema, asthma, and environmental and food allergies. While peripheral eosinophilia can provide a clue in the setting of gastrointestinal symptoms, it is not necessary for the diagnosis. Approximately 30% of patients with EGE do not have hypereosinophilia. Secondary causes of eosinophilic intestinal inflammation noted above should be excluded by pertinent investigations. Parasitic infections should be excluded by stool studies. In patients with ascites, paracentesis documenting ascitic eosinophilia can be diagnostic. Radiography can be helpful, especially in the muscular and serosal subtypes. Upper gastrointestinal series can show an irregular appearance of the antral surface of the stomach in mucosal EGE and a string sign (Fig. 2) in gastric outlet obstruction resulting from muscular EGE. (51, 52, 68). Abdominal ultrasound can detect pyloric muscle hypertrophy in muscular EGE, and ascites in the serosal subtype. Abdominal computerized tomography can show nodular, irregular folds and thickening of the stomach and intestinal wall (69).

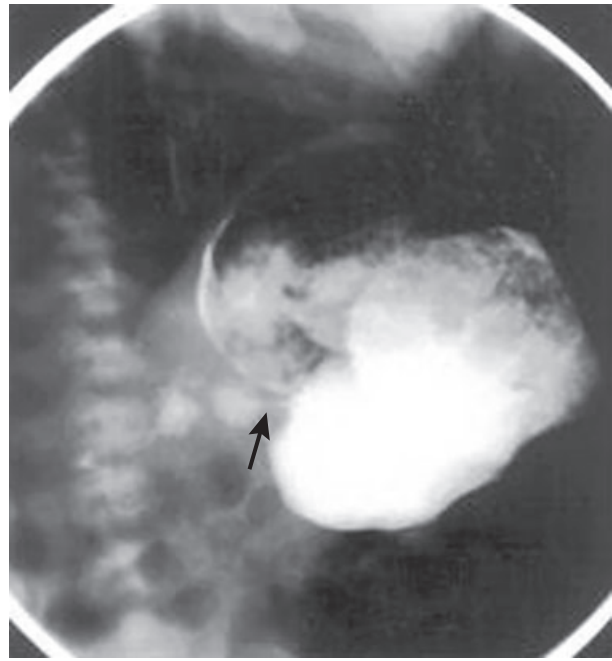


Fig. 2. An upper gastrointestinal barium study showing a 'string sign' in a child with eosinophilic gastritis.

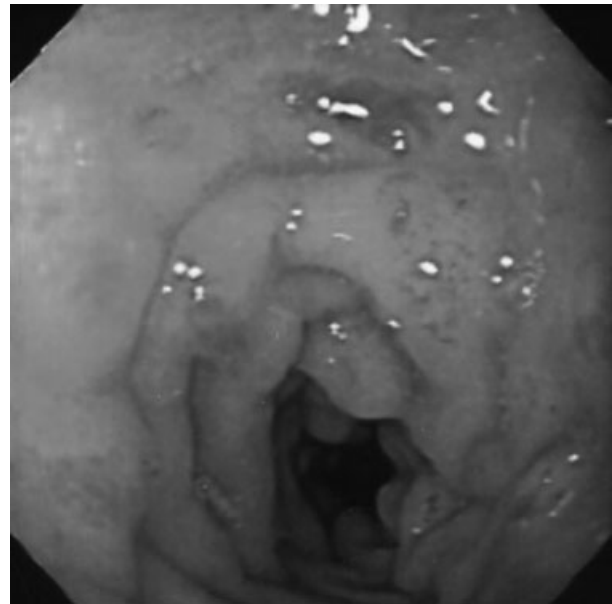


Fig. 3. An endoscopy image from the second portion of the duodenum showing mucosal edema and multiple erosions in a patient with a diagnosis of eosinophilic duodenitis.

Macroscopic abnormalities such as erythema, erosions, ulcers and polyps can be seen on endoscopy in the mucosal subtype (Fig. 3). Consensus on cut-off points between normal and pathological number of eosinophils in the gastrointestinal tract is lacking but several stud-

ies provide useful data. DeBrosse et al. (70) showed that varying concentrations of eosinophils are seen in the gastrointestinal tract of healthy children, with the highest concentration being in the cecum. Colonic eosinophilia was examined with regard to eosinophil density and location in 69 children with varied diagnoses (71). Patients with inflammatory bowel disease had a higher eosinophil density than those with irritable syndrome and allergies. A study based on autopsy findings in children without known gastrointestinal disorders (72) showed that mucosal eosinophils ranged from less than 10 eos/hpf in the duodenum to more than 40 eos/hpf in the cecum. Intestinal eosinophilia may also be influenced by variations in geographic location, environmental temperature, season, ingested and aeroallergen exposure, and parasitic infections (73). Because of the patchy distribution and variable depth of diseased areas, histologic confirmation can be challenging. Several mucosal biopsies from each of multiple sites, and surgical exploration with full thickness biopsies in selected cases can be helpful for definitive diagnosis and management.

Allergy evaluation should be considered when there is a clinical suspicion for allergies. Specific IgE blood tests and skin prick tests detect IgE-specific antibody to various allergens. In non-IgE-mediated allergies to foods, symptom correlation with ingested foods and response to elimination diets may be used as the basis for skin patch testing.

#### Treatment

Management is mainly directed toward any identified triggers. As with EE, strong circumstantial evidence for an underlying allergic cause for many cases of EGE has made dietary restrictions and corticosteroids the most popular therapeutic strategies. Other treatment options for patients with EGE include mast cell inhibitors and leukotriene receptor antagonists. Due to the scarcity of evidence-based data regarding various treatment options, decisions regarding therapeutic choices are guided mostly by the multitude of case reports and expert reviews. Treatment is tailored to the individual patient by taking into account food allergies, safety, efficacy, cost, and compliance.

The principles of dietary therapy discussed in the previous section on EE are also applicable to the management of EGE. Predicting response to dietary restrictions in EGE is difficult, as the currently available data are based on small retrospective reports, most of which describe

combination treatments. However, dietary therapy as exclusive therapy of EGE has shown to be successful in a few cases (52, 55, 74), including ones with gastric outlet obstruction. In contrast to EE, systemic corticosteroids are more frequently used in EGE, either alone or in addition to dietary therapy, despite their negative side effect profile. Surgical treatment is reserved for patients with gastrointestinal obstruction (51, 68, 75) who have failed dietary therapy. Surgical options in those presenting with gastric outlet obstruction consist of pyloromyotomy, gastrojejunostomy, and partial gastrectomy. Relief of mechanical obstruction through surgical resection can be transient, as symptoms have been reported to recur, necessitating further medical and dietary therapy.

#### Prognosis

The natural history of EGE has not been well described, but clinical studies point to a chronic relapsing course for patients with this diagnosis. The long term follow-up (2.5–5.5 yr) of six children with EGE and protein-losing enteropathy initially treated successfully with an elemental diet has been described recently—despite some liberalization of the diet, clinical remission could be maintained only by continued dietary restrictions (55). This study emphasizes the chronic nature of EGE and the importance of long-term follow-up.

Larger, prospective, multicenter studies are needed to further investigate the pathogenesis, safe and effective management options, natural history, and long-term outcome of patients with EGE.

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### Multiple Choice Questions

*Question 1.* A 12-month-old male was diagnosed clinically with gastroesophageal reflux disease based on the symptoms of fussiness, vomiting and poor feeding. He was breast-fed for the first 8 months of life and subsequently switched to a cow's milk-based formula. He has been on an adequate dose of proton pump inhibitor for the past 3 months with no improvement. Review of systems was significant for eczema. What is the next best step?

- A. Continue use of proton pump inhibitor with addition of metoclopramide.

- B. Skin patch testing.
- C. Esophagogastroduodenoscopy with biopsies.
- D. Esophageal pH-impedance study
- E. Switch to a soy-based formula.

*Question 2.* The required diagnostic features of primary eosinophilic gastroenteritis include all of the following except:

- A. Symptoms and signs of gastrointestinal disease.
- B. The presence of peripheral eosinophilia.
- C. The absence of parasitic infection.
- D. The absence of eosinophilia in extra-intestinal organs.
- E. Histopathologic evidence of prominent gastrointestinal eosinophilia.

*Question 3.* Which of the following statements regarding eosinophilic esophagitis is true?

- A. The diagnosis of eosinophilic esophagitis is frequently associated with asthma, eczema and allergies.
- B. Successful treatment of patients with eosinophilic esophagitis usually predicts a disease cure.

- C. Patients with eosinophilic esophagitis predominantly have IgE-mediated food allergies.
- D. Antihistamines have an established role in the treatment of eosinophilic esophagitis associated with allergies.
- E. All the above.

*Question 4.* Which of the following statements about eosinophilic gastroenteritis is false?

- A. Eosinophilic gastroenteritis may affect any area of the digestive system and clinical manifestations depend on the site and degree of involvement.
- B. Mucosal disease is considered to be the least common subtype of eosinophilic gastroenteritis and usually presents with eosinophilic ascites.
- C. Several mucosal biopsies from multiple sites can be helpful for definitive diagnosis and management of eosinophilic gastroenteritis.
- D. The natural history of eosinophilic gastroenteritis is characterized by a waxing and waning course.
- E. All of the above.

Correct responses to the questions: 1 – C, 2 – B, 3 – A, 4 – B.