Eosinophilic Gastrointestinal Disorders

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KEYWORDS

• Eosinophilic esophagitis • Eosinophilic gastroenteritis • Eosinophilic proctocolitis
• Proton pump inhibitor-responsive esophageal eosinophilia • Food allergens

KEY POINTS

- Eosinophilic esophagitis (EoE) is an atopic disease that is characterized by an isolated infiltration of eosinophils into the epithelium of the esophagus.
- A diagnosis of EoE requires an esophageal biopsy while on a proton pump inhibitor for at least 6 to 8 weeks.
- Proton pump inhibitor–responsive esophageal eosinophilia should always be differentiated from EoE.
- Both medication and dietary therapy options should be considered in patients with EoE.
- Eosinophilic gastroenteritis is described as a pathologic eosinophilic infiltration of any portion of the gastrointestinal tract, and eosinophilic proctocolitis is defined as an abnormal number of eosinophils in the colon alone.

EOSINOPHILIC ESOPHAGITIS

Introduction

Eosinophilic esophagitis (EoE) is an atopic disease that is characterized by an isolated infiltration of eosinophils into the epithelium of the esophagus. EoE is triggered by specific allergens, almost always food antigens; there has been significant research in this area over the past 30 years in order to determine the nature of these specific allergens.[1]

Definition

The 2013 revised guidelines for the diagnosis and management of this disease state that EoE is defined as a clinicopathologic disorder that meets the following criteria[1]:

1. Presence of symptoms related to esophageal dysfunction

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2. Presence of greater than or equal to 15 eosinophils per high-power field on esophageal biopsy after a trial of a proton pump inhibitor (PPI)
3. Isolation of this mucosal eosinophilic predominance to the esophagus

Of note, symptoms of EoE are often similar to those of gastroesophageal reflux; therefore, the presence of eosinophils on esophageal biopsy is needed to make the diagnosis of EoE.

Prevalence

EoE has increased in prevalence over the past 10 years. The reported prevalence of EoE in 2003 was 4.3 per 10,000 children aged 0 to 19 years. The pediatric male to female ratio is approximately 3:1.[2]

Cause

EoE is thought to occur in genetically susceptible individuals through predominantly non–immunoglobulin E (IgE)-mediated allergic responses to allergens. These allergens are thought to be predominantly food, although other studies have suggested additional environmental allergens, such as aeroallergens, as potential triggers.[3] In general, when food allergens enter the body through a disrupted epithelial barrier, it is postulated that local esophageal antigen presenting cells interact with this antigen. Subsequently, a cascade of proinflammatory cytokines, such as interleukin (IL)-5 and IL-13, as well as chemokines, such as eotaxin-1 and eotaxin-3, are triggered. This trigger results in recruitment of eosinophils to the esophagus.[4]

The first EoE genetic susceptibility locus was recently described at locus 5 q 22.[5] One of the genes at this locus is thymic stromal lymphopoietin, a T-helper 2 proinflammatory cytokine gene that has been associated with other allergic diseases in the past.

Clinical Symptoms

Symptoms of EoE are detailed in **Table 1** and **Box 1**.[6]

Table 1
Common symptoms of eosinophilic esophagitis

Younger Children	Older Children and Adolescents
Vomiting	Heart burn
Chronic nausea	Epigastric pain
Regurgitation	Dysphagia
Irritability/feeding difficulties	Nighttime cough
	Food impaction

Data from Liacouras CA, Markowitz JE. Eosinophilic esophagitis: a subset of eosinophilic gastroenteritis. Curr Gastroenterol Rep 1999;1:253–8.

Box 1
Less common symptoms of eosinophilic esophagitis

Growth failure

Hematemesis

Esophageal dysmotility

Failure to thrive

Malnutrition

Data from Liacouras CA, Markowitz JE. Eosinophilic esophagitis: a subset of eosinophilic gastroenteritis. Curr Gastroenterol Rep 1999;1:253–8.

Some children drink an overabundance of fluids with meals or chew their food excessively in order to compensate for these symptoms. Additional allergic symptoms, such as asthma, eczema, and allergic rhinitis, are present in up to 50% of patients. Complications of EoE include hiatal hernia as well as esophageal strictures, perforation, and fungal infection. Because heartburn is a common symptom of EoE, it is important to consider EoE in patients who have chronic reflux symptoms.

Diagnosis

When considering this diagnosis, patients should be placed on a PPI. After at least 6 to 8 weeks on the PPI, patients should undergo an upper endoscopy with biopsy. An esophageal biopsy is always necessary in order to diagnose EoE. Specifically, at least 15 eosinophils per high-powered field must be present on biopsy, and these eosinophils must be isolated to the esophagus. Although the distal esophagus is typically most affected, biopsies should be taken from multiple levels of the esophagus, as EoE is a patchy disease.[7] In order to make a diagnosis of EoE, biopsies must also be taken from the stomach and duodenum to be sure that excessive eosinophilia is not present. Increased eosinophilia in the stomach or duodenum would instead suggest eosinophilic gastroenteritis.

Visual endoscopic findings include concentric ring formation (called trachealization), vertical linear furrows, and white patches or plaques scattered along the mucosal surface. These findings are present in up to 70% of patients with EoE but are not pathognomonic for the disease.[8] The remaining 30% of those with EoE have visually normal esophageal mucosa. These facts reinforce the need to obtain an esophageal biopsy in order to make the diagnosis of EoE (**Box 2**).

Box 2
Differential diagnosis of eosinophilic esophagitis

- Eosinophilic gastrointestinal diseases
- Proton pump inhibitor–responsive esophageal eosinophilia
- Celiac disease
- Crohn disease
- Infection
- Hypereosinophilic syndrome
- Achalasia
- Drug hypersensitivity
- Vasculitis
- Pemphigus
- Connective tissue diseases
- Graft versus host diseases

There are no current serologic, radiologic or stool tests that have been shown to be diagnostic of EoE.

Allergy Testing

In addition to an evaluation by a gastroenterologist, consultation with an allergist is often helpful because patients often have other features of atopy including asthma,

eczema, allergic rhinitis and IgE-mediated food allergies. Although allergy testing is not diagnostic of EoE, skin prick testing (SPT) should be considered in order to identify IgE-mediated food allergens and, less frequently, aeroallergens.[9] These allergens may also crossover and be potential EoE allergen triggers. In addition to SPT, atopy patch testing may be considered in order to identify non–IgE-based food allergens, as the food reactions in EoE are due to these cell-mediated reactions.

Proton Pump Inhibitor–Responsive Esophageal Eosinophilia

PPI–responsive esophageal eosinophilia (REE) should always be differentiated from EoE. PPI-REE is either related to gastroesophageal reflux, an independent disorder, or a possible subset of EoE. Despite not understanding the exact cause of PPI-REE, it is important to determine if esophageal eosinophilia do not respond to a PPI, as the following treatment approach for EoE mandates this course of action. Ngo and colleagues[10] identified several patients with esophageal eosinophilia that normalized after administration of a PPI for 1 month. Short-term aggressive dosing of the PPI should be considered; the pediatric dosage of the PPI can be up to 1 mg/kg twice daily (maximum 30–40 mg twice a day) and should be administered for 6 to 12 weeks before upper endoscopy and biopsy.

Management of Eosinophilic Esophagitis

Both medical and dietary therapy should be considered in patients with EoE. Historically, systemic steroids were the first medication that mitigated symptoms as well as normalized the number of eosinophils in the esophageal mucosa in these patients. However, chronic systemic corticosteroids cannot be used long-term because of side effects, such as decreased linear growth, increased appetite, hypertension, bone changes, and mood alterations. Although this is not currently recommended as a first-line treatment in EoE, oral corticosteroids are still a useful short-term treatment approach for patients with severe dysphagia, poor weight gain, and small-caliber esophagus.

Current first-line medical treatment of EoE is swallowed, topical corticosteroids. These medications include fluticasone propionate, which is sprayed into the pharynx and swallowed rather than inhaled, and swallowed viscous budesonide.[11] Swallowed topical corticosteroids are delivered along the surface of the esophagus, which leads to symptom improvement and histologic normalization within several weeks. Recommended dosing for fluticasone is age and weight based and varies from 110 to 880 mg twice daily; dosing for swallowed budesonide is 0.5 to 1.0 mg twice a day. Patients should not eat, drink, or rinse the mouth for 20 to 30 minutes after use. The initial treatment course is 2 to 3 months, followed by a repeat upper endoscopy. If patients have achieved histologic remission, then the steroids can be weaned (followed by another upper endoscopy). The disease almost always recurs once the medication is discontinued. The side effects of topical corticosteroids are significantly decreased compared with those of systemic steroids. However, some patients develop epistaxis, dry mouth, or esophageal candidiasis.[11–14]

Dietary modification has also been found to be an effective treatment. After identifying the appropriate dietary antigens, patients experience both an improvement in symptoms and histologic resolution. Potential dietary modifications include initiation of a hypoallergenic, elemental diet, eliminating the 6 most common food allergens (milk, eggs, wheat, soy, nuts, shellfish) or selectively eliminating particular foods from the diet. Kelly, Markowitz, and Liacouras demonstrated that greater than 95% of children completely resolve their EoE if given a strict amino acid–based formula as the sole source of dietary nutrition.[15,16] Children on this diet ingest only this formula

for a period of time to allow the esophagus to heal. After the esophageal mucosa normalizes, foods are systematically reintroduced. Clinical symptoms may take up to several weeks to recur after reintroduction of a particular food. This diet is often difficult to adhere to for older children because of the large volume of formula required to meet caloric needs and the inability to eat solid foods while on the diet. Most pediatric patients on this regimen cannot tolerate this formula by mouth and instead require administration via a nasogastric tube.

Alternatively, in the mid 2000s the idea of using targeted elimination diets was introduced. Kagalwalla and colleagues[17] showed that a 6-food elimination diet without allergy testing resulted in resolution of EoE symptoms and improvement, but not elimination, of the esophageal eosinophil count in approximately 75% of patients.[17] These targeted elimination diets are executed in conjunction with serial endoscopy with biopsy. After specific foods are removed from the diet for at least 6 to 8 weeks, patients then undergo a repeat endoscopy to assess the esophageal eosinophil count. If the count has normalized, then these foods must be assessed individually to determine the exact food allergen that triggers the disease. On the other hand, if there is no improvement in the eosinophil count after removal of the foods, further dietary restriction must be initiated. This process continues for several cycles until the exact EoE food allergen triggers have been identified and removed and the esophageal eosinophil count has normalized. The most common EoE trigger foods identified through this process are dairy, eggs, soy, corn, wheat, and beef.

Other Therapy

New medications that target specific cytokines and immune mediators are being studied as potential treatment options for patients with severe EoE. These medications include anti-IL-5, very late activating antigen, and monoclonal eotaxin antibody.

EOSINOPHILIC GASTROENTERITIS (GASTROENTEROCOLITIS)

Introduction and Definition

Although there are no specific diagnostic criteria for eosinophilic gastroenteritis (EoG), it is generally described as a pathologic eosinophilic infiltration of any portion of the gastrointestinal tract. It can be superficial or infiltrative in nature.[18,19]

Cause

The cause is currently unknown; however, EoG is thought to be the result of both IgE-mediated and non–IgE-mediated processes.[20] The prevalence is unknown.

Clinical Symptoms

Common symptoms include those associated with malabsorption, including growth failure, weight loss, diarrhea, and hypoalbuminemia. Other symptoms, such as intermittent abdominal pain, vomiting, dysphagia, and bloating, can be seen as well. Severe disease manifestations are uncommon and include gastrointestinal bleeding, iron-deficiency anemia, and protein-losing enteropathy. Ascites is rare in these patients.

Diagnosis

There are currently no standard EoG diagnostic criteria. Diagnosis is typically made based on a constellation of clinical symptoms and histologic findings. Patients usually have one or more of the clinical symptoms described earlier, along with an increase in eosinophil count within the gastrointestinal tract found on endoscopic biopsy. Of note,

mucosal eosinophils can be present in any portion of the gastrointestinal tract; however, these eosinophils must not be limited to the esophagus alone. Most patients have an increased antral eosinophilia. Goldman and Proujansky[21] reported that 100% of 38 pediatric patients with EoG who were studied had eosinophils present in the gastric antrum, 60% in the esophagus, 79% in the proximal small intestine, and 52% in the gastric corpus.

Approximately 70% of patients with EoG have a peripheral eosinophilia. Laboratory testing should include allergy testing (which is often unrevealing) and infectious studies including stool ova and parasite tests, serum EBV PCR, giardia antigen and stool *Helicobacter pylori* testing. These patients may also undergo D-xylose absorption tests as well as lactose hydrogen breath tests to assess possible malabsorption, which may suggest small intestinal damage.[22–27] Rheumatologic testing and inflammatory bowel disease serologies may also be considered.[28,29]

Radiologic contrast imaging may show edema, luminal narrowing, or wall thickening. Areae gastricae is a lacy mucosal pattern of the gastric antrum that is sometimes present in EoG.[30]

The differential diagnosis for EoG is expansive (**Box 3**).[31] An evaluation for other possible causes of eosinophilic infiltration should be conducted before diagnosing EoG.

Treatment

There is no consensus as to ideal treatment. In some cases, dietary therapy with an elemental formula has successfully treated this disease.[32,33] Most patients respond to systemic corticosteroids; however, although many have remittance of symptoms while on a steroid regimen, most will have recurrence of symptoms once the steroids are weaned. They may require multiple steroid courses or chronic, low-dose steroid treatment.[34] Alternatively, 6 mercaptopurine, methotrexate, and budesonide may be used.[35–37] Regardless of the treatment option chosen, endoscopy with biopsy is often required to determine the extent of disease.

EOSINOPHILIC PROCTOCOLITIS

Introduction and Definition

Eosinophilic proctocolitis (EoP) is also known as allergic proctocolitis or milk-protein proctocolitis. It is characterized by the acute onset of rectal bleeding in infants. Specifically, it is defined as an abnormal number of eosinophils in the colon. However, an endoscopy is often not performed in these infants; EoP is instead diagnosed clinically based on the gradual onset of gastrointestinal bleeding that resolves with initiation of a protein hydrolysate formula.

Cause

The mature gastrointestinal tract is typically an effective barrier to prevent intact ingested food antigens from stimulating the immune system. However, in newborns, this barrier is immature and these intact antigens are able to permeate the intestinal wall and induce an immune response.[38] Cow's milk and soy are the two most common food antigens that trigger EoP. Because most of the commercially available formula is cow's milk based or soy based, children with EoP must find an alternative nutritional formula.[39] Additionally, breastfed babies account for up to 50% of EoP cases. It is thought that these infants are having an allergic immune response to food antigens that the mother ingests and are transferred into the breast milk.[40]

Box 3
Differential diagnosis of eosinophilic gastroenteritis

Allergic diseases
Food allergies
Hypereosinophilic syndrome

Gastrointestinal diseases
Appendicitis
Celiac disease
Hypertrophic pyloric stenosis
Inflammatory bowel disease

Immunologic diseases
Chronic granulomatous disease

Rheumatologic diseases
Connective tissue disease
Systemic lupus erythematosus
Scleroderma
Dermatomyositis
Polymyositis
Polyarteritis nodosa

Other
Churg-Straus syndrome
Inflammatory fibroid polyp
Malignancy

Infectious diseases
Ancylostoma caninium (hookworm)
Anisakis
Ascaris
Epstein-Barr virus
Enterobius vermicularis (pinworm)
Eustoma rotundatum
Giardia lamblia
Helicobacter pylori
Schistosomiasis
Strongyloides Stercoalis
Toxocara canis
Trichinella spiralis

Medications

Azathioprine

Carbamazepine

Clofazimine

Enalapril

Gemfibrozil

Gold

Data from Barak N, Hart J, Sitrin MD. Enalapril-induced eosinophilic gastroenteritis. J Clin Gastroenterol 2001;33:157–8.

Clinical Symptoms

EoP typically presents in well-appearing infants. Common presenting symptoms are summarized in **Box 4**. These patients do not present with vomiting or abdominal distention. Untreated EoP with chronic blood loss often leads to anemia and/or poor growth. In addition to infants, there is a second cohort of patients that first present in adolescence or early adulthood.

Diagnosis

The differential diagnosis for EoP is noted in **Box 5**. EoP is a clinical diagnosis. However, there are several laboratory tests that may aid in diagnosis. These tests include fecal leukocytes, stool bacterial culture, and stool *Clostridium difficile* testing. Children with EoP will often have fecal leukocytes and may specifically have eosinophils; however, they should not have fecal bacterial pathogens, such as *Salmonella* or *Shigella*. If they are colonized with *C difficile*, then this testing may be positive; however, this may not be the cause of their rectal bleeding.[41] On serologic examination, these patients may have a mild peripheral eosinophilia, hypoalbuminemia, or anemia.

Some of these children undergo flexible sigmoidoscopy. Although not essential for diagnosis, this information is often helpful in determining the cause of the bleeding. Documentation of erythema, friability, or ulceration in the colon supports an EoP diagnosis. However, a grossly normal-appearing colon does not definitively rule out EoP. Histologically, patients with EoP typically have patchy, focal aggregates of eosinophils within the lamina propria with normal crypt architecture.[42–45]

SPT or serum IgE allergy testing for specific foods is unreliable in these patients.

Treatment

Ideal treatment of infants with EoP is initiation of a protein hydrolysate formula.[46] Although symptoms may resolve very quickly after discontinuing the antigenic agent

Box 4
Common symptoms of eosinophilic proctocolitis

Gradual-onset rectal bleeding

Diarrhea

Increased mucous production

Eczema and/or reactive airway disease

Well-appearing child

Box 5
Differential diagnosis of eosinophilic proctocolitis

Infectious disease
- *Enterobius vermicularis (pinworm)*
- *Ancylostoma caninium (hookworm)*
- *Salmonella*
- *Shigella*

Inflammatory bowel disease

Drug reactions

Vasculitis

(ie, cow's milk formula or soy formula), resolution may take 4 to 6 weeks. Specifically, grossly bloody stool should resolve within 3 to 7 days and occult blood should resolve within several weeks.[47] If symptoms persist beyond 4 to 6 weeks, alternative causative antigens and/or alternative diagnoses should be considered. In breastfed infants, the mother should restrict cow's milk and soy-containing foods. These infants have an excellent prognosis, and many of them may tolerate cow's milk and/or soy after reintroduction between 1 and 3 years of age. If a reaction occurs with milk reintroduction at 12 months old, children are often rechallenged every 3 to 6 months. If they continue to have allergic reactions, they should be referred to an allergist. Individuals who present as adolescents typically have a more chronic and relapsing disease course.

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