

Gastrointestinal Manifestations of Food Allergies

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KEYWORDS

- Eosinophilic esophagitis • Eosinophilic gastroenteritis
- Food allergy • Allergy testing

INTRODUCTION

IgE-mediated food hypersensitivity affects 4% of children in the United States, with increasing incidence rates over the last 10 years. In addition, an increasing number of children with food allergy are reporting other concurrent allergic diatheses such as asthma, eczema, and allergic rhinitis. The eosinophilic gastrointestinal disorders (EGIDs), often a manifestation of food allergy, have become increasingly prevalent over the past 20 years, with eosinophilic esophagitis affecting at least 4/10,000 US children, with case reports on all continents except Africa.^{1,2}

Manifestations of food allergy range from clinical anaphylaxis, mediated primarily by specific IgE and immediate hypersensitivity, to EGIDs, which are mediated through combined IgE hypersensitivity and delayed-type hypersensitivity. Subsets of EGIDs such as eosinophilic colitis seem to be largely IgE independent. Additional diseases that involve food intolerance include autoimmune processes, such as in celiac disease. Understanding the multiple mechanisms and manifestations of food allergy is of paramount importance when choosing the appropriate diagnostic modality and interpreting the test results. Immediate hypersensitivity reactions to foods are assessed by testing that evaluates the presence and/or levels of food-specific IgE. This can be achieved using skin prick testing (SPT) or serum specific IgE levels. Serum food-specific IgE levels can have prognostic usefulness in children with a history of urticaria, respiratory distress, hypotension, and other clinical symptoms of anaphylaxis. In contrast, autoantibody testing for tissue transglutaminase and endomysial IgA are used in the diagnosis of celiac disease. Food atopy patch testing is intended to evaluate a delayed hypersensitivity to foods but remains a research tool.

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This article reviews the clinical manifestations, pathogenesis, testing modalities, and treatments of food allergies that involve the gastrointestinal (GI) tract.

EOSINOPHILIC ESOPHAGITIS

Clinical Features

Eosinophilic esophagitis (EoE) is a clinicopathologic condition defined by diffuse eosinophilic infiltration of the esophagus. It is becoming increasingly recognized in adults and children, and the first consensus guidelines for its diagnosis and management were published in 2007.² The recommended guideline diagnostic criteria were based on published literature and expert opinion, and were defined as: (1) characteristic symptoms, (2) 15 eosinophils/high power field (HPF) or greater, and (3) exclusion of other disorders, including failure of response with high-dose proton pump inhibitors (PPI) therapy, or normal pH monitoring.²

EoE was first described in the mid-1970s by Dobbins and colleagues³ and Landres and colleagues,⁴ who reported 2 adult men with symptoms of dysphagia, epigastric pain, esophageal spasms, and eosinophilia of the esophagus with negative pH probes. In 1993, Atwood and colleagues⁵ published a retrospective review of 12 patients with increased esophageal eosinophils. In this study, 11 of 12 patients had normal pH monitoring and 7 of 12 were atopic. Most patients had dysphagia and frequent food impaction, and a mean of 56 eosinophils/HPF compared with 90 patients with pH-probe-proven gastroesophageal reflux (GER) who had mean eosinophils of 3.3 eosinophils/HPF.

Since its first description, the reports of EoE have steadily increased, with currently reported incidence rates of 1.25/10,000 and prevalence of 4.3/10,000 in children less than 19 years of age.¹ It is more common in young White males, and affected patients have high rates of concurrent atopy.⁶ Greater than 70% of patients have a history of asthma, eczema, food allergies or food sensitization, environmental allergy, or chronic rhinitis, and up to 75% have a personal or family history.² Current reports show that a subset of patients have a genetic variant of EoE and reported disease risk genes for EoE include eotaxin-3 and thymic stromal lymphopoietin and a single nucleotide polymorphisms at the transforming growth factor $\beta 1$ (TGF $\beta 1$) promoter may have disease-modifying effects on therapeutic response. Eotaxin-3 genotype GG was statistically significant in patients with EoE versus controls and comprised 14% of the patients with EoE.⁷⁻⁹

Classic EoE symptoms include abdominal pain, vomiting, and dysphagia, although symptoms vary by age.² Infants and toddlers present with gagging, choking, feeding refusal, or poor growth. Whereas GER symptoms tend to improve in the second half of the first year, symptoms from EoE may not. Feeding difficulties likely arise from nausea, dysphagia, or the attempt to avoid pain with eating, which are perpetuated by continual negative reinforcement. When evaluating these children, primary swallowing dysfunction, cardiac or respiratory disease, and underlying anatomic abnormalities must also be considered and evaluated.

School-aged children tend to present with pain or vomiting. Pain can vary in location, frequency, and severity, with complaints of chest, epigastric, or periumbilical pain being most common.² Symptoms rarely occur in association with a particular food trigger, tend to be intermittent, and tend not to predict the severity of inflammation.¹⁰ In some instances, parents may recall an infant in whom reflux symptoms began early in life, were associated with eczema, and worsened with the introduction of solid foods.¹¹

Dysphagia and food impaction are more common in adolescents and adults. The association of dysphagia with EoE has been reported as high as 80% and is the

most frequent indication for endoscopic evaluation in adults.^{12–14} Endoscopic ultrasound has shown the thickening of the entire mucosa and muscular layers of the esophagus, which may affect esophageal motility.¹⁵ Dysphagia has not been directly related to the duration of inflammation or degree of eosinophilic infiltration, but chronic inflammation with subsequent tissue remodeling has been postulated, and dysphagia complaints correlate directly with episodes of dysmotility in pediatric patients.¹⁶ Adult patients with EoE have chronic complaints of dysphagia when treated with intermittent dilation only.¹⁷

Histologic Features

The esophagus, unlike other areas of the GI tract, is normally devoid of eosinophils. However, esophageal eosinophilia can occur with other diseases including GER disease, connective tissue disorders, parasitic infections, inflammatory bowel disease, and as a drug reaction. In addition, adults with allergic rhinitis can have esophageal eosinophilia during the pollen season independently of an EoE diagnosis.¹⁸ Other causes of esophageal eosinophilia must be investigated before diagnosing primary EoE.

Histologically, EoE esophageal biopsies have several characteristic features, including eosinophil microabscesses, degranulation, and superficial layering as well as basal zone hyperplasia and vascular papillary elongation.² EoE is diagnosed when there are at least 15 eosinophils or more per HPF on 400 $\times$ light microscopy using a hematoxylin and eosin stain (**Fig. 1**).² The eosinophil count of the highest density seen (peak eosinophils) is currently used in diagnosis. Unlike acid-induced esophageal eosinophilia, EoE is a patchy, diffuse disease. Procuring 5 biopsies increases the

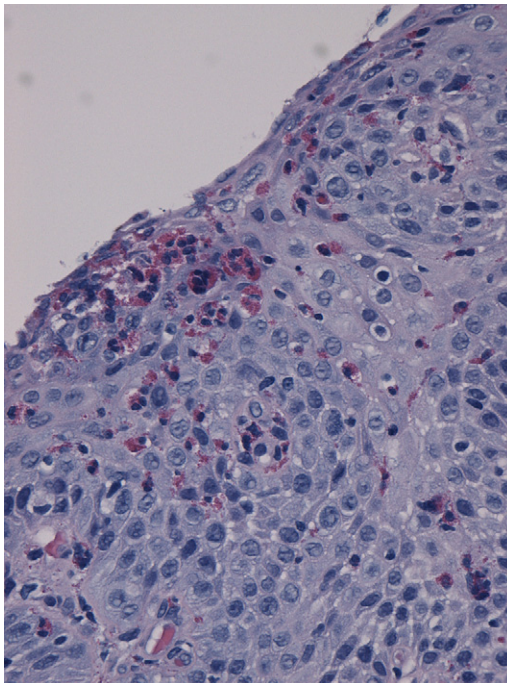


Fig. 1. Eosinophilic esophagitis. Eosinophilic abscesses and numerous eosinophils.

diagnostic yield to more than 90%. In addition, obtaining biopsies from at least 2 levels of the esophagus is recommended.¹⁹

Endoscopic Features

Endoscopic findings can be obvious or subtle. Up to 30% of patients with histologic EoE have an endoscopically normal mucosa.² However, classic EoE findings include linear furrowing, concentric rings (or felinization/trachealization), white exudates that mimic *Candida*, friability, or an attenuated subepithelial vascular pattern (Fig. 2).² Small-caliber esophagus, characterized by a uniformly narrowed esophagus, also has been described in patients with EoE with dysphagia.²⁰ Ongoing inflammation may lead to esophageal strictures, the most severe EoE complication reported to date.

Distinction of EoE from GER

Almost 2 decades ago, Winter and colleagues²¹ reported distal and proximal esophageal eosinophilia in patients with GER. Whereas GER biopsies tend to have fewer than 7 eosinophils in the distal esophagus, EoE biopsies show significantly more severe eosinophilia.^{22,23} Liacouras and colleagues²⁴ showed an average of 34.2 ± 9.6 eosinophils/HPF in patients with EoE compared with children with esophagitis who responded to PPI therapy (2.26 ± 1.16 eosinophils/HPF, $P < .001$). Case-control studies of patients with EoE versus GER show that EoE is more often associated with younger age, dysphagia, endoscopic findings such as rings and furrows, and eosinophil degranulation, severe basal zone hyperplasia, and lamina propria fibrosis.^{25–27}

Because of the similarities in symptom complex, the clinical distinction between GER and EoE is particularly challenging. However, dysphagia and anorexia/early satiety have been reported to both correlate with inflammation, remodeling, and to distinguish GER from EoE in children.²⁸ Symptomatically, children with GER tend to improve with acid suppression therapy, whereas patients with EoE remain partially or completely symptomatic despite acid blockade.² Adult studies have shown that infusion of acid into the esophagus of patients with EoE causes significant pain.²⁹ However, the interplay between EoE and acid may be complex, involving an unclear relationship between eosinophilic secretory factors as well as epithelial changes

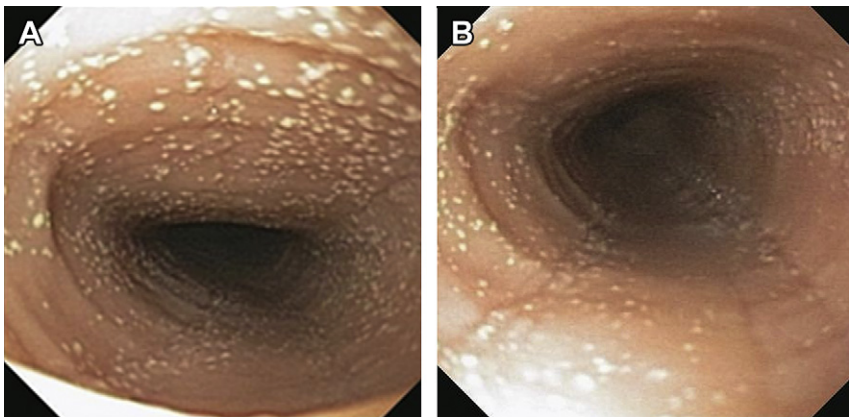


Fig. 2. Esophageal exudates in EoE (A). Linear furrowing and concentric rings (felinization/trachealization) in the esophagus (B).

secondary to acid damage.³⁰ Consistent with this hypothesis, Ngo and colleagues³¹ described 3 patients with mean esophageal eosinophil counts of 36 (range 21–52) who responded both clinically and histologically to isolated acid suppression. For this reason, a trial of acid suppression before establishing the diagnosis of EoE is recommended.³² In addition, this complexity underscores the importance of repeat endoscopic and biopsy evaluation after each therapeutic intervention in patients with EoE.

Disease Mechanisms

EoE combines immediate and delayed-type hypersensitive reactions to inhaled and ingested antigens. Murine EoE models have been instructive in dissecting the mechanistic pathways of esophageal inflammation. Experimental EoE is instigated by intranasal aeroallergens (*Aspergillus*, *Dermatophagoides*) and gavage food allergens (ovalbumin).^{33–35} Disease initiation depends on the presence of T cells but is independent of IgE.³⁶ Animals deficient in CD4+ T cells, eotaxin receptor CCR3, interleukin 15 (IL-15) receptor α , IL-13 receptor α , or IL-5 are all relatively to completely protected from experimental EoE, showing the importance of these pathways in EoE.^{7,37,38}

Gene microarray studies have significantly contributed to our understanding of human EoE pathogenesis.⁷ Compared with normal children or patients with GER, children with EoE have a 53-fold increase in the expression of eotaxin-3, a chemokine that functions as an eosinophil chemoattractant. Both IL-5 and IL-13 are increased and seem to function upstream of eotaxin-3. Treatment of cultured human esophageal epithelial cells from patients with EoE with IL-13 causes increased eotaxin-3 gene expression.³⁹ More recently, IL-15, which can function in a similar manner to IL-2, has been shown to be increased in pediatric patients with EoE, is expressed in dendritic cells in EoE, increases IL-5 and IL-13 production from T cells as well as eotaxin-3 production from epithelial cells, and is detectable in the serum of patients with EoE.³⁷ CD8+ cells are increased in biopsies of patients with EoE, and it is possible that IL-15 is important in their genesis and maintenance.^{40,41}

IL-5 is important for both eosinophilopoiesis and eosinophil trafficking into the esophagus. In addition, IL-5 in combination with eotaxins activates eosinophils. Patients with EoE show increased deposition of eosinophil granule products, including major basic protein, eosinophil derived neurotoxin, and eosinophil peroxidase.^{42–44} These products can potentially affect esophageal function by increasing tissue damage and epithelial proliferation.⁴⁵

In IgE-mediated hypersensitivity, mast cells classically mediate the downstream effects of specific IgE. EoE biopsies have shown increased numbers of mast cells as well as increased mast cell degranulation compared with non-EoE biopsies, suggesting mast cell activation.⁴⁶ In addition, there are increased numbers of tryptase-positive mast cells and IgE-positive cells as well as increased numbers of cells bearing the high-affinity IgE receptor, Fc ϵ RI, in the esophagus of patients with EoE.^{47,48} Whereas tryptase-positive mucosal mast cells are decreased after topical corticosteroid treatment,⁴⁹ the submucosal mast cell pool of tryptase-chymase double connective tissue mast cells remains static.⁵⁰ A mast cell gene profile is increased in pediatric patients with EoE.^{7,51} Mast cells are increased in number in the esophageal muscularis mucosa and their products are able to affect esophageal smooth-muscle function in vitro, suggesting an important function of mast cells in EoE pathogenesis.⁵⁰ A local capacity for immunoglobulin class switch occurs in the esophagus but whether local IgE production represents a mucosal food-specific antigen response remains to be shown.⁴⁷ Increased levels of esophageal IL-13 could promote local immunoglobulin class switch to IgE production in EoE.

The role of systemic food-specific IgE remains to be further elucidated in EoE. Although most patients have sensitization to food antigens, the role of IgE in predicting foods that instigate or propagate EoE is unclear and SPT or serum IgE-based dietary eliminations are variably successful.

Pathogenesis of Complications

The most severe consequence of EoE is fixed esophageal stenosis requiring repeated dilation. Subepithelial sclerosis was first reported in adult patients with long-standing EoE.¹⁷ Children, both with and without stricture-associated EoE, have subepithelial remodeling, an esophageal process with a pathogenesis akin to asthmatic airway remodeling.⁵² Increases in TGF β 1 and its signaling pathway, phosphorylated Smad2/3, are found in the subepithelium of individuals with EoE. Increased angiogenesis, a component of esophageal remodeling, and vascular activation with vascular cell adhesion molecule 1 form adhesive conduits for inflammatory cell trafficking.⁵² In addition to increased collagen deposition, increased amounts of matrix proteins such as periostin allow eosinophil accumulation.⁵³ Animal models have shown that IL-5 and eosinophils are necessary for tissue remodeling, whereas in vitro studies show that TGF β 1 and eotaxin-3 increase periostin expression in esophageal fibroblasts.³⁸

Food Allergy Testing in EoE

Immediate hypersensitivity

Food testing that evaluates immediate hypersensitivity reactions evaluates the presence of specific IgE. SPT is performed by placing food extracts or fresh foods on the skin and pricking the skin. Cutaneous mast cells carrying food-specific IgE are stimulated to degranulate, which causes a cutaneous urticarial reaction. SPT gauges both the presence and function of specific IgE.

Serum IgE testing assesses the levels of food-specific IgE. In the context of a clinical history of anaphylaxis or immediate food hypersensitivity reaction (urticaria, vomiting, angioedema), the quantity of serum specific IgE can have predictive values for the reaction to specific foods. However, it is critical to understand that although many people generate food-specific IgE that is detectable by SPT or in vitro testing they can be clinically tolerant to the food and have no reaction on ingestion. In some cases, removal of IgE-positive foods in a clinically tolerant person can result in immediate hypersensitivity on food reintroduction, implying that continued food ingestion is important for maintaining tolerance. Although most patients with EoE have detectable levels of food-specific IgE, they do not have anaphylaxis. The reason for this remains unclear.

Serum or skin testing for foods in EoE reveals that 70% to 80% of patients with EoE have positive food testing.² Serum IgE testing detects more foods than SPT but the clinical implication and usefulness of low-level sensitization to foods (in the range of 1–5 IU/mL) is unclear.⁵⁴ The most commonly positive foods in patients with EoE who undergo SPT or serum IgE testing are cow's milk, hen's egg, soy, wheat, corn, rice, oat, beef, chicken, peanuts, and white potato.^{54,55}

Delayed hypersensitivity

Delayed hypersensitivity testing evaluates the presence of cellular inflammation in response to foods. T-cell memory is critical to the onset of delayed-type hypersensitivity. The use of atopy patch testing has been validated, standardized, and shown to provoke a cutaneous cellular immune response in diseases such as contact dermatitis and eczema. The usual antigens in these cases are metals, occupational chemicals,

and aeroallergens such as house dust mite. Food patch testing has been evaluated in EoE in order to assess foods that cause a delayed reaction. Single food extracts in Finn chambers are placed on the back for 48 hours. The reactions are read at 72 hours and graded using a scoring system that evaluates the presence and severity of erythema, induration, papules, and vesicles. The most commonly positive foods on patch testing of patients with EoE are cow's milk, hen's egg, wheat, soy, corn, barley, oat, rice, beef, and potato.⁵⁵ Positive predictive values from 1 center range from 54% (potato) to 94% (beef), whereas negative predictive values range from 59% to 97%.⁵⁵ The presence of a cutaneous cellular immune response has not yet been shown in EoE, large numbers of non-EoE control patients have not been evaluated, and the interpretation of food patch tests has not been standardized or validated yet in EoE. Food patch testing remains a research tool in EoE.

Evidence that EoE is a Food Allergic GI Disease

Murine models of esophageal eosinophilia can be promoted by food antigens, specifically ovalbumin.³⁵ Human data invoking foods as triggers of EoE come from the success of elimination diets as EoE therapy. Elemental formulas are the most successful dietary intervention, with histologic resolution in more than 94% of patients.^{56,57} However, unpalatable taste requiring nasogastric or gastric tube insertions, lack of insurance coverage in many states, and difficulty with adherence limit the use of elemental diets.

In vitro studies looking at dendritic cells from patients with EoE and food allergic patients show increased levels of Th2 cytokine production when cultured in vitro with autologous CD4+ cells and increased serum levels of IL-5 and IL-13.⁵⁸ It is possible that, similar to patients with eosinophilic gastroenteritis (EGE), patients with EoE have increased numbers of CD4+, IL-5+, and IL-4- cells but this remains to be evaluated.⁵⁹

Kagalwalla and colleagues⁶⁰ first described the use of an empiric 6-food elimination diet in children. Avoidance of cow's milk, hen's egg, soy, wheat, fish, shellfish, peanuts, and tree nut resulted in histologic remission in 74% of pediatric patients, again invoking immunologic food reactions in the esophagus as the basis for EoE. Consistent with atopy patch test and SPT-based diets, the most common food antigens in children were cow's milk and hen's egg. The same avoidance diet in adults leads to 70% resolution or improvement, with disease recurrence on food reintroduction. Milk and wheat were the most common adult EoE triggers (Nirmala Gonsalves, MD, personal communication, 2010).

The long-term induction of tolerance to EoE triggering foods and the potential implications for loss of tolerance and onset of IgE-mediated allergy when using diets that eliminate IgE-positive foods remain to be studied in EoE.

EoE Therapy

As a food-triggered disease, EoE can be successfully managed using elimination diets, as detailed earlier. Other mainstays of EoE management are the use of swallowed corticosteroids that deposit topically on the esophagus. By treating inflammation locally, topical corticosteroids control allergic inflammation and allow a wide diet to be consumed. Success rates vary but randomized placebo-controlled trials in children show that puff and swallowed fluticasone can be as effective as oral prednisone and significantly superior to placebo.^{49,61} Oral viscous budesonide in combination with acid blockade daily is an effective EoE therapy, with response rates of 87% compared with placebo.⁶² Repeat endoscopy with biopsy should be performed after changing therapy or foods, because documentation of histologic resolution is required

in disease management. There are no surrogate markers, including symptoms, that obviate repeated endoscopy in patients with EoE.

Therapeutic Maneuvers in EoE

Dilation therapy and food disimpaction are required less frequently in children than in adults with EoE. However, when dilation is required, care must be taken to avoid perforation. Several case studies in the literature support a higher perforation risk in EoE, believed to be caused by mucosal remodeling and fibrosis leading to a less compliant or fragile esophageal wall.^{63,64} However, recent studies have reported that perforation caused by dilation in patients with EoE may be safer than previously believed.^{63,65,66} The role of antiinflammatory therapy in reducing or obviating dilations warrants further study.

EOSINOPHILIC GASTROENTERITIS

Clinical, Histologic, and Endoscopic Features

First described more than 50 years ago by Kaijser,⁶⁷ EGE is a clinicopathologic entity characterized by increased eosinophils in the stomach and small intestine, and less commonly the colon. It is rare, and the underlying pathophysiology is not clear. It is diagnosed primarily in the third to fifth decade of life, and affects both genders equally. The incidence is not clear, likely because of lack of recognition and underreporting.⁶⁸

The definition of EGE is complicated by the baseline, normal eosinophilia of the non-esophageal regions of the GI tract. They are highest in the cecum, ascending colon, and terminal ileum.^{69,70} There is no consensus guideline regarding the number of eosinophils required for diagnosis, but rather the combination of eosinophil location, depth, other histologic findings or lack thereof, the clinical context, and lack of signs of other diseases with eosinophilia help to direct diagnosis.⁷¹

Primary EGE can be atopic or nonatopic but is often believed to be a food allergic disorder, potentially with a genetic susceptibility.⁷² The most common cause of secondary EGE is parasitic infection but inflammatory bowel disease, celiac disease, and connective tissue diseases such as scleroderma can also be associated with EGE. Peripheral eosinophilia may be seen in more than 50%, but not consistently, and its significance in terms of diagnostic criteria has not been established.⁷³

The stomach has been reported to be involved in 26% to 81% of cases, and the small intestine in 28% to 100% of cases.^{74,75} The most frequently described symptoms are abdominal pain, diarrhea, nausea, vomiting, and weight loss.^{74–77} Symptoms may wax and wane, and it is not uncommon for diagnosis to be delayed because of lack of consistency in symptoms. The most commonly accepted classification system was developed by Klein and colleagues⁷⁸ in 1970, in which the disorder was divided into 3 subtypes: mucosal, muscularis, and serosal.

Mucosal disease is the most frequently encountered, which is likely in part because of the technical limitation in obtaining deep-layer biopsies via standard endoscopy. Individuals with mucosal-type disease tend to have IgE-mediated food allergy or other atopy.⁷⁹ Other presentations of mucosal disease include anemia caused by GI bleeding, gastric and duodenal ulcers, or protein-losing enteropathy caused by malabsorption.^{71,73,80–83}

Muscular disease tends to present with obstructive symptoms, and several unique presentations have been reported. Infants may present with gastric outlet obstruction, mimicking hypertrophic pyloric stenosis. Thickening of the intestinal wall, strictures,

pancreatitis, intussusception, and obstruction by a cecal mass have also been described.^{75,77,84,85} Diagnosis of muscular and serosal types may require laparotomy and full-thickness biopsy.

Serosal disease is associated with abdominal bloating, marked increase in eosinophils, ascites, increased peripheral eosinophilia, and better response to steroids. Talley and colleagues⁷⁴ published one of the largest experiences with EGE, in which they compared symptoms, allergic history, and serum parameters among patients with EGE and control individuals and reported that abdominal bloating and peripheral eosinophil count were the only parameters found to be statistically different. However, obstructive jaundice, acute abdomen, intussusception, and bowel obstruction have also been described.^{86–91}

Diagnosis

Endoscopy and histology are required for diagnosis. Endoscopic findings vary from normal to nodular with friability, erythema, polypoid lesions, or ulcerations.⁷² Biopsies show increased eosinophils but the histologic finding of eosinophilia must be evaluated in the clinical context, and secondary causes such as inflammatory bowel disease and celiac disease that can also be associated with intestinal eosinophilia must be evaluated. Like EoE, EGE disease is patchy and therefore multiple biopsies should be obtained.

Diagnosis is made more difficult by the technical limitation of standard endoscopy. The distal limit of upper endoscopic biopsies is the third portion of the duodenum, whereas the proximal limit of colonic endoscopies is the terminal ileum. With newer endoscopic techniques such as balloon enteroscopy, more distal small bowel biopsies may be obtained and aid in EGE recognition.

There are no radiographic findings specific to EGE, although computed tomography of the abdomen may show nodular and irregular thickening of gastric folds.⁹¹ Ultrasound may also be helpful in assessing antral and bowel wall thickness.⁹² Barium contrast may show bowel wall thickening or strictures.

Pathogenesis

Patients with atopic EGE often have multiple food sensitizations with positive SPT. However, elimination diets based on SPT results have variable success. However, elemental formula can have significant success.⁹³ Together the success of these interventions speaks to the important role of food intolerance in EGE.

Because the usual response of the GI tract is tolerogenic, shifts in sensitization to foods can lead to significant intestinal disease, and the role of food antigens in EGE continues to be investigated. Most recently Prussin and colleagues⁵⁹ reported that peripheral, food-specific CD4+ T cells in allergic patients with anaphylaxis produce both IL-4 and IL-5, whereas allergic EGE was singularly associated with a Th2 population that was IL-4–/IL-5+ cells. The numbers of IL-4+,5+ cells in peanut-allergic patients directly correlated with IgE levels. However, the link between the presence of peripheral IL-4–,5+ cells and GI T cells and eosinophils remains ambiguous. In addition, earlier work showed that patients with allergic EGE had duodenal CD4+/IL-4+ cells that proliferated to milk.⁹⁴ These cells were also noted to release IL-5 and IL-13 but not IL-4 in response to antigen, again implicating the importance of these interleukins to food-related GI disease. Together, these studies provide evidence for a mechanism of eosinophil chemoattraction and activation via IL-5 in patients with a GI Th2 phenotype and EGE.

Treatment

Patients with cow's milk allergy and EGE can have IgE to casein and whey proteins. It is reasonable to perform SPT to foods and, if not limited by the numbers of positive foods, to trial an elimination diet. Amino acid-based formulas can be trialed for EGE if there are multiple positive foods on IgE testing or if no food triggers can be found on IgE testing but the patient wishes to pursue dietary management. Although proliferative responses of peripheral blood mononuclear cells have been reported for milk, peanut, and soy proteins in patients with EGE, the extension of this disease mechanism to food patch testing has not been studied rigorously.

A recent clinical trial reported that the biologic agent anti-IgE was successful in decreasing eosinophil counts and symptoms in patients with EGE, underscoring a role for IgE in EGE.⁹⁵ Although IL-5 can drive esophageal eosinophilia, its role in the pathogenesis of EGE remains less clear and trials that were geared to assess the role of anti-IL-5 therapy in EoE showed that there were no changes in the levels of T cells, eosinophils, or mast cells in the duodenal or gastric mucosa of patients with EoE treated with anti-IL-5.⁹⁶

The treatment of EGE can be complex, requiring systemic immunomodulatory therapy with prednisone, 6-mercaptopurine, and azathioprine.⁹⁷ Because EGE is characterized by relapses and remissions, patients often require recurrent steroid courses, with serosal disease having been reported to respond to systemic corticosteroids. Long-term remission may be possible with the use of the leukotriene receptor antagonist montelukast.⁹⁸ Because EGE has been associated with infections from helminths and *Helicobacter pylori* as well as systemic processes such as lupus erythematosus and posttransplantation syndrome, it is of paramount importance to determine if the disease is primary or secondary EGE before embarking on therapy. Depending on the location of intestinal involvement, topical corticosteroids such as entocort, a formulation of budesonide that targets right-sided intestinal disease, can be instituted.

EOSINOPHILIC COLITIS/PROCTOCOLITIS

Most commonly a benign disease of infancy, milk and soy trigger proctocolitis manifests as bloody, mucus-containing stools in infancy and is easily treated by the removal of the triggering antigen. Up to 60% of cases occur in breastfed babies, with onset during the first 6 months of life, and resolution by age 2 years old, with many children tolerating regular diets by 1 year of age.^{99,100} Dietary elimination leads to rapid resolution of symptoms within 72 to 96 hours.⁹⁹ Because the diagnosis is based on clinical history and improvement with elimination of cow's milk in the breastfeeding mother, or with a semihydrolyzed or extensively hydrolyzed formula, neither flexible sigmoidoscopy nor colonoscopy is routinely indicated. Gross visual findings in the rectosigmoid colon may reveal erythema or erosions, whereas histologically one may see acute inflammation and eosinophilia. Although T cells are likely the source of immunologic memory, the use of food patch testing is not warranted in these infants.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergic disorder characterized by severe GI or systemic reactions to a food trigger, particularly milk or soy. Symptoms resolve with elimination of exposure to the inciting food. After the first case series in 1967 of 21 infants with diarrhea and variable

hemodynamic instability with exposure to milk protein,¹⁰¹ the diagnostic criteria have been formalized to include: (1) onset of symptoms typically at age less than 2 months, (2) diagnosis at age younger than 9 months; and (3) resolution of symptoms when the food antigen is eliminated.¹⁰²

FPIES typically presents with significant GI symptoms, primarily vomiting and diarrhea within 4 hours of food ingestion.¹⁰³ More than 75% of infants appear ill, and in some patients, systemic signs such as hypotension necessitate hospitalization.¹⁰³ Common presentation in infants includes a septic appearance with a metabolic acidosis, dehydration, lethargy, and bloody stools. Because of this, children are often evaluated first for sepsis, metabolic disorders, or acute abdominal processes before the recognition of the triggering food antigen. Other signs such as hypoalbuminemia, poor weight gain, hyperthermia, thrombocytosis, peripheral polymorphonuclear lymphocytosis, and methemoglobinemia have also been reported.^{102–105} The severity of symptoms and lack of awareness of FPIES often delay the diagnosis.

Milk and soy are the most common food triggers, with as high as a 50% cross-reactivity between milk and soy.^{102,106} Solid foods have also been implicated, particularly rice.^{105,107,108} Most patients have negative SPTs and serum IgE test results.¹⁰² Patch testing may be a promising modality to aid in diagnosis.¹⁰⁹

FPIES is a clinical diagnosis. The gold standard for diagnosis is a positive oral food challenge but this is often not necessary and can be dangerous if the reaction involves hypotension. When challenges are done, intravenous access and a minimum of 4 hours of observation are necessary. Endoscopy is not routine because the diagnosis can often be made clinically based on symptoms with exposure to the food trigger, and improvement with removal of the causative food. Histologic changes include increased eosinophils in the lamina propria and focal cryptitis, with overall preservation of architecture.^{110–112}

SUMMARY

Food reactions can have GI manifestations that cause significant tissue disease and patient morbidity. It is essential to use the proper diagnostic testing, including endoscopy with biopsy and food allergy testing, and to interpret test results appropriately in order to choose the best therapeutic intervention. New manifestations of food allergies, especially EoE, are increasing in prevalence and constitute a new and significant health care burden.

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