

Association of Eosinophilic Gastrointestinal Disorders with Other Atopic Disorders

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KEYWORDS

- Eosinophilic esophagitis • Atopy • Asthma
- Food allergy • Atopic dermatitis

Atopy involves an exaggerated immune response to common environmental allergens. Atopy can be defined in various ways: elevated total IgE; physician diagnosis of asthma, allergic rhinitis (AR), or atopic dermatitis (AD); or a positive allergy test (skin prick test or specific IgE to an allergen). In general, allergic/atopic diseases are associated with an expansion of T helper (Th) 2 cell population and secretion of cytokines (interleukin [IL]-4, IL-5, and IL-13) that favor IgE synthesis and eosinophilia. The most common atopic diseases are asthma, AR, food allergy, and AD.

Atopic diseases have common features: inflammation (often eosinophilic), hyper-responsiveness to stimuli, remodeling of tissues, and Th2 cellular production. Asthma is a chronic, inflammatory lung disease characterized by reversible airway obstruction and increased airway hyperresponsiveness. Thickening of airway tissue observed in asthma includes subepithelial fibrosis, increased matrix deposited in the submucosa, and increased smooth muscle (hyperplasia and hypertrophy). The symptoms of hyper-responsiveness are experienced as cough or wheeze with exercise, cold air, or other stimuli. The airway inflammation in asthma consists of Th2 cells and eosinophils and, in severe disease, neutrophils are found in bronchoalveolar lavage and lung biopsies.¹ AR involves eosinophilic inflammation of the nasal membranes triggered by an IgE-mediated response to environmental proteins.² Similar to asthma, AR has nasal hyper-responsiveness seen as sneezing in response to stimulation by allergens. AD is

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a disease of chronic skin inflammation with eosinophilic inflammation and Th2 cells in early lesions on skin biopsies. In chronic lesions, a mixed picture of Th1 cells and spongiosis is observed. In asthma, remodeling occurs with chronic lesions, homologous to the thickened skin, lichenification, in the AD. AD can be triggered by IgE-mediated sensitivity to food or aeroallergens and non-IgE-mediated reactions. The third common component, hyperresponsiveness, is seen as itching to normal stimuli such as dry skin (xerosis).³ Another form of atopy is food allergies. Food allergies can be classified into two broad categories: IgE-mediated and non-IgE-mediated. Classic IgE-mediated food allergies involve mast cell degranulation following exposure to food proteins, causing urticaria, rhinorrhea, emesis, diarrhea, wheezing, angioedema, and anaphylaxis. Non-IgE-mediated food allergies include cell-mediated disease processes, such as food protein-induced enterocolitis, dermatitis herpetiformis, and eosinophilic esophagitis (EoE).⁴ In asthma, AR, AD, and food allergies, the acute hypersensitivity reaction is mediated by mast cell degranulation following cross linking of IgE and its receptor. The subsequent release of preformed mediators results in swelling from increased blood flow and increased vascular permeability. However, a late-phase reaction can also occur, characterized by infiltration of tissues by neutrophils, eosinophils, macrophages, and Th2 cells that help to sustain inflammation.

Similar to eosinophilic inflammation seen in atopy, the presence of increased eosinophils in the gastrointestinal tract, without other known cause, is seen in a group of conditions known as eosinophilic gastrointestinal disorders (EGIDs). The most common of these disorders, namely EoE, is hypothesized to be caused by IgE- and cell-mediated reactions (non-IgE-mediated) to foods and other triggers. The mixed picture is similar to that of AD.

This article discusses the similarities between EoE and other atopic disorders. The authors first review the existing murine and human data that suggest a link between asthma, AR, AD, and food allergy themselves, followed by the link between EoE and these allergic conditions. This article also discusses atopic conditions in patients who have eosinophilic gastroenteritis (EG), a disease that occurs with much less frequency than EoE.

SIMILARITIES BETWEEN EOSINOPHILIC GASTROINTESTINAL DISORDERS AND ATOPIC DISORDERS

Rise in Atopic Diseases and Eosinophilic Gastrointestinal Disorders

Over the past few decades, the reported prevalence of allergic diseases has increased dramatically. In industrialized countries, approximately 25% to 30% of the population suffers from AD, food allergy, or AR.⁵ Data from the Centers for Disease Control and Prevention National Health Information survey confirm a rise in all atopic diseases. The reported prevalence of asthma in 1990 was only 3%. According to 2007 data, the prevalence has increased to 7.7%.⁶ A similar rise in AD prevalence was also noted between 1998 (7.3% of children under 17) and 2006 (10% of children under 17).⁷ Mirroring this rise in allergic disorders has been an increase in the diagnosis of EGIDs, in particular EoE. Perth, Australia, has seen an 18-fold rise in the prevalence of EoE over 10 years.⁸ At the authors' institution in Philadelphia, they saw a 35-fold increase between 1994 and 2003.⁹

Common Pathology: Eosinophilic and T Helper 2 Inflammation

EGIDs are a spectrum of disease that includes EoE, EG, and eosinophilic colitis. EGIDs are characterized by eosinophilic inflammation of the gastrointestinal tract in the absence of other secondary causes of eosinophilia.¹⁰ The normal esophagus is

void of eosinophils and their presence signifies either gastroesophageal reflux or EoE in most cases. Unlike the esophagus, the stomach, small intestine, and colon normally contain eosinophils, which aid in parasitic defense and do not cause tissue damage. However, an increase in tissue eosinophilia may signify EG, eosinophilic colitis, a parasitic disease, drug allergy, or inflammatory bowel disease. This eosinophilic inflammation in EGIDs mirrors the eosinophilic inflammation seen in asthma and AR.

Similar to thickening of the basement membrane in the lung in asthma and lichenification of the skin in AD, thickening of the esophagus in EoE is observed. In EoE, the membrane has an increased basal layer. Aceves and colleagues¹¹ have seen increased collagen and fibrosis on esophageal biopsies in EoE. They have also observed a mechanism for this thickening on EoE that is similar to that of asthma, with increases in vascular cell adhesion molecule (VCAM)-1, profibrotic molecule, transforming growth factor-beta (TGF- β) and transcription factor, Smad2/3 in esophageal biopsies, which is similar to changes observed in asthma.^{12,13} In murine models, IL-13 has been shown to play a critical role.

One frequently cited explanation of allergic disease involves the Th1 versus Th2 paradigm. Following antigen presentation by a dendritic cell, the naïve T cell becomes polarized to either a Th1 or Th2 cell. The Th1 subclass produces interferon-gamma (which helps clear viruses and intracellular pathogens) and down-regulates Th2 cells and the production of IgE. Th2 cells produce IL-4, IL-5, and IL-13 and down-regulate Th1 cells. Th2 cells promote isotype switching to IgE and the production of eosinophils, which confers protection against parasitic worms but also creates a favorable environment for the development of atopy.³

Th2 cells and their cytokines have been seen in EoE and other atopic diseases (asthma, AD, and AR). Simon and colleagues^{14–16} have demonstrated high expression of the Th2 cytokines, IL-5 and IL-13, in patients who have acute AD. Assessment of bronchoalveolar lavage fluid from patients who have asthma has shown elevated levels of IL-4 and IL-5 cytokines.¹ Similarly, in nasal lavage samples from patients who have AR, high levels of IL-4, IL-5, and IL-13 can be detected.¹⁷ Straumann and colleagues¹⁸ have demonstrated that EoE is also associated with a Th2 allergic phenotype. In patients who have EoE, esophageal biopsy specimens were found to have greater numbers of T cells and mast cells and increased expression of IL-5. In mouse models of EoE, IL-5 knockout mice are resistant to developing disease.¹⁹ Chemokines are small 8- to 10-kilodalton molecules that attract cells to specific locations. These homing signals (chemokine and their receptors) for Th2 cells and eosinophils are also increased in EoE and atopic disease, and include thymus and activation-regulated chemokine (TARC) and CXC chemokine receptor 3 (CXCR3) in asthma;^{20,21} decreased TARC levels after immunotherapy in AR;²² cutaneous T-cell-attracting chemokine (CTACK) and TARC in the peripheral blood in AD;²³ and eotaxin-3 in EoE,²⁴ which indicates further pathogenetic links between atopic disease and EoE.

A common end point in asthma, AD, and EoE is remodeling. Some patients who have asthma develop airway remodeling and a permanent decline in lung function thought to be due to subepithelial fibrosis and angiogenesis.²⁵ For AD, the remodeling is seen in chronic lesions as lichenification and thickening of the skin.²⁶ In patients who have untreated EoE, the development of strictures is a concern. Aceves and colleagues¹¹ have demonstrated basement membrane thickening and increased vascular activation in untreated patients who have EoE, which is similar to changes seen in airway remodeling with elevated TGF- β and VCAM-1 expression. Adults who have EoE have more strictures and food impaction than children, suggesting a natural course of disease.²⁷

Similarities in Murine Models of Atopy and Eosinophilic Gastrointestinal Disorders

In addition to the prevalence and biopsy similarities, murine models predict a similar mechanism of disease pathogenesis. Spergel and colleagues²⁸ originally created a mouse model linking AD and asthma. Mice were first exposed to ovalbumin allergen by the epicutaneous route (an allergen patch was applied to a shaved area on the back), which induced AD-like changes to the skin. Following sensitization, a single aerosolized exposure to the same allergen induced airway hyperresponsiveness to methacholine and eosinophilia on bronchoalveolar lavage.

In a murine model of EoE, Akei and colleagues²⁹ used the same epicutaneous sensitization as Spergel with *Aspergillus fumigatus* or ovalbumin. These mice did not develop EoE after skin sensitization alone, although they did develop AD-like skin changes. However, following the single intranasal challenge to allergen, the development of marked EoE was observed. The investigators concluded that epicutaneous sensitization to allergen primes the esophagus for inhaled allergen-induced EoE in their model, similar to asthma.⁹ The importance of Th2 cytokines and signaling in this model was further demonstrated with the use of specific knockout mice. IL-5 knockout mice were completely resistant to developing EoE using this protocol. IL-13, IL-4, and STAT 6 knockout mice developed milder forms of EoE.²⁹ Other similarities between the murine models were that CD4+ T cells were necessary for the development of AD³⁰ and Th2 cytokines were necessary for the development of airway sensitization,¹¹ as described in the EoE model.

The model created by Akei and colleagues²⁹ provides evidence for a link between AD and EoE, and Mishra and colleagues³¹ created a murine model that suggests a link between asthma and EoE. This model was adapted from a protocol used to create airway inflammation. Anesthetized mice were exposed to 100 µg of *Aspergillus fumigatus* intranasally. A total of nine treatments were given over the course of 3 weeks. These mice developed esophageal eosinophilia and epithelial cell hyperplasia. Although mice exposed to intranasal allergen developed EoE, the same allergen delivered by oral or intragastric route failed to elicit eosinophilia. Furthermore, the eosinophilia was isolated to the esophagus, with no eosinophils seen in the stomach or small intestine.

Association of Atopic Diseases to Each Other: Linkage Between Asthma and Allergic Rhinitis

Human data also mimic the murine models of disease, demonstrating a connection between different atopic conditions. In the United Airway model, (linkage of asthma-AR), AR and asthma are linked by an anatomic and immunologic connection between the upper and lower airways. A European population-based survey showed a threefold asthma increase in subjects who suffered from AR.³² The treatment of AR with nasal corticosteroids is associated with a reduced risk for asthma-related ER visits and hospitalizations and decreased airway hyperreactivity.^{33,34} Conversely, inhaled steroid use has been shown to decrease eosinophilia in the nose and AR symptoms, despite the lack of direct medication contact.³⁵

Braunstahl and colleagues^{36,37} have helped elucidate the pathophysiology of the connection between the upper and lower airways. In one study, human subjects who had AR who underwent nasal allergen provocation developed tissue eosinophilia and up-regulation of adhesion molecules in the nasal and bronchial epithelium.³⁷ In a related experiment, atopic subjects who underwent a bronchial allergen challenge were shown to develop inflammatory cell infiltrate and increased expression of IL-5 in the nasal mucosa.³⁶

Atopic March: The Link Between Atopic Dermatitis and Asthma

A similar link exists between AD and asthma, known as the atopic march. Typically, AD marks the first manifestation, followed by the emergence of food allergy, asthma, and AR. AD may improve or even disappear over time.³⁸ The evidence is from longitudinal, genetic, and mechanistic studies. Gustafsson and colleagues³⁹ conducted a longitudinal study of 94 children who had AD aged 4 months to 3 years. After 7 years, one third of the patients had resolution of AD. However, 43% had developed asthma and 45% had developed AR. In another study, involving 2270 children who had AD, aged 2 years to 17 years, 33% of the patients had either asthma or AR and 38% had both asthma and AR.⁴⁰ In the general population, 8.5% of children have asthma and 25% have AR,^{6,41} which suggests that AD is an important risk factor in the development of other allergic diseases.

The proposed mechanism for this relationship is based on the supposition that the skin acts as the site of primary sensitization.³⁸ Sensitized T cells then would migrate to the nose and lungs, causing asthma and AR. Recent genetic studies suggest patients who have “leaky skin,” as evidenced by filaggrin mutations,⁴² have an increased risk for asthma and AD. The allergen penetrates the leaky skin, causing sensitization and airway disease, like the murine model.²⁸

Sensitization to Allergens and Atopy

Sensitization to food allergens has also been shown to be predictive of future asthma. In a birth cohort of 100 infants in England, patients who had skin prick test sensitivity to egg and cow’s milk were more likely to develop asthma later in life (odds ratio 10.7; 95% CI 2.1–55.1).⁴³ Likewise, sensitization to inhalant allergens, in particular *Alternaria* mold and dust mites, is associated with asthma.⁴⁴

COMMON CLINICAL FEATURES OF EOSINOPHILIC GASTROINTESTINAL DISORDER AND ATOPIC DISEASES

Like other allergic conditions, EoE is a chronic disease that leads to either persistent symptoms or, at times, intermittent “flares.” Infants and young children often present with persistent vomiting, failure to thrive, or abdominal pain, whereas adolescents and adults present with abdominal pain, dysphagia, or food impaction. Those who have dysphagia will often modify their behavior and learn to eat slowly and cautiously, similar to asthmatics, who modify their behavior by limiting physical activity. The flaring observed in EGIDs is similar to the exacerbations seen in asthma and AD with baseline underlying inflammation. Another common feature in atopic disease is hyperresponsiveness to stimuli, seen as coughing and wheezing to methacholine in asthma, and itching in AD. It appears that patients who have EGIDs have an increased sensitivity to acid reflux or gastrointestinal symptoms, but this has not been confirmed in a rigorous manner.

The treatment approach for EoE is similar to that for other forms of atopy. The key to therapy is avoidance of known allergens or triggers. In EoE, food is often the culprit and thus, removal is recommended. Removal of the allergen leads to normalization of esophageal biopsies, indicating the role of food allergens in EoE.^{9,45} In asthma, removal of the aeroallergen (animal dander or dust mites) leads to reduction of symptoms and airway inflammation.^{46,47} If dietary management of EoE fails or is not tolerated by the patient, topical “swallowed” forms of corticosteroids are used to control the underlying inflammation and symptoms. Similarly, topical steroids are the cornerstone of the authors’ approach to treating asthma, AD, and AR.^{48,49}

Link Between Eosinophilic Esophagitis and Atopic Diseases

The authors and others have reported that most children and adults who have EoE have concomitant atopy (**Table 1**). In contrast, 20% of adults in the general United States population have AR and 6.7% of adults have asthma (the prevalence of asthma in children in the United States is 8.5%)⁵⁰ and approximately 17% of children in the United States are affected by AD.⁵¹ At the authors' institution, a 14-year follow-up of more than 600 pediatric patients who had EoE showed that two thirds had evidence of other allergic disease,⁵² approximately threefold greater than the general population. Data from Cincinnati also indicated a high prevalence of environmental (79%) and food allergies (75%) in children who had EoE.⁵³ In addition, genetic links between allergy and EoE are likely. Of 381 patients who had EoE, 164 were found to have AR, or AD in a first-degree relative.⁹ Guajardo and colleagues⁵⁴ reported an even higher prevalence of AR (77%) and asthma (51%) in immediate family members.

Adults who have EoE appear to show similar atopic features as children. For instance, Roy-Ghanta and colleagues⁵⁵ recently evaluated 23 adult patients who had EoE and found that most showed evidence of sensitization to environmental aeroallergens (78%) and the presence of specific IgE to food allergens (82%). Simon and colleagues⁵⁶ have described a similar pattern of increased atopy in 31 adult patients who had EoE. Of these adult patients who had EoE, 68% experienced asthma, AD, or AR. The prevalence of atopic diseases in EoE in children and adults is summarized in **Table 2**.

The prevalence of atopic diseases in EoE varies; some studies have reported it to be as low as 50%, whereas others report it to be as high as 80%. The differences could be due to the particular region where the study was done or the physician diagnosing the disorder. Studies done by an allergist-immunologist have a higher prevalence of atopic diseases than a similar study done by a gastroenterologist. This difference could be a selection bias or it may reflect the fact that an allergist-immunologist can make the diagnosis sooner because he/she sees those diseases more frequently.

Link Between Eosinophilic Esophagitis and Food Allergens

The strongest evidence for food allergy as a cause of EoE comes from the clinical response of patients who are placed on restricted or elemental diets. In 1996, Kelly and

Table 1 Studies showing the development of other atopic diseases in patients who have atopic dermatitis, allergic rhinitis, or egg allergy					
Study	Number in Study	AD → Asthma ^a	AD → AR ^a	AR → Asthma ^a	EA → Asthma (OR)
Kapoor et al ⁴⁰	2270	33%	33%	—	—
Ricci et al ⁶⁹	252	34%	57%	—	—
Gustafsson et al ³⁹	96	43%	45%	—	—
Greisner et al ⁷⁰	306	—	—	21%	—
Wright et al ⁷¹	129	—	—	32%	—
Sibbald et al ⁷²	—	—	—	—	—
Kotaniemi-Syrjanen et al ⁷³	82	—	—	—	2.85
Rhodes et al ⁴³	63	—	—	—	10.70

Abbreviations: EA, egg allergy; OR, odds ratio.
^a Percentage is the prevalence of the second atopic disease developing in the initial population.

Table 2

Studies showing the frequency of atopic disease in patients who have eosinophilic esophagitis

Author/Year [Ref]	No. EoE Patients	Age (y)	Asthma	AR	AD	FA (Anaphylaxis)
Spergel et al. 2008 ⁵²	620	9.1 ± 3.1	50%	61%	21%	5.7%
Assa'ad et al. 2007 ⁵⁸	89	6.2 ± 4.8	39%	30%	19%	9.0%
Sugnanam et al. 2007 ⁵⁹	45	3 mo to 16 y	66%	93%	55%	24.0%
Guajardo et al. 2002 ⁵⁴	39	8 ± 12	38%	64%	26%	23.0%
Roy-Ghanta et al. 2008 ⁵⁵	23	18 to 57	26%	78%	4%	—

Abbreviation: FA, food allergy.

colleagues⁴⁵ examined 10 children who had persistent GERD and esophageal eosinophilia refractory to pharmacotherapy; in fact, 6 of the 10 patients had already received Nissen fundoplication as a treatment of medically resistant GERD. Following a 6-week trial of elemental formula, a significant decrease in esophageal eosinophils and clinical symptoms was observed in all of the patients, with 8 patients demonstrating complete resolution.⁴⁵

At the authors' institution, with their last published report of the 160 patients who had EoE treated with an elemental diet, 97% achieved symptom resolution and esophageal biopsy normalization. The use of specific elimination diets of foods identified by skin prick testing and patch testing led to improvement in 75% of cases.⁹ In the authors' current practice, which includes more than 700 children who have EoE, they have found that 98% responded to elimination or elemental diet (Jyonouchi, Brown, and Spergel, unpublished data, August 2008).

Additional support for food allergy as a participant in EoE is provided by Kagalwalla and colleagues,⁵⁷ who demonstrated improvement of EoE in patients after implementation of an empiric six-food elimination diet. Instead of extensive skin testing, these investigators eliminated, for a 6-week period, the six most common food allergens (milk, soy, egg, wheat, nuts, and seafood) from the diets of 35 patients who had EoE and compared them with a control group of children who had EoE who were provided with an elemental diet alone. They found significant improvement in esophageal eosinophils (<10 per high-power field) for the six-food elimination group (74% of patients), as compared with an 88% response in children treated with an elemental diet.

Most patients who have EoE have evidence of IgE-mediated sensitization to food based on in vitro-specific IgE or skin prick testing. However, the reported incidence of actual food-induced anaphylaxis has been variable. In the cohort reported by Assa'ad and colleagues⁵⁸ and in the authors' patient population, the incidence has been 9% and 8.1%, respectively. Rates of food anaphylaxis were significantly higher in the data reported by Sugnanam⁵⁹ and Guajardo⁵⁴ (24% and 23%). The difference of 8.1% and 23% both from Cincinnati Children's Hospital is probable due to two reasons (time period studied and method of studies).^{55,58} The higher number was found in a Web-based study versus lower number in the chart review.

Evidence indicates that the mechanism underlying the immunologic reaction to foods in EoE is not only IgE mediated but also cell mediated. In his cohort, Kelly and colleagues⁴⁵ demonstrated that the introduction of skin test-negative foods into the diet could induce clinical disease. Further support comes from the finding that flares of symptoms following reintroduction of offending foods occurred within 30 minutes for some patients, but took up to 8 hours for others. In the authors' experience, some patients remain asymptomatic for days to months with food

reintroduction, and esophageal inflammation is found on repeat biopsy. To help address this issue, they have used patch testing as a tool for identifying delayed, cell-mediated allergic reactions in EoE/EG. In pediatric patients, they have found this testing method, along with skin prick testing, to be effective in guiding management. The combination of skin prick and patch testing had a negative predictive value of 88% to 100% for 20 foods (except milk), whereas the positive predictive value was greater than 74% for the most common foods causing EoE.⁶⁰

The link between foods and EoE is not as clear in adult patients because limited data exist regarding the use and efficacy of elemental and elimination diets. In one study, Simon and colleagues⁶¹ evaluated the effect of wheat and rye removal from the diet in six adults, who had skin tests (sensitization) to these foods. These patients were also sensitized to grass pollen, which can account as wheat/rye cross react with grass pollen. First, the patients underwent double-blind placebo-controlled food challenges to wheat and rye. The food challenges failed to provoke any EoE symptoms. In addition, a 6-week trial of wheat and rye removal from the diet failed to produce any histologic improvement in biopsy. However, a series of case reports published in abstracts indicates that diet can also be helpful in adults. Gonsalves reported a 50% response rate in adults on a six-food elimination diet and near 100% resolution on an elemental diet.⁶²

ROLE OF AEROALLERGENS AND EOSINOPHILIC ESOPHAGITIS

Some evidence suggests that aeroallergens may play a causative role in the development of EoE in humans. A seasonal variation in cases of newly diagnosed EoE has been described, with fewer cases being diagnosed in the winter when the air contains less pollen.⁶³ Magnusson and colleagues⁶⁴ have demonstrated increased duodenal eosinophils and mast cells during pollen season in non-EoE patients allergic to birch pollen. Similarly, esophageal biopsies from patients who have AR during pollen season have shown elevated numbers of eosinophils compared with controls. However, the number of eosinophils observed was lower than values typically seen in patients who have EoE (5.5 ± 7.3 eosinophils per high-power field in the proximal esophagus and 3.2 ± 3.7 eosinophils per high-power field in the distal esophagus).⁶⁵

In a study of adult patients, the symptoms of AR and asthma significantly preceded the onset of dysphagia and EoE diagnosis. This finding raises the possibility that sensitization to aeroallergens similar to the murine model created by Mishra could also cause EoE in humans.³¹ Fogg and colleagues⁶⁶ described a 21-year-old female patient who had asthma, AR, and EoE, who suffered seasonal flares of esophageal inflammation. The patient was skin test and patch test negative to foods and her diet remained stable during the observation period. Esophageal biopsies taken during the spring or summer pollen months revealed moderate-to-severe EoE. However, biopsies performed during the winter months showed little or no esophageal inflammation. The one case reported by Fogg also noted worsening symptoms during pollen seasons.

In the authors' EoE population, they have confirmed seasonal/pollen variation in 55 patients, with worsening symptoms and esophageal eosinophilia during pollen seasons. Food allergies were still the primary cause of disease in these patients. However, during pollen season in the spring or fall, an exacerbation of disease (confirmed by biopsy) was documented. Full disease control was achieved only during non-pollen seasons and on proper dietary therapy.⁵²

Although direct deposition of pollens onto the esophageal mucosa is one potential mechanism for inflammation, experimental evidence points toward other potential

pathways. Greiff and colleagues³⁵ have previously demonstrated that eotaxin, which plays a key role in eosinophil migration into the esophagus, is secreted by the nasal mucosa of patients who have AR. Eotaxin release by nasal mucosa on exposure to aeroallergens provides a possible explanation as to why AR can lead to flares of EoE in some patients. Intranasal steroid therapy has been shown to decrease nasal secretion of eotaxin in patients who have AR and in the authors' patients they recommend its use regularly.

EOSINOPHILIC GASTROENTERITIS AND ATOPY

EG remains a rare disease and the exact incidence is difficult to estimate. Eosinophilic infiltration is seen throughout the gastrointestinal tract and must be differentiated from inflammatory bowel disease, Crohn's disease, or other gastrointestinal pathology. Clinical symptoms include abdominal pain, nausea, diarrhea, and vomiting. EG can be classified according to the depth of eosinophilic infiltration into the gut wall: mucosal, submucosal, muscularis, and serosa. As with EoE, an increased prevalence of atopic conditions has been reported in patients who have EG. Results from a Web-based registry of patients who had EG ($n = 57$) showed a high incidence of AR (63%), drug allergies (53%), asthma (39%), and eczema (40%).⁵⁴

Insights into the pathogenesis of EG come from the diabetic biobreeding lymphopenic (lyp) rat model. The Lyp gene encodes a guanosine triphosphatase (GTPase) of the immunity-associated protein (GIMAP5), which may protect cells from apoptosis. Lyp/lyp mutation homozygous mice developed gastroenteritis strikingly similar to human EG.

Affected mice developed weight loss, listlessness, diarrhea, and gut ascites. Examination of the large and small intestines revealed increased eosinophils, mast cells, and basophils. Lyp/lyp T cells expressed high levels of IL-4, IL-5, and IL-13, which confirmed a Th2 phenotype. Mice also expressed high levels of serum IgE.⁶⁷

The importance of IgE-mediated mechanisms in EG is supported by the work done by Foroughi and colleagues.⁶⁸ In their open-label study, nine patients who had EG were treated with omalizumab, a monoclonal anti-IgE antibody. Treatment was shown to decrease peripheral eosinophilia and lower eosinophil numbers in the gastric antrum and duodenum. The fact that only a partial decrease in the absolute eosinophil count was seen in most patients suggests that non-IgE-mediated mechanisms are also involved in the pathogenesis. Additionally, omalizumab led to a 63% reduction of symptoms at 8 weeks and a 70% reduction of symptoms at 16 weeks.

The role of food allergy in the pathogenesis of EG is supported by the success of elemental food diets. Chehade and colleagues⁷⁴ reported that children who had EG and protein-losing enteropathy who were placed on an elemental diet showed a significant decrease in symptoms. The efficacy of specific food elimination diets based on skin prick testing and patch testing for foods has not been well studied in this population of patients.

SUMMARY

The emergence of EGIDs has paralleled a rise in atopic diseases such as asthma, AR, AD, and food allergy. Significant similarities exist between EoE and other allergic diseases, including common cell types (mast cells and eosinophils), cytokines (IL-4, IL-5, and IL-13), and chemokines. Patients who have EoE and EG have a higher incidence of asthma, AR, AD, and food allergy. The underlying pathogenesis is still being pursued. Once understood, therapeutic interventions may be available not only to treat EoE or EG but also to prevent their development.

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