

Update review

Eosinophilic esophagitis: Pathogenesis, genetics, and therapy

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Eosinophilic esophagitis (EE) is a recently recognized disorder characterized by the accumulation of eosinophils in the esophagus. Symptoms of EE frequently mimic those of gastroesophageal reflux disease, but the 2 diseases are quite distinct in terms of the histopathology and response to therapy. We demonstrate that EE involves the interplay of numerous genes, especially the eosinophil chemoattractant eotaxin-3, allowing molecular distinction from other forms of esophagitis and consideration of targeted therapeutic intervention. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Eosinophilic esophagitis, eosinophils, eosinophil-associated gastrointestinal disorder, allergy, eotaxin

DIFFERENTIAL DIAGNOSIS

Unlike all other segments of the gastrointestinal tract, the esophagus is normally devoid of eosinophils, and therefore the finding of esophageal eosinophils denotes pathology. However, the presence of esophageal eosinophils is not specific for a particular disorder because eosinophil infiltration in the esophagus occurs in a variety of states, including eosinophilic esophagitis (EE), eosinophilic gastroenteritis, gastroesophageal reflux disease (GERD), chronic (noneosinophilic) esophagitis (CE), parasitic and fungal infections, inflammatory bowel

Abbreviations used

CE: Chronic esophagitis
CLC: Charcot-Leyden crystal
EE: Eosinophilic esophagitis
GERD: Gastroesophageal reflux disease
hpf: High-powered field
SNP: Single nucleotide polymorphism

disease, hypereosinophilic syndrome, scleroderma, and drug injury. Therefore differentiating EE from these other disorders, especially GERD and CE, is often a challenge,¹ and misdiagnosis can have adverse effects on patient outcomes.

SYMPTOMS AND DISEASE CHARACTERISTICS

Patients with primary EE commonly report symptoms that include difficulty feeding, failure to thrive, vomiting, epigastric or chest pain, dysphagia, and food impaction.²⁻⁶ These symptoms appear to occur in a progressive order because they are the presenting symptoms from infancy into adulthood, respectively. Patients with EE are predominantly young males² and have relatively high levels of eosinophils (>20-24 peak eosinophils/×400 high-powered field [hpf])^{7,8} in the esophageal mucosa, extensive epithelial hyperplasia, a high rate of atopic disease, and normal pH monitoring of the esophagus compared with patients with GERD.

EPIDEMIOLOGY

Although the incidence of primary EE has not been rigorously calculated, an increasing number of cases have been noted over the last decade. Markowitz and Liacouras⁹ found that 8% to 10% of their pediatric patients with GERD-like symptoms who were unresponsive to acid blockade actually had EE. Fox et al¹⁰ also reported that 6% of their patients with esophagitis had EE. We found that EE occurred in approximately 1:1500 in the greater Cincinnati pediatric population over a 5-year

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time period (unpublished data).¹¹ Straumann and Simon¹² have documented a prevalence of approximately 1:4000 adults in Switzerland over a 16-year observation period. Interestingly, a recent study revealed approximately 0.4% (approximately 4:1000) in a random adult Swedish population.¹³

Although EE has now been reported in Asia, Australia, Europe, and North and South America, the incidence and prevalence of EE varies substantially among different racial groups. Notably, the majority of the reported cases are among white subjects from Western countries. Within the United States, in the patients we identified, more than 95% are white. We suspect that the remaining 5%, African-American and Hispanic patients, might inherit more than average European ancestry. Although EE is an atopy-associated disease, the clustering in white subjects is distinct from allergic respiratory disease, which preferentially affects nonwhite subjects.

ESOPHAGEAL EOSINOPHIL LEVELS AND HISTOPATHOLOGY

It has been proposed that the number and location of eosinophils is helpful when trying to differentiate EE from GERD. Up to 6 eosinophils/hpf ($\times 400$) might be mostly indicative of GERD, whereas more than 20 to 24 eosinophils/hpf appears to be mostly indicative of EE,⁶⁻⁸ especially when these levels are encountered while patients are receiving anti-GERD therapy. The level of eosinophils in the esophagus negatively correlates with response to conventional anti-GERD therapy. In particular, esophageal eosinophil levels of greater than 23 eosinophils/hpf have been reported to correlate with lack of responsiveness to anti-GERD therapy.⁸ These levels might be diagnostic of EE rather than GERD/CE, especially in patients already receiving anti-GERD therapy. Patients with intermediate levels of eosinophils (7-20 eosinophils/hpf) often present a diagnostic dilemma for several reasons. First, the cutoff value for eosinophil concentrations for the diagnosis of EE has not been vigorously determined. Second, EE is often a patchy disease, and therefore depending on the number of biopsy specimens obtained, the maximum level of eosinophils might have great variability.² A recent study suggests a combination of methods: greater than 24 eosinophils in 1 hpf or 15 or more eosinophils in at least 2 hpfs is an appropriate diagnostic criteria.¹⁴ In addition to high eosinophil levels, other features distinguish EE from GERD. The anatomic location of eosinophils to both the proximal and distal esophagus denotes EE, whereas the accumulation of eosinophils mainly in the distal esophagus is characteristic of GERD.¹⁰ In addition, esophageal tissue from patients with EE typically demonstrates a thickened mucosa with basal layer hyperplasia and papillary lengthening,¹⁵⁻¹⁷ and this appears to be more pronounced than in patients with GERD.¹⁵⁻¹⁷ Radiographic and endoscopic studies have shown many findings, including strictures, mucosal rings, ulcerations, whitish papules, and polyps^{18,19}; however, nearly 20% of patients with EE have normal

endoscopic appearances,²⁰ necessitating the importance of endoscopic biopsies. Clearly, the detection of a molecular biomarker or biomarkers for EE would aid in disease diagnosis.

PATHOGENESIS OF EE

The cause of EE is poorly understood, but allergy has been implicated. The majority of patients have evidence of food and aeroallergen hypersensitivity, as defined by skin prick test responses, RAST results, or both; however, only a minority have a history of food anaphylaxis,¹⁰ indicating distinct mechanisms compared with classical IgE-mediated mast cell/basophil activation. Substantial evidence is accumulating that EE is associated with T_H2-type immune responses. In particular, increased levels of eosinophil-active T_H2 cytokines (eg, IL-4, IL-5, and IL-13), as well as mast cells, are present in the esophagi of patients with EE, although the number of patients examined has been very limited (<10).^{3,21,22} In addition, experimental models of EE can be induced in mice by means of allergen exposure, especially in the respiratory tract after mucosal or epicutaneous sensitization, as well as by means of overexpression of T_H2 cytokines (IL-5 and IL-13).^{23,24} Collectively, these experimental systems demonstrate an intimate connection between the development of eosinophilic inflammation in the respiratory tract and esophagus not only in response to external allergic triggers but also to intrinsic T_H2 cytokines. It is interesting to note that patients with EE sometimes report seasonal variations in their symptoms; preliminary studies have recently documented seasonal changes in esophageal eosinophil levels, especially in the proximal esophagus.^{25,26}

By using whole-genome microarray expression profile analysis, the dysregulated expression of approximately 1% of the human genome has been recently described.²¹ Interestingly, the EE transcript profile markedly distinguishes patients with EE from patients with CE; the latter mainly express genes comparable to those of healthy individuals. Of the entire dysregulated genome, the gene with the greatest overexpression and correlation with esophageal eosinophilia is eotaxin-3, which is induced 50- to 100-fold compared with that seen in control individuals.²¹ Comparison of allergic and nonallergic patients with EE revealed that the gene transcript signature was markedly conserved across these 2 major patient phenotypes. This demonstrates that the effector phase of the disease is conserved between individuals, despite the driving trigger of the inflammation.

Experimental modeling in mice has established that T_H2 signaling is required for induction of experimental EE. In particular, mice with the targeted deletion of signal transducer and activator of transcription 6 are protected from allergen and IL-13-induced experimental EE.^{23,27,28} Furthermore, IL-13-deficient mice have impaired allergen-induced EE.²⁹ Recently, investigators have also identified variable increases in IL-4, IL-5, and IL-13 production by mucosal and peripheral blood eosinophils

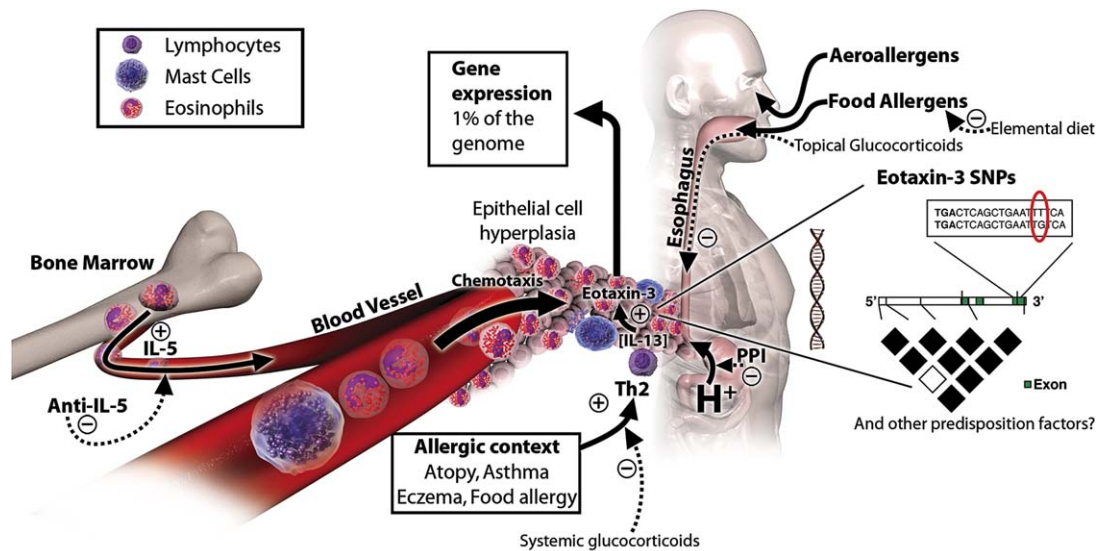


FIG 1. A proposed model to explain molecular and cellular mechanisms involved in EE pathogenesis, eotaxin-3-associated eosinophil recruitment, and treatment. Aeroallergen, food allergen, and skin sensitization have been implicated in EE pathogenesis. Elemental diet, glucocorticoids, and anti-IL-5 treatments improve the microscopic features of EE acting at different levels on the disease pathogenesis. Proton pump inhibitors (PPI) inhibit H^+ secretion by parietal cells of the stomach and only partially improve EE features. Hyperplastic epithelial cells of the esophagus overexpress eotaxin-3, likely in response to IL-13. Eotaxin-3 overexpression allows chemoattraction of $CCR3^+$ cells. Inheritance of EE disease suggests a genetic predisposition. An SNP in the eotaxin-3 gene has been associated with EE. The linkage disequilibrium pattern (ID'I) of the SNPs in the eotaxin-3 gene, based on the genotype data in a European population from the HapMap database, is presented. ID'I is the measure of the correlation between 2 SNPs; it ranges from 0 (in linkage equilibrium) to 1 (in strong linkage disequilibrium). Except for the SNP pair +76 and -5419 with an ID'I of 0.71, the other SNP pairs (shown in black) are in strong linkage disequilibrium (ID'I = 1). As such, the genotype of one SNP speaks for the others.

in EE.^{22,30,31} Because IL-4 and IL-13 are potent inducers of the eotaxins, it is interesting to speculate that IL-13 might induce EE by upregulating the production of eotaxin-3. Of note, IL-13 selectively induces eotaxin-3 in keratinocytes from the skin.³² Notably, the esophageal tissue from patients with EE markedly overexpresses eotaxin-3, but not eotaxin-1 or eotaxin-2, suggesting that IL-13-induced signaling in esophageal epithelial cells might specifically induce eotaxin-3 (Fig 1).

GENETICS OF EE

Over the past several years, evidence is accumulating that EE has a strong familial association.¹¹ In our own experience, nearly 10% of parents of patients with EE have a history of esophageal strictures, and approximately 8% have biopsy-proved EE.¹¹ Among approximately 300 pediatric probands we have recruited into a research databank to date, 26 of them have at least 1 sibling or parent with EE (data not published). In addition, Patel and Falchuk³³ have recently reported 3 adult brothers with dysphagia who were found to have EE.

One widely used measure of familial aggregation is the sibling recurrence risk ratio, known as λ_S , which compares the sibling recurrence risk versus the general population prevalence.³⁴ A λ_S value of larger than 1 indicates the

increased risk of development of the disease among siblings of the proband compared with that of the general population. Given that the population prevalence for EE is approximately 5 per 10,000,¹¹ we estimated that the sibling recurrence risk ratio λ_S for EE is approximately 80. Compared with common allergic disorders, such as atopy or asthma (λ_S is estimated at approximately 2),³⁵ the considerably high sibling recurrence risk ratio in EE indicates that genetics is likely to have a relatively large role.

ASSOCIATION WITH THE EOTAXIN-3 GENE

Our genetic study on a single nucleotide polymorphism (SNP; +2496T>G, rs2302009) in the eotaxin-3 gene has shown association with EE by both population-based case-control comparison and family-based transmission disequilibrium testing.²¹ Of note, this SNP located in the 3'-untranslated region of the eotaxin-3 mRNA might affect mRNA stability. Notably, the induction of inflammatory cytokines is often controlled at the level of mRNA stability. Moreover, this SNP might disrupt a putative AU-rich element sequence and thus modify the mRNA levels, responsiveness to glucocorticoids, or both. Interestingly, eotaxin-3 (+2496T>G) is in strong linkage disequilibrium with upstream genetic variants, making an approximately 7-kb haplotype block in the white

population (<http://www.hapmap.org>, Fig 1). Taken together, this genetic variant (+2496T>G) or those in strong linkage disequilibrium with it is likely to contribute to EE susceptibility.

POTENTIAL ROLE OF INFLAMMATORY CELLS IN EE

Clinical investigations have demonstrated extracellular deposition of major basic protein in the esophagi of patients with EE.³⁶ *In vitro* studies have shown that eosinophil granule constituents are toxic to a variety of tissues, including intestinal epithelium.³⁶ Charcot-Leyden crystal (CLC) proteins, remnants of eosinophil degranulation, are the only eosinophil-associated mRNA strongly overexpressed in biopsy specimens of patients with EE.²¹ CLC protein is found on microscopic examination of stools obtained from patients with eosinophilic gastroenteritis, raising the possibility that CLC protein or other eosinophil granule components (eg, eosinophil-derived neurotoxin) could be used in combination with other markers as noninvasive biomarkers. Indeed, we have found a correlation between EE and blood eosinophil-derived neurotoxin, eotaxin-3, and eosinophil levels.³⁷

Evidence is emerging that lymphocytes and mast cells are also involved in EE pathogenesis.²² Indeed, esophageal lymphocytes and mast cell levels are increased in EE. This increase in cell numbers is corroborated by the increased expression of lymphocytes and mast cell-specific genes. Although lymphocytes have not been formally examined, T_H2 cell-derived IL-5 appears to have a fundamental role in EE, as demonstrated by the ablation of allergen and IL-13–induced esophageal eosinophilia in response to neutralizing anti-IL-5 antibody treatment, IL-5 gene targeting, or both.^{23,24,27,28}

EE THERAPY

There is no uniformly agreed on therapy for EE, probably because of the lack of controlled clinical trials and studies on the natural history of the disorder. At present, therapy for EE is based on antigen elimination trials, anti-inflammatory approaches, and physical dilatation when strictures are present.³⁸ From the onset, anti-GERD therapy is indicated for the initial treatment of EE because acid can trigger esophageal eosinophilia, albeit generally of lower magnitude than that associated with EE. If anti-GERD therapy is unsuccessful, specific food allergen elimination (a restricted diet)^{39,40} or an exclusive elemental (amino acid–based) formula is recommended. In a retrospective study conducted on 381 patients over a 10-year period, Liacouras et al³⁸ demonstrated that the removal of dietary antigens significantly improved clinical symptoms and esophageal histology in 98% of patients. Although very efficient, these are often unsatisfactory or practically difficult. Although a diet consisting of an exclusive elemental (amino acid–based)

formula is often effective, this might not be well tolerated (especially in older individuals) because it frequently requires a surgically placed feeding tube, can be financially costly (eg, thousands of dollars per month), and is unpalatable. Glucocorticoids (systemic or topical) have been used with satisfactory results in some patients. Systemic steroids are used for acute exacerbations, whereas topical steroids are used to provide long-term control. However, it has recently been appreciated that a significant fraction of patients are steroid resistant.^{41,42} Anti-IL-5 therapy is very effective at ablating the development of experimental EE in murine models and appears to also improve eosinophil infiltration in the esophagus in an early clinical trial;^{43,44} a large-scale anti-IL-5 trial for EE is currently underway. In a preclinical trial anti-human IL-13 has been shown to be useful,⁴⁵ and it will be of interest to eventually examine the effect of IL-13 blockade in patients with EE. Other anti-inflammatory approaches, such as leukotriene receptor antagonists, have been advocated, but they have not been shown to reverse esophageal pathology.^{46,47} Because IgE effector cells, such as mast cells and basophils, are a source of proinflammatory chemokines, cytokines, and proteases, it is also possible that anti-IgE therapy might have anti-inflammatory effects in EE. It is important to note that EE is a chronic disorder that requires ongoing therapy; the disease almost uniformly returns when therapy is discontinued (eg, glucocorticoids are stopped or diet is liberated).

CONCLUSION AND FUTURE DIRECTIONS

It is now well accepted that atopic disorders, such as asthma and eczema, are complex diseases involving the interplay of multiple genes interacting with environmental factors, ultimately contributing to disease susceptibility. Initial analyses indicate a relatively strong genetic contribution in EE compared with other atopic diseases, indicating that fewer genes might be involved in disease pathogenesis compared with the more than 100 genes that have now been implicated in respiratory allergy.⁴⁸ It is now important to examine the association of EE with candidate genes that are biologically relevant in EE. Apart from the candidate gene approach, with the advance of genotyping technology, it is now feasible to conduct a genome-wide linkage analysis to identify the genetic variants associated with the susceptibility to EE. It is worthy to note that several groups have revealed that approximately 75% to 80% of patients with EE are allergic to known aeroallergens, food antigens, or both.^{11,38,39} It will be of interest to investigate whether the genetics that underlie atopy and EE are similar, at least in part. Indeed, the eotaxin-3 SNP has been associated with respiratory allergy in a Korean population.⁴⁹

Advances in understanding the molecular pathogenesis of EE started only 4 years ago. Because of the lack of data and agreement, the cutoff value of esophageal eosinophil concentrations has not yet been agreed on. Although an empiric threshold level of eosinophils might prove useful

for disease classification, we recommend that the EE gene transcript signature, including overexpression of eotaxin-3, be considered in disease definition. Further studies should focus on the molecular mechanisms involved in EE pathogenesis, its differentiation from the pathogenesis of atopy in general, and the involvement of inflammatory cells and inflammatory mediators. We envision that molecular diagnostics, similar to the approach currently being taken to classify cancer, will be applied to EE and become useful for diagnosis and differentiation from GERD and prediction of therapeutic responsiveness and prognosis. It is important to note that the mechanisms by which any therapeutic intervention improves EE have not been established, highlighting the value of translational research aiming to develop optimal EE therapy. We anticipate that mechanism-based therapeutic intervention (eg, anti-eotaxin-3, CCR3 antagonists, anti-IgE, anti-IL-5, and anti-IL-13) will prove to be successful therapies for EE.

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