
Eosinophilic Esophagitis: An Autoimmune Esophageal Disorder

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Eosinophilic esophagitis (EoE) represents a chronic, immune/antigen-mediated esophageal inflammatory disease associated with esophageal dysfunction resulting from severe inflammation. The incidence and prevalence of EoE have been increasing in the past decade; however, the reason for this increase is unclear. There is a chronic inflammatory infiltrate that is present in EoE which promotes inflammation, symptoms, and dysfunction. In addition to eosinophils, interleukin (IL)-5 expressing T cells, B cells, eotaxin-3, IL-13, and IgE-bearing mast cells are present in EoE and are thought to contribute to the disease process. Eosinophils are pro-inflammatory and modulate multiple aspects of the immune response. Eosinophils produce a wide range of inflammatory cytokines, chemokines, granulocyte-monocyte colony-stimulating factors, and tumor necrosis factors.

Once activated, eosinophils release granule components, which are toxic to a variety of tissues. Transforming growth factor 1 is a pro-fibrotic molecule produced by epithelial and inflammatory cells, is overexpressed in EoE, and plays a role in esophageal remodeling. Fibrous remodeling in EoE could be associated with symptoms of dysphagia and may explain and predict future esophageal strictures and dysmotility. EoE is a complex disease involving multiple activation pathways, a large number of cells, and various inflammatory molecules. It, along with other atopic disease, is becoming increasingly prevalent and has an important genetic load and may represent as an immunological tolerance disorder of the GI tract.

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Background

In 1991, Atwood et al. described a new clinicopathologic syndrome of intraepithelial esophageal eosinophilia in individuals with dysphagia and normal 24-hour esophageal pH monitoring. This syndrome was distinct from gastroesophageal reflux disease (GERD) and represented the disease we now know as eosinophilic esophagitis (EoE).¹ The incidence and prevalence of EoE has been increasing in the past decade. However, the reason for this rise is not certain, and it may be secondary to increased awareness, increased usage of upper gastrointestinal endoscopy, or a result of the hygiene hypothesis.² The hygiene hypothesis focuses on the idea that improvements in sanitation and treatment of infectious disease have lead to decreased exposure to microorganisms during childhood and subsequent increased incidence of allergic or autoimmune processes.³ Epidemiological

studies show that EoE is more commonly seen in male patients and in those with a history of atopic disease.

Diagnosis

EoE represents a chronic, immune-/antigen-mediated esophageal inflammatory disease associated with esophageal dysfunction resulting from severe inflammation.^{4,5} The most recent consensus recommendations for the diagnosis and treatment of EoE defines the disease with the histological presence of eosinophil-predominant inflammation. The minimum threshold of 15 eosinophils per high-power field (eos/hpf) in at least 1 endoscopic esophageal mucosal biopsy (peak value) taken at upper gastrointestinal endoscopy is needed for the diagnosis of EoE.⁵ The disease process should be isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded. In a few circumstances, patients may have strong clinical evidence for EoE and have less than 15 eos/hpf. Therefore, it is recommended that pathologists report all abnormalities associated with EoE, including the peak eosinophil value, eosinophilic microabscesses, surface layering of eosinophils, extracellular eosinophilic granules, lamina propria fibrosis, dilated intracellular spaces, and basal cell hyperplasia. The main

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differential diagnosis for symptoms and the histopathological findings is GERD. Therefore, GERD must be excluded either by a normal 24-hour pH or impedance study or by persistent eosinophilic inflammation despite proton pump inhibitor (PPI) therapy. The relationship between EoE and GERD is complex, and one may exacerbate the other.

Typical endoscopic findings include esophageal rings; a thickened, sometimes pale, mucosa; linear furrows; white exudates; and less often, a narrow caliber esophagus. A normal esophagus at endoscopy does not exclude the diagnosis of EoE. Erosions or ulcerations identify mucosal breaks and are not findings of EoE but rather of GERD. Radiography is not a recommended routine diagnostic test for EoE but can be helpful in select cases to characterize anatomic abnormalities. When a stricture is suspected, communication with a radiologist is important so that the caliber and distensibility of the esophageal lumen along its entire length will be fully assessed.

Clinical Presentation

Symptoms can vary according to age; younger children may present with frequent regurgitation, odynophagia,

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emesis, abdominal pain, poor weight gain, chest pain, or food intolerance, while older children and adults usually present with food impaction or dysphagia.⁶ Food intolerance requires specific questions on how patients eat food—prolonged chewing of food, avoidance of certain types of food, utilizing water to wash down food, or food sticking. Physical exam findings are nonspecific and can include failure to thrive, peripheral edema (secondary to hypoalbuminemia), or no specific findings. There is no single lab marker that has been found to diagnose EoE. There are no pathognomonic clinical or endoscopic features unique to EoE.

Pathogenesis

There is a chronic inflammatory infiltrate that is present in EoE that promotes inflammation, symptoms, and dysfunction (Fig). In addition to eosinophils, interleukin (IL)-5-expressing T cells, B cells, eotaxin-3, IL-13, and IgE-bearing mast cells are present in

EoE-contributing to the allergic process of this condition.^{5,7} Eosinophils are pro-inflammatory and modulate multiple aspects of the immune response.

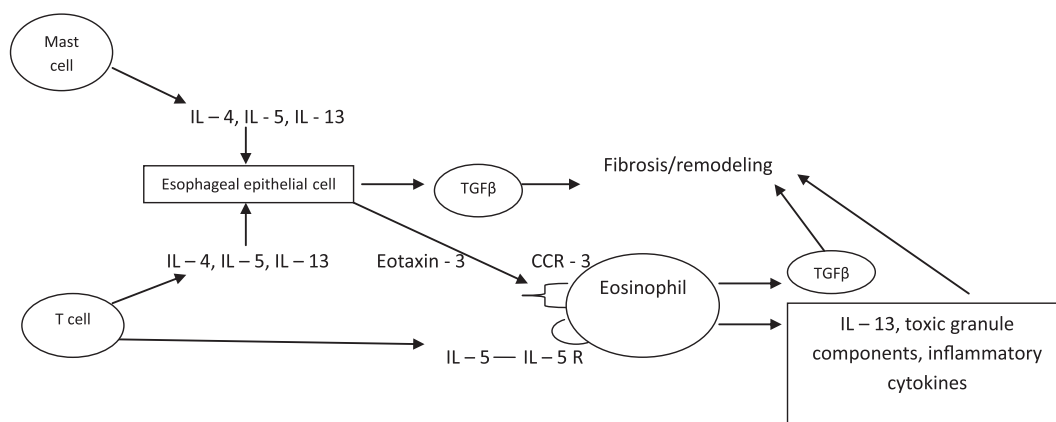


Fig. Pathogenesis of eosinophilic esophagitis.

Eosinophils produce a wide range of inflammatory cytokines, chemokines, granulocyte-monocyte colony-stimulating factors, and tumor necrosis factors. Once activated, eosinophils release granule components, which are toxic to a variety of tissues. These components are cytotoxic and increase local reactive oxygen species and stimulate mast cell degranulation. The eosinophil is critical to many aspects of the histopathology of EoE, and mice deficient in the eosinophil lineage have a significant reduction in basal layer and lamina propria collagen thickness and fail to develop esophageal strictures as detected by barium esophagram.^{8,9}

Eosinophil localization to the lamina propria in the gastrointestinal (GI) tract is regulated by eotaxins, chemokines constitutively expressed throughout the GI tract.¹⁰ Whole-genome-wide expression analysis by Blanchard et al. noted the gene encoding the eosinophil-specific chemoattractant eotaxin-3 (CCL26) was the most highly induced gene in EoE patients compared to its expression level in healthy individuals. Esophageal eotaxin-3 messenger ribonucleic acid and protein levels strongly correlated with tissue eosinophilia and mastocytosis. Esophageal eotaxin-3 levels strongly correlated with disease severity, and a single nuclear polymorphism (SNP) in the eotaxin-3 gene was associated with disease susceptibility. A genetic deletion in the eotaxin receptor, cysteine-cysteine chemokine receptor 3 (CCR3), demonstrated protection against developing EoE in mice.¹¹ CCR3, expressed primarily on eosinophils, receives signals from multiple T helper type 2 (Th2)-associated chemokines and is found to have increased expression in EoE.¹² Studies have suggested that peripheral eosinophilia and increased serum eotaxin-3 and eosinophil-derived neurotoxin levels correlate with esophageal eosinophil density.¹³

Esophageal gene expression is emerging as a key molecular analysis that will help differentiate EoE from other esophageal eosinophilia states and identify treatment responding patients. A strong link between atopy and EoE has been described in both pediatric and adult EoE patient groups.^{14,15} Most patients with EoE (~75% of cases) show signs of atopy, defined by reactivity to allergens by skin-prick testing or identification of a specific IgE in serum.¹⁶ It has been shown

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that IgE-bearing mast cells are increased in the esophageal mucosa of patients with EoE, especially in atopic patients.^{17,18} Mast cells play a role in EoE, as they have been shown to directly promote tissue remodeling and to activate eosinophils. Mast cells are normally present in the mucosa and the submucosa of the esophagus; they are involved in cross-linking of IgE, which binds to the high-affinity receptor

and becomes activated after engagement with an antigen. Mast cell activation has been found to occur locally in EoE, since ultrastructural changes in cytoplasmic granules are detectable by electron microscopy.¹⁸ Esophageal epithelial mast cells have been shown to be increased in number and correlate with eosinophil counts and eotaxin-3 in the mucosa of EoE patients.^{18,19} Mast cells have also been shown to express CCR3 and respond to CCR ligands.^{8,12} Aceves et al.²⁰ found that mast cells were the predominant cell type increased in the smooth muscle in patients with EoE, suggesting that they play a role in mediating esophageal dysmotility.

Similar to other atopic diseases, EoE is linked to a strong genetic element. Recently, it was found that an association between a SNP in the gene encoding thymic stromal lymphopoietin (TSLP) is a risk factor for EoE.²¹ TSLP is an IL-7-like cytokine that regulates host adaptive immune responses through dendritic cell and T-cell interactions. The absence of the protective minor allele (G) was found to be associated with an increased TSLP expression and basophil infiltration in the esophageal epithelium. TSLP has been previously linked to a key regulator of allergic sensitization initiation.²²

Non-IgE-mediated forms of EoE exist in which no relevant allergens can be identified by measuring IgE or performing skin-prick tests. Additionally, studies have shown that 5–10% of patients treated with oral immunotherapy for desensitization to IgE-mediated food allergy develop EoE, indicating a non-IgE mechanism.²³ Studies have stated that seasonality is associated with EoE, suggesting a potential role for aeroallergens in patients with EoE.⁵ A thorough evaluation by an allergist or immunologist is recommended because of the high rates of concurrent asthma, allergic rhinitis, eczema, and food allergy/anaphylaxis. In select cases, additional testing for asthma and allergies is

recommended to improve the diagnosis and control of concurrent atopic disease.

These non-IgE, T-cell-mediated hypersensitivity reactions are characterized by the activation of antigen-specific T cells and subsequent recruitment of inflammatory cells. Of all the cytokines produced by Th2 cells, IL-5 is the most specific for eosinophils. IL-5 is produced primarily by Th2 cells, although additional sources include productions by mast cells and eosinophils. IL-5 has been found to increase the pool of eotaxin-responsive eosinophils and prime eosinophils to respond to CCR3 ligands.²⁴ It has been found to induce eosinophil growth, differentiation, activation, and survival of eosinophils.¹⁸ Mishra et al. reported that the Th2 cytokine IL-5 is necessary and sufficient for the induction of eosinophil trafficking to the esophagus. They found that IL-5 deficient mice were resistant to EoE when challenged with allergen exposure.²⁵ IL-5 may induce eosino-

phil trafficking to the esophagus by either enhancing eosinophil responsiveness to chemokines expressed in the esophagus or upregulating the receptors involved in eosinophil trafficking to the esophagus.²⁵ Despite clinical and murine studies noting the central role of IL-5 in the allergic mechanism of EoE, anti IL-5 biological therapy has shown limited clinical efficacy.²⁶

IL-13 is a Th2 cell-derived cytokine produced at increased levels in allergic tissues and thought to be a central regulator in eosinophilic diseases. Blanchard et al.²⁷ performed real-time polymerase chain reaction and microarray analysis on RNA extracted from esophageal epithelial cells and found that IL-13 mRNA levels were largely reversible with steroid treatment and that esophageal epithelial cells were found to markedly produce eotaxin-3 after IL-13 stimulation. IL-13 has been found to promote fibrosis, angiogenesis, and epithelial hyperplasia, which contribute to esophageal remodeling in EoE.²⁸ The IL-13-induced epithelial cell-produced gene that is most overexpressed in the esophagus of patients with EoE is eotaxin-3.

Transforming growth factor (TGF) β 1 is a pro-fibrotic molecule produced by epithelial and inflammatory cells, and this has been noted to be overexpressed in EoE and plays a role in esophageal remodeling.²⁹ Fibroblast growth

factor (FGF) is a pro-fibrotic cytokine that is released by a variety of cells and may promote fibrosis and angiogenesis. Plasma and local FGF expression was found to be increased in EoE patients compared to healthy controls and gastroesophageal reflux disease subjects.³⁰ Fibrous remodeling in EoE could be associated with symptoms of dysphagia and may explain and predict future esophageal strictures and dysmotility. Esophageal eosinophil activation occurs as shown by eosinophil degranulation and can subsequently result in EoE-associated fibrosis.

Treatment

Current treatment goals of EoE include resolution of clinical symptoms, prevention of disease relapse, prevention of complications such as fibrosis and strictures, prevention adverse reactions from treatment, and maintain quality of life. Treatment options for EoE vary vastly and include proton pump inhibitors, topical corticosteroids, systemic steroids, mast cell inhibitors, leukotriene receptor antagonists, immunomodulators, elemental diet, allergen-specific elimination diet, and empiric six-food elimination diet. Treatment is individualized and based on a discussion with the family regarding outcomes of different therapies, likelihood of acceptance by the child, the lifestyle of the child, and the suitability of the treatment to the family. In 1995, Kelly et al.³¹ first demonstrated that clinical symptoms and esophageal eosinophilic inflammation in children with EoE were reversed by the exclusion of all intact proteins from the diet and by the substitution with an amino-acid-based elemental diet. Although widely used and effective, dietary changes are difficult to maintain in the pediatric population. It is recommended that a trial of PPIs be initiated in symptomatic children with histological findings of esophageal eosinophilia. A second EGD should be performed under PPI therapy.⁵ Long-term treatment with PPIs has been documented to show improvement in symptoms, but without histologic improvement in patients with EoE.³² Additionally, a long-term side effect of EoE is the formation of strictures. Levine et al.³² found no increase in fibrosis while on PPI therapy, despite persistent eosinophilic inflammation. Corticosteroids improve the clinicopathologic features of EoE in most patients;

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however, when discontinued, the disease almost always recurs.³³ Additionally, there is potential for significant toxicity, so the long-term use of systemic steroids is not recommended. In extremely severe symptoms, a short course of oral corticosteroids can provide immediate relief of the patient's symptoms. Topical corticosteroids can be effective in inducing remission in EoE; however, chronic use in children can potentially affect growth. In addition to esophageal candidiasis, steroid resistance has been reported as an adverse effect of topical preparations.³⁴ Various studies on interleukin-specific antibodies have found histologic changes in EoE, but without significant improvement of symptoms.^{35,36}

Conclusion

EoE is a complex disease involving multiple activation pathways, a large number of cells, and various inflammatory molecules. It, along with other atopic disease, is becoming increasingly prevalent, has an important genetic load, and is an immunological tolerance disorder of the GI tract. There is promise in identifying a potential biomarker with respect to disease activity and response to therapy. Currently, there are many unresolved questions on treatment choice and duration. Interpretation of the vast number of studies is difficult as there is much variability in dosing regimens, duration of treatment, and study end points. Treatment should be individualized in an effort to minimize morbidity. Long-term follow-up is needed in these patients to prevent the development of esophageal strictures.

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