Mechanism of Eosinophilic Esophagitis

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KEYWORDS

• Esophagus • Eosinophils • Eotaxin • Interleukin • Mast cells • Remodeling

The esophagus is the only segment in the gastrointestinal (GI) tract that is devoid of eosinophils, whereas most of the other leukocytes reside in the esophagus at baseline in a healthy state.[1,2] The esophagus is lined with mucous membrane and muscles that act with peristaltic action to move swallowed food down to the stomach. The epithelium of the esophagus is squamous but not keratinized like skin; therefore, keratinocytes are directly exposed to the esophageal content, which indicates that the esophageal epithelium may have a significant role in the induction of esophageal inflammation. The accumulation of eosinophils in the esophageal mucosa is the cardinal pathologic finding that occurs secondary to several unrelated diseases and is reported in several esophageal diseases, such as hypereosinophilic syndrome, eosinophilic gastroenteritis, drug reactions, fungal/parasitic infections, gastroesophageal reflux disease (GERD), and eosinophilic esophagitis (EoE).[1–11] EoE is a commonly observed medical problem and is well documented in pediatric patients, but the adult form has only recently gained recognition as a distinct entity. EoE is characterized by an increase in esophageal eosinophilia, basal cell hyperplasia, and several other esophageal abnormalities that include furrows, the formation of fine concentric mucosal rings (corrugated esophagus), and esophageal strictures (narrowing),[3–9] associated with extensive tissue remodeling and fibrosis.[10,11]

CLINICAL CHARACTERISTICS OF EOSINOPHILIC ESOPHAGITIS

Esophageal eosinophils are not pathognomonic for EoE because eosinophil infiltration in the esophagus occurs in various states, including GERD. Differentiating EoE from other esophageal disorders, specifically GERD, is often a challenge.[12] Patients who have primary EoE commonly report symptoms that include difficulty feeding, vomiting, chest pain, dysphagia, and food impaction;[13–16] these symptoms appear to occur

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sequentially as the disease progresses from infancy into adulthood.[17] Dysphagia and food impaction are commonly observed in adult patients who have EoE.[18–20] However, longitudinal studies from childhood into adulthood are not yet available. Patients who have EoE are predominantly young men[13,14] and have high levels of eosinophils in the esophageal mucosa, extensive epithelial hyperplasia, and a high rate of atopic disease compared with patients who have GERD.[21,22] In particular, esophageal eosinophil levels of greater than 24/high-power field have been reported to correlate with lack of responsiveness to anti-GERD therapy;[23,24] these concentrations may be diagnostic of EoE rather than GERD, especially in patients already on anti-GERD therapy. A recent expert panel established as part of the First International Group of EoE Researchers recommended that a cutoff of 15 eosinophils/high-power field is sufficient for the diagnosis of EoE, provided that GERD has been eliminated as the diagnosis;[25] for research purposes a higher threshold level was recommended. Additionally, esophageal biopsies from EoE demonstrate a thickened mucosa with basal layer hyperplasia and papillary lengthening. Radiographic and endoscopic studies have shown many findings, including small-caliber esophagus, strictures, mucosal rings, ulcerations, whitish papules, and polyps.[8,15,16,26–28] EoE has been found to be associated with esophageal dysmotility but the cause of the motor disturbances is unclear. The eosinophil and mast cell activation and degranulation have been postulated as a possible cause of EoE pathogenesis.[29–31]

FOOD AND ENVIRONMENTAL ALLERGENS ARE LINKED TO EOSINOPHILIC ESOPHAGITIS

Food allergies affect an estimated 6% of children and 3.7% of adults in the United States and during the past decade, food allergies and their manifestations have substantially increased.[32,33] Food allergies can be classified into those that are IgE-mediated and those that are non–IgE-mediated. IgE-mediated reactions develop when food-specific IgE antibodies residing on mast cells and basophils come into contact with, and bind to, circulating food allergens and activate the cells to release potent mediators and cytokines. In non–IgE-mediated food allergic disorders, multiple inflammatory cells and their mediators play a role in immunopathogenesis. Most patients who have EoE (90%) have evidence of food and aeroallergen hypersensitivity, yet only a subset (10%–30%) has a history of food anaphylaxis.[34] Recent literature on pediatric patients who have EoE confirms that nearly all patients respond to an elemental diet, with resolution of symptoms and normalization of biopsies;[34] reintroduction of foods causes symptoms and esophageal eosinophilia to return.[35] Patients who have EoE have also been reported to exhibit seasonal variations in their symptoms and changes in their esophageal eosinophil levels. The mucosal eosinophil counts were elevated during the spring and summer and were suppressed during the winter,[36] indicating a role for aeroallergens. Studies of animal models have also linked EoE to aeroallergens and allergic diseases.[37] These findings indicate that sensitization pathways could occur in human EoE, and antigen-presenting cells may play an important role in the pathogenesis of EoE. An average of three to six foods per patient were directly linked to the development of esophageal eosinophilia and the common foods identified were milk, egg, soy, chicken, wheat, beef, corn, and peanuts.[34,35] Taken together, this finding provides supportive evidence that food and aeroallergen sensitization is causally involved in EoE (**Fig. 1**).

CELLULAR MEDIATORS THAT INFLUENCE THE OCCURRENCE OF EOSINOPHILIC ESOPHAGITIS

The current understanding of the pathophysiology of EoE comes from basic immunologic studies and clinical observation and treatment. Many eosinophils were detected