

Pathogenesis and clinical features of eosinophilic esophagitis

Key words: Allergy, eosinophils, eotaxin, esophagitis, gastroesophageal reflux, IL-5

In comparison with other gastrointestinal segments, the esophagus is immunologically unique; for example, it normally does not contain resident eosinophils.¹ Nevertheless, the accumulation of eosinophils in the esophagus is a commonly observed medical problem in patients with diverse diseases that include gastroesophageal reflux, eosinophilic esophagitis, eosinophilic gastroenteritis, and parasitic infections.²⁻⁶ Classifying patients with eosinophilic esophagitis has been somewhat confusing in the literature; we propose a new classification scheme (Table I). Primary esophageal eosinophilic disorders are divided into atopic, nonatopic, and familial forms and represent intrinsic disorders of the esophagus. Primary eosinophilic esophagitis is distinguished from secondary disorders (eg, gastroesophageal reflux, drug reactions, infections, esophageal leiomyomatosis) on the basis of specific esophageal pathology.⁷⁻¹⁰ For example, primary eosinophilic esophagitis (previously also called *idiopathic eosinophilic esophagitis*, *atopic esophagitis*, and *allergic esophagitis*) is characterized by high numbers of eosinophils in the esophagus, diffuse eosinophilia involving the proximal and distal esophagus, and extensive esophageal histopathologic changes (eg, epithelial hyperplasia). Most patients with primary eosinophilic esophagitis also have a high rate of atopic sensitization to aeroallergens and food antigens; these patients are referred to as patients with primary atopic eosinophilic esophagitis. Primary eosinophilic esophagitis can also occur in a familial form, with apparent autosomal dominant penetrance (unpublished findings). Gastroesophageal reflux might also occur in a subset of

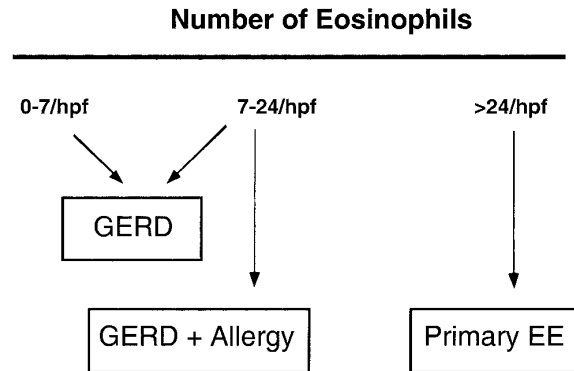


FIG 1. Eosinophil numbers distinguish primary eosinophilic esophagitis from gastroesophageal reflux disease. Gastroesophageal reflux disease (GERD) and primary eosinophilic esophagitis (EE) can be differentiated by the number of eosinophils in the distal esophageal mucosa. In standard gastroesophageal reflux, the esophageal mucosa usually has elevated but relatively low eosinophils per 400 $\times$ high-power field (hpf). In contrast, patients with primary eosinophilic esophagitis have relatively high eosinophil numbers. In addition, patients with primary EE generally have involvement of the proximal and distal esophagus, whereas patients with GERD have disease limited to the distal esophagus. Patients with intermediate numbers of esophageal eosinophils might have an intermediate phenotype with both GERD and allergy. We propose that there is a continuum between GERD and primary EE, in at least a subset of patients.

patients with eosinophilic esophagitis, but these patients and others with secondary eosinophilic esophagitis generally have less extensive pathologic changes in the esophagus than are seen in patients with primary eosinophilic esophagitis.¹⁰ Quantitative analysis of esophageal eosinophil numbers is helpful in distinguishing these disorders (Fig 1). Primary eosinophilic esophagitis is clinically distinguished from gastroesophageal reflux by the more common occurrence of dysphagia and food impaction. Interestingly, recent clinical studies have suggested that the number of eosinophils in the esophagus negatively correlates with response to conventional gastroesophageal reflux therapy.¹¹ It is interesting to consider that a subset of patients with gastroesophageal reflux, especially those with relatively high eosinophil numbers (>7 to 24 per high-power field), might have an allergic component to their gastroesophageal reflux (Fig 1). These patients might benefit from control of allergen exposure and from therapeutic intervention directed against allergy. In addition, patients with eosinophilic esophagitis can have their clinical symptoms and eosinophilic infiltrations ameliorated by

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Supported in part by National Institutes of Health grants R01 AI42242-03, and R01 AI45898-02; the Human Frontier Science Program; the Burroughs Wellcome Fund Translational Research Award; and the International Life Sciences Institute (all granted to M.E.R.).

Received for publication September 12, 2001; revised September 14, 2001; accepted for publication September 14, 2001.

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J Allergy Clin Immunol 2001;108:891-4.

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0091-6749/2001 \$35.00 + 0 1/39/120095

doi:10.1067/mai.2001.120095

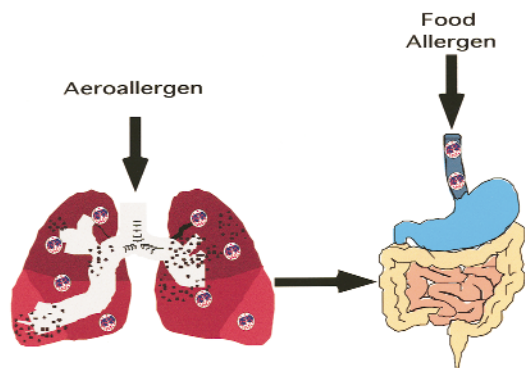


FIG 2. Connection between respiratory and esophageal eosinophilic inflammation. We propose that at least 1 pathway for the development of eosinophilic esophagitis involves sensitization to aeroallergen in the respiratory tract. Sensitized individuals swallow and/or ingest aeroallergens deposited in the upper gastrointestinal tract by inhalation and subsequently develop a hypersensitivity response that leads to eosinophil infiltration into the esophagus. Alternatively, esophageal eosinophilia might occur in response to the asthmatic inflammation in the lung if communicating T cells and eosinophils exist in these tissues. Some patients might also develop primary eosinophilic esophagitis by having hypersensitivity responses to dietary antigens. Collectively, the current studies indicate that the esophagus is a unique immunologic organ in comparison with the stomach and intestine and that it uses immunologic responses similar to those of the lung.

an elemental diet or by anti-inflammatory therapy (cromoglycate or glucocorticoids).^{12,13} This suggests that sensitized individuals might develop esophageal eosinophilic inflammation in response to exposure to food allergens. Although the role of allergens in the induction of eosinophilia in the esophagus has been debated,⁸ recent experimental studies have established a linkage. Exposure of anesthetized mice to repeated challenges of aeroallergen (eg, extracts of *Aspergillus fumigatus*) through use of a standard protocol to induce allergic airway inflammation promotes marked eosinophilic esophagitis. The allergen-induced esophageal eosinophilia is accompanied by intraepithelial eosinophils, extracellular granule deposition, and epithelial cell hyperplasia—features that mimic the pathophysiologic changes observed in individuals with various forms of eosinophilic esophagitis.⁸ Importantly, the eosinophilic inflammation occurs in the lungs and esophagus but not in the stomach or intestine; this demonstrates an intimate immunologic connection between the lung and esophagus. In these experimental systems, it is likely that sensitization occurs by pulmonary exposure, inasmuch as oral or intragastric allergen exposure alone fails to elicit eosinophilia. Mechanistically, it is interesting to speculate that sensitization occurs through the respiratory tract (lung) and that when sensitized individuals subsequently swallow or ingest aeroallergens deposited in the upper gastrointestinal tract by inhalation, they develop a hypersensitivity response that leads to eosinophil infiltration into the esophagus. Alternatively, esophageal eosinophilia might occur in response to lung inflammation by

TABLE I. Classification scheme for eosinophil-associated esophageal disorders*

Primary disorders
Primary eosinophilic esophagitis (also known as idiopathic eosinophilic esophagitis and allergic esophagitis)
Atopic
Nonatopic
Familial
Secondary eosinophilic disorders
Eosinophilic gastroenteritis
Hypereosinophilic syndrome
Secondary noneosinophilic disorders
Iatrogenic eosinophilic esophagitis
Infection associated eosinophilic esophagitis
Primary gastroesophageal reflux
Esophageal leiomyomatosis
Vasculitis (periarteritis nodosa)
Connective tissue disease (scleroderma)

*For a further differential diagnosis, refer to the following article: Ahmad M, Soetikno RM, Ahmed A. The differential diagnosis of eosinophilic esophagitis. *J Clin Gastroenterol* 2000;30:242-4.

shared communicating T cells and eosinophils in these tissues. Taken together, these studies suggest that asthma and aeroallergen exposure are mechanistically linked to the development of eosinophilic esophagitis (Fig 2).

In this issue of the Journal, Dr Hans-Uwe Simon and his colleagues report a significant advance in understanding of the immunopathogenesis of primary eosinophilic esophagitis. The 8 patients investigated had features typical of primary eosinophilic esophagitis, including high esophageal eosinophil numbers, predominance of males among those with the condition, relatively normal peripheral blood eosinophil counts, lack of histologic involvement of the stomach and small intestine, and, importantly, the absence of gastroesophageal reflux disease. In their study, the investigators demonstrate that in addition to the accumulation of eosinophils in the esophagus, there are substantial increases in esophageal mast cells and T cells. Although the T cell phenotype was only identified by CD3 staining, T cells were shown to overexpress IL-5, an eosinophil growth and activating factor produced by T_H2 cells. These findings are in agreement with a clinical study demonstrating elevated levels of IL-4-secreting T cells in esophageal lesions of patients with secondary eosinophilic esophagitis.⁷ In their article, Straumann et al also report the overexpression of the proinflammatory mediator TNF- α , a cytokine that induces eosinophil activation as well the expression of eosinophil-adhesion molecules on vascular endothelium. The expression of the eosinophil-selective chemokine eotaxin was also examined; surprisingly, it was not shown to be overexpressed. Although these data are limited by the analysis of only a small number of subjects and by limited immunophenotyping, they implicate a broader leukocyte and cytokine involvement in primary eosinophilic esophagitis than previously appreciated. In fact, these studies suggest that the immunopathogenesis of primary eosinophilic esophagitis

is mechanistically linked to asthma, inasmuch as the cells and cytokines implicated in both processes are similar. These findings are consistent with the critical role of IL-5 in the induction of allergen-induced experimental esophagitis.¹⁴ The esophagus thus appears to use similar pathways, involving CD4⁺ T cells and IL-5, for the induction of eosinophilic inflammation to those operational during allergic pulmonary inflammation. Although the role of eosinophils in eliciting esophageal injury has been debated, the lack of allergen-induced esophageal epithelial hyperplasia in IL-5-deficient mice suggests an etiologic role for eosinophils in promoting epithelial proliferation.¹⁴ Consistent with an effector role of gastrointestinal eosinophils, experimental analysis of eosinophil-associated gastrointestinal inflammation has revealed a critical role for eosinophils in the pathogenesis of the disease process.^{15,16} Eosinophils are sources of a variety of cytokines, including growth factors (eg, transforming growth factor α) that might be involved in promoting epithelial hyperplasia.¹⁷ In addition to regulating eosinophilopoiesis, IL-5 primes eosinophils to have enhanced responsiveness to chemokines such as eotaxin.¹⁸ In experimental allergen-induced eosinophilic esophagitis, the accumulation of eosinophils in the esophagus is dependent in part on eotaxin. However, eotaxin-deficient mice still show markedly elevated eosinophil numbers in the esophagus in comparison with baseline wild-type mice or mice treated with placebo alone. This indicates the cooperation of eotaxin with other eosinophil-active chemoattractants in the regulation of eosinophil trafficking to the esophagus. Eosinophils respond to a variety of chemokines, including other CCR3 ligands (MCP-2, MCP-3, RANTES, eotaxin-2, and eotaxin-3), and these may also be involved.^{17,19,20}

Establishing that eosinophilic esophagitis is an IL-5-, T_H2-cell-, and mast cell-associated disease process suggests that the immune mechanisms involved in asthma are also likely to be involved in eosinophilic esophagitis (Fig 2). Thus, therapeutic intervention strategies for patients with eosinophilic esophagitis could be based, at least in part, on strategies used to treat asthma. In our practice, patients with eosinophilic esophagitis are first skin-tested to a panel of food and aeroallergens, and atopic patients (approximately 80%) are subsequently treated with strict allergen avoidance/elimination. In addition, topical delivery of glucocorticoids to the esophagus (achieved by modifying the standard use of a metered dose inhaler) and an elemental diet are also effective therapy in some patients.^{12,13,21} The recent findings concerning the immunopathogenesis of eosinophilic esophagitis suggest that humanized anti-IL5, a therapeutic reagent currently being studied for patients with asthma,²² might also be useful for the treatment of eosinophilic esophagitis. Although the incidence of primary eosinophilic esophagitis has not been established, there appears to be a recent mini-epidemic, especially in pediatric populations.²³ We propose that primary eosinophilic esophagitis is a severe manifestation of atopy and that the rising incidence is epidemiologically

and pathogenetically linked to the allergy epidemic.²⁴ We have recently established a World Wide Web site (<http://www.Cincinnatichildrens.org/eosinophils/>) dedicated to collecting and disseminating information about eosinophil-associated gastrointestinal diseases. Interestingly, nearly one half of the registered patients have eosinophilic esophagitis. It is hoped that the report by Straumann et al, the established Web site, and the recent flurry of publications concerning eosinophilic esophagitis will stimulate future investigations designed to understand the pathogenesis and treatment of these complex inflammatory disorders of the esophagus.

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We thank Andrea Lippelman for editorial assistance.

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