

Eosinophilic Esophagitis: Should We Consider Aeroallergens?

THOMAS E. SCARBOROUGH, JR., M.D.

ABSTRACT

Eosinophilic esophagitis (EE) is an inflammatory condition with pronounced eosinophilic infiltration. It is commonly associated with atopic disease and may be mediated through an allergic mechanism. There is a clear association between food allergies and EE. However, the role of aeroallergens in EE is unclear. In hopes of enhancing the current understanding of aeroallergens in EE the literature was reviewed for relevant articles. A number of animal and human studies support the likely role of aeroallergens in EE. The animal studies convincingly show provocation of EE with aeroallergens through a T-helper lymphocyte type 2 (Th2) mechanism. These studies are complemented by human data that show a correlation with aeroallergens and eosinophilic infiltration. Taken together, the literature suggests aeroallergens may contribute to the development of EE. (Pediatr Asthma Allergy Immunol 2007; 20[3]:177–180.)

INTRODUCTION

EOSINOPHILIC ESOPHAGITIS is a condition of eosinophilic infiltration of the esophagus that presents with varied clinical manifestations. EE should be considered in any patient that presents with failure to thrive, vomiting, abdominal pain, food impaction, or dysphagia. The pathogenesis of EE is not fully elucidated, although it has an underlying inflammatory pinning. The esophagus normally has no eosinophils,¹ but many disease processes can elicit eosinophilic infiltration including: gastroesophageal reflux disease (GERD), parasite infection, inflammatory bowel disease, collagen vascular disease, and allergy.² A large number of patients with EE have skin test-positive results and atopic clinical manifestations. This points to an allergic role in the expression of EE. It is common for allergists to screen for food allergens when evaluating patients with EE, but less common to screen for aeroallergens. This article hopes to enhance the current understanding of aeroallergens in EE by reviewing relevant data.

EE occurs secondary to a misdirected inflammatory process that appears allergic in nature. Allergy is an inflammatory condition provoked by a cellular imbalance that favors a robust inflammatory Th2 response.³ Typical target organs are skin, nose, and lungs. However, allergy should not be considered a localized event, but a systemic process with mucosal expression of disease. Therefore, any mucosal surface may become

University of Washington/Children's Hospital Regional Medical Center, Seattle, Washington.

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involved in expression of allergic disease. As a result, EE has come to the attention of the allergy community secondary to its interrelation with atopic disease.

Approximately 75% of individuals diagnosed with EE have atopic clinical features, and a similar percentage have skin tests that are positive to food and aeroallergens.^{4,5} Food is important in the immunopathogenesis of EE. Elimination diets based on skin-prick and patch testing correlate with improvement in histological and clinical features.^{6,7} Based on these studies the correlation between food and EE has become well established. However, not all individuals with EE are food allergic or respond to elimination diets.⁸ This group of patients is poorly studied. Many are atopic individuals with positive skin tests to aeroallergens. However, the role of aeroallergens in EE is not well defined. A few studies have suggested that aeroallergens are important in the pathogenesis of EE. The data comes from both murine and human studies, although the human data is limited.

ANIMAL STUDIES

In 2001, Mishra et al.⁹ reported the first study that implicated aeroallergens in the pathogenesis of EE. This murine model provided information that intertwined allergic response in the lung and inflammation in the esophagus. In this experiment, mice were intranasally challenged with *Aspergillus fumigatis* provoking a strong eosinophilic response in the lungs. This same process also stimulated a strong influx of eosinophils into the esophagus. The esophageal histological features of these mice were similar to human patients with EE. Interestingly, these same mice did not develop EE when challenged with *A. fumigatis* by oral or intragastric routes. Intranasal challenges with ovalbumin (OVA) and *Ascaris* (APF), other allergens known to induce lung inflammation, also elicited esophageal eosinophilic infiltration. This study also defined the importance of IL-5 in the development of EE, as IL-5-deficient mice showed no eosinophilic infiltration of the esophagus. This data strongly supports aeroallergens in the induction of an allergic inflammatory response in the lungs as well as the esophagus. The mechanism by which the esophagus develops hypersensitivity is not known. In this study, a direct allergen stimulus from the swallowing of nasally placed allergen is possible. However, esophageal inflammation is speculated to depend on primary sensitization in the lung.

The association of allergic airway disease and eosinophilic infiltration of the esophagus was evaluated in a subsequent murine experiment. Mishra et al.¹⁰ showed that intratracheally delivered IL-13 was able to induce EE. This technique eliminated the swallowing of intranasally placed reagents, such as that in the previously discussed experiments. This experiment suggests a role of a lung induced immune response in the expression of EE. This effect was inhibited in mice with genetic backgrounds deficient in IL-5, eotaxin-1, and STAT6. These findings strongly implicate a Th2-mediated mechanism of disease.

Interestingly, more recent studies have provided evidence that epicutaneous allergen sensitization may provide the prerequisite inflammatory milieu needed for provocation of EE. In these experiments, Akei et al.¹¹ showed that mice sensitized to OVA and *A. fumigatis* via the skin developed EE after a single intranasal challenge. Prior to intranasal challenge there were no eosinophils in the esophagus. Further studies defined the importance of IL-5 in this process. Other mediators of allergen induced Th2 response were also important, although to a lesser extent than IL-5. Just as other studies have shown, this data supports a systemic process invoked by an allergic epicutaneous response.

HUMAN STUDIES

Aeroallergens have also been implicated in human EE. A case study reported by Fogg et al.¹² followed a female patient with a past history of intermittent asthma and allergic rhinitis, as well as recurrent symptoms consistent with EE. She underwent repeated endoscopic biopsies in and out of pollen season over several years. She had eosinophilic infiltration of the esophagus during pollen season consistent with EE. The histological findings on biopsy coincided with her symptoms of persistent reflux. Repeat biopsies out of pollen season showed rare to no eosinophils in the esophagus. She had extensive skin-prick testing and

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patch testing to foods, all of which were negative. Skin-prick testing was positive to various pollens. This case study is suggestive of EE exacerbations provoked by pollen exposure.

The role of aeroallergen sensitization in esophageal mucosal disease was examined by Onbasi et al.¹³ In these experiments they evaluated eosinophils in the esophagus of atopic patients. A group of 38 pollen allergic patients with allergic rhinitis and/or asthma underwent esophageal biopsies during pollen season. These patients had no symptoms of EE. Control groups included nonallergic patients without GERD and nonallergic patients with GERD. Results showed a modest increase in esophageal eosinophils in the atopic patients during pollen season. An increased number of eosinophils in the esophagus was associated with severity of asthma and peripheral eosinophil level in atopic patients. These data implicate aeroallergens as a driving force behind esophageal eosinophil infiltration.

A recent study by Wang et al.¹⁴ examined the seasonal incidence of EE. They performed a retrospective analysis of 234 patients diagnosed with EE over a 6-year period. Their results showed a significant seasonal variation in the number of EE cases. The lowest incidence of new cases occurred in the winter. They surmise that this data is associated with the relative decrease in aeroallergen exposure in the winter.

CONCLUSION

Current data suggests aeroallergens may contribute to the development of EE. A significant portion of this data comes from murine models. The data from these studies support a Th2-mediated inflammatory process in the pathogenesis of EE. Human data is less convincing, but several studies hint at a role of aeroallergens in the provocation of generalized eosinophilic infiltration of the esophagus. All the data provide further evidence that allergy is a systemic process that may express signs of disease on any mucosal surface. The immunopathological mechanism of EE, although incompletely understood, appears to be allergic in nature and triggered by food and/or aeroallergens. Therefore, a thorough history and skin-prick testing for foods, as well as aeroallergens, is warranted in the proper setting.

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Address reprint requests to:
Thomas E. Scarborough, Jr., M.D.
University of Washington
Children's Hospital Regional Medical Center
Seattle, WA 98105

E-mail: scarbt@u.washington.edu

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