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The link between allergies and eosinophilic esophagitis: implications for management strategies

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Abstract

Eosinophilic esophagitis (EE) has an increased incidence of diagnosis similar to other atopic diseases. We present a recent literature review of the common features between atopic diseases (i.e., asthma, allergic rhinitis and atopic dermatitis) and EE. All of the disorders have allergen triggers and evidence of a possible Th2 inflammation at the site of disease. Murine models have also shown similar features with the importance of T cells and Th2 cytokines for the development of disease. The diseases share underlying inflammation with the potential for remodeling with an increase in TGF- β expression in asthma and EE. However, differences do exist between the diseases in treatment and pathogenesis. For EE, there are two basic treatment options: avoidance of the food triggers or treatment of the eosinophilic inflammation with corticosteroids.

Keywords

allergic rhinitis; asthma; eosinophilic esophagitis; murine models; Th2 cytokines

Allergy is defined as an abnormal immune response to a harmless protein. Pollens, pet dander and dust mites may lead to allergic rhinoconjunctivitis, worsening atopic dermatitis (AD) or asthma flares. Food proteins, such as milk, egg, soy, wheat and peanut, may lead to IgE-mediated reactions such as hives or anaphylaxis, cell-mediated immune reactions such as colitis, or a combination of IgE-mediated and non-IgE-mediated reactions such as AD or eosinophilic esophagitis (EE). The most common allergic conditions are allergic rhinoconjunctivitis, AD, asthma and food allergy, all of which appear to be on the rise. EE, a 'newly recognized' disease, is a condition in which high numbers of eosinophils are present in the esophagus, despite adequate acid blockade. The link between allergies and EE is

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threefold. Patients with EE often have one or more form(s) of atopy/allergy. Similar histopathological features can be seen between asthma, AD and EE. Lastly, management strategies are similar (Box 1).

Definition of EE

Eosinophilic esophagitis is a chronic condition in which patients have eosinophilic inflammation isolated to their esophagus (an area typically void of eosinophils) [1]. It is thought to be a newer disease entity described as early as 1977 [2], with the first series report in 1985 [3], and classical features reported for the last 15 years [4]. EE has been diagnosed with increasing frequency over the last 15 years, in part owing to increased recognition and increased incidence of disease [5-7]. Young children present with failure to thrive or classic gastroesophageal reflux symptoms, school-aged children present with abdominal pain or vomiting, and older adolescents/adults present with food impaction and dysphagia [1,8-12].

The First International Gastrointestinal Eosinophil Research Symposium (FIGERS), bringing together gastroenterologists, allergists and pathologists, defined EE as a “primary clinicopathological disorder of the esophagus”. Currently, there is no diagnostic test or laboratory marker to diagnose or follow the disease. Diagnosis is made by suspicious history, a 2-month trial of antireflux medications (up to 2 mg/kg/day of proton pump inhibitor) or a normal 24 h intra-esophageal pH monitoring study, and esophageal biopsy. For diagnosis, pathology must reveal 15 eosinophils or more per high-powered field (HPF) in one or more specimens in the absence of other causes (e.g., drug allergy, infections, inflammatory bowel disease and eosinophilic gastroenteritis) [1]. Gastroesophageal reflux disease (GERD) can cause esophageal eosinophilia [13] and it was seen in 40% of the patients with more than 15 eosinophils/HPF in a pediatric series by Dranove *et al.* [14]; and in 70% of patients in an adult series with up to 40 eosinophils/HPF in a small series by Ngo [15,16]. The overlap of GERD and EE represent a complex issue for pediatric and adult patients [16-18]. For example, in the first adult series of EE, two out of 13 patients were found to still have significant acid reflux on pH testing while on adequate reflux medication [4]. Thus, the predominant pathophysiology then was considered to be atopy at that time. A complete review of this important topic (GERD vs EE) is well beyond the narrow scope of this targeted review and is reviewed in other articles [17].

Box 1. Comparison between eosinophilic esophagitis and atopy

- Similarities between EE and atopy
 - Increased prevalence in the last 10 years
 - Allergen driven
 - Increased Th2 cytokines at the site of inflammation
 - Cutaneous sensitization can cause disease in murine models
 - Inflammation is T-cell dependent in murine models
 - Fibrosis is seen in airways and esophageal tissue
 - Corticosteroids are effective
- Differences between EE and atopy
 - Foods are the predominant allergen for EE
 - Aeroallergens are the predominant allergen for asthma and allergic rhinitis

- Antihistamines and leukotriene antagonists are not effected in EE
- Dietary therapy is effective in EE, but not asthma or allergic rhinitis

EE: Eosinophilic esophagitis.

The appearance of mucosal rings, furrowing, strictures and white plaques are often seen upon visual inspection [8-12,19]. However, up to a third of patients with EE may have a normal-appearing esophagus [11]. Therefore, biopsy must be performed for diagnosis. As EE is thought to be a patchy disease, multiple esophageal biopsies (five would lead to 100% sensitivity in adults and six in children) should be obtained in establishing the diagnosis of EE [20,21].

Like asthma, EE is a chronic disease. The vast majority of patients do not ‘outgrow’ the disease. In a 12-year study of adults, no patients had remission [9], and in a 14-year study of pediatrics, only 2% had remission of disease [6].

Increased prevalence of atopic disease & EE

The reported prevalence of allergic diseases (i.e., asthma, allergic rhinitis [AR], AD and food allergy) and EE has increased over the last few decades. Data from the CDC National Health Information survey (NHIS) confirms a rise in all atopic diseases [22,23]. The reported prevalence of asthma rose from 3% in 1990 to 7.7% in 2007 [24]. The prevalence of children with AD rose from 7.3% in 1998 to 10% in 2006 [25,26], and the prevalence of AR in the USA approaches 16% (Figure 1) [27]. An estimated 25–30% of the population in industrialized countries has AD, food allergy or AR [28]. Although the prevalence of EE does not approach that of other atopic diseases, the numbers are on the rise [10]. The disease has been reported in every continent except Africa [29-34]. In Western Australia, Cherian described an 18-fold increase in cases between 1995 and 2004 in Western Australia [35]. At The Children’s Hospital of Philadelphia (PA, USA), there was a 35-fold increase in newly diagnosed EE cases, from two cases in 1994 to 72 cases in 2003 [11]. Our recent publication extends the data to 124 new cases in 2006 [6]. A total of 5–10% of pediatric patients and 6% of adult patients with poorly controlled gastroesophageal reflux are thought to have EE [36-38]. These pediatric results confirm the studies of adult populations lead by Straumann and colleagues, which showed an increase in prevalence from two out of 100,000 individuals in 1989 to 23 out of 100,000 individuals in 2004 in Olten Country, Switzerland (Figure 1) [7].

Link between EE & atopic diseases

In our cohort of 620 pediatric patients, two-thirds of patients with EE had concomitant atopy, of which 231 had asthma (37%), 243 had AR (39%) and 78 had AD (13%) [6]. These prevalences of atopy (i.e., asthma, AR and AD) are approximately three-times higher than what is expected in the general population. Other centers also report a higher prevalence of atopy with environmental and/or food allergies in pediatric or adult patients with EE, with a general rate of 60–70%; 50% higher than the general population [8,39,40].

Link between EE & atopy: human data

The inflammatory cells found in patients with asthma, AR, AD and food allergy are similar to those found in patients with EE. Th2 cells and eosinophils are found in early lesions of AD and in patients with asthma [41,42], and eosinophils are found in nasal secretions of those with AR [43]. Mast cells are found in all atopic conditions. The activation of mast cells by IgE-mediated reactions leads to a cascade of inflammation leading to the accumulation and activation of Th2 cells, eosinophils and neutrophils. Researchers in Madrid found that the esophagus of patients with EE had 300-times the density of eosinophils compared with controls,

and significantly higher levels of T cells and mast cells compared with patients with gastroesophageal reflux [44].

Studies in humans also reveal the importance of Th2 cytokines, such as IL-4, IL-5 and IL-13, in atopic diseases, including EE [45,46]. Th2 chemokines and their receptors are also important in EE and atopic disease. A genome-wide microarray expression on esophageal biopsy indicate that eotaxin 3 (one of many chemokines important for trafficking of eosinophils) was highly induced and a single-nucleotide polymorphism (SNP) was associated with increased susceptibility to disease [36]. Other important molecules in the development of EE may be periostin. Periostin is induced by IL-13 and regulates eosinophil recruitment and adhesion [47].

Similar to asthma and AD [48-51], a possible genetic component plays a role, with changes in SNPs in 14% of patients with EE [36]. In addition, several reports indicate a very strong familial association with EE [52-54].

One active area of research in all atopic conditions is remodeling. Lichenification and thickening of the skin may occur in AD [42], a permanent decline in lung function may occur in asthmatics [55], and narrowing or stricture formation in the esophagus may occur in untreated EE [6,11,12]. However, narrowing occurs in only a very small percentage of adult patients as strictures are only seen in 5–15% of adult series, and these are usually only in patients with longstanding untreated disease [4,9]. Children with untreated EE have basement membrane thickening and increased vascular activation, similar to changes seen in airway remodeling with increased SMAD2/3 and TGF- β [56,57].

Similar pathophysiology between EE & atopy as evidenced by murine models

Murine models predict a similar mechanism of disease pathogenesis between atopy and EE. The murine models have found similar results to the human studies and can be further examined through the use of molecular and knock-out studies. In 1998, a mouse model linking AD and asthma was developed by Spergel and colleagues [58]. Epicutaneous exposure to ovalbumin (OVA) allergen by patch placement (on a shaved area of the back) led to AD-like changes on the skin. When OVA was administered via a single aerosolized exposure, airway hyper-responsiveness to methacholine and eosinophilia on bronchoalveolar lavage was found [58]. More recently, Akei and colleagues utilized the same model linking AD to EE [59]. Mice were sensitized to *Aspergillus fumigatus* or OVA epicutaneously, which led to AD-like skin changes (without esophageal changes). Following a single intranasal challenge to the same allergen, these mice developed significant EE [59]. In addition, a mouse model was able to link asthma and EE. Repeated intranasal exposure to *A. fumigatus* led to eosinophilia in both the airway and the esophagus (not stomach or small intestine). When the same allergen was delivered orally, there was no eosinophilia in the airway or the esophagus [60].

The role of B cells and T cells (CD3⁺, CD4⁺ and CD8⁺) in the development of experimental EE was studied utilizing the *Aspergillus* model. Recombination-activating gene (*RAG*)-1-deficient mice (lack B cells and CD3⁺ T cells) did not develop experimental EE. B-cell-deficient mice and CD8-deficient mice developed EE similar to asthma and AD models [61]. Interestingly, CD4-deficient mice had only partial blunting of esophageal eosinophilia, with complete blunting of airway eosinophilia [61]. These studies in mouse models have shown the importance of CD4⁺ T cells in both EE as well as asthma [62,63].

Other studies looked at signaling through CD4⁺ T cells; more specifically, at the roles of IL-5, IL-4, IL-13 and signal transducer and activator of transcription (STAT)-6 in the development of experimental EE. These cytokines have been found to be important in all forms of allergic disease. When knock-out mice were studied, IL-5 knock-out mice were found to be completely

resistant to developing EE. IL-13, IL-4 and STAT-6 knock-out mice developed milder forms of EE [59], indicating the importance of Th2 cytokines.

More recent studies looked at the importance of regulatory T cells in the development of experimentally induced EE. Regulatory T cells limit T-cell function and proliferation. *FOXP3* is a novel transcription gene that is expressed on naturally occurring and induced regulatory T cells. *CD45RB* is expressed on effector and regulatory T cells. *CD45R^{low}* cells are thought to have a role in controlling immune responses in asthma. A newly published study, looking at *FOXP3* and *CD45RB*, found increased numbers of effector T cells and decreased numbers of regulatory T cells in mouse models of EE and in human tissue [64,65].

As we gain more understanding of the pathophysiology of EE, we are able to manage and treat the disease better.

Link between EE & atopy: approach to treatment

When treating patients with EE, it is important to assess the severity and progression of the disease in individual patients. Many patients have mild disease, especially in the adult population [9]. The therapy decision requires a balance of disease severity and effect on the patient's quality of life versus the treatment effects on quality of life and potential side effects. Furthermore, treatment options vary from diet to oral steroids to swallowed steroids and others, each with their own advantages and disadvantages. In addition, the final decision on treatment depends on the physician and the patient (Box 2).

Role of food allergy in EE

In most cases of pediatric EE, an underlying food allergy has been found to be the culprit. Convincing work from Kelly and colleagues revealed the use of an elemental diet and a few basic foods in ten patients with refractory EE, six of whom had *Nissen funduplications*. All children improved and eight of the original children had complete resolution on biopsy [30]. Further work by others have found elemental diets to be successful, including our institution, with success rates of 98% [11,66].

Not all patients require elemental formulas for the treatment of their EE. Dietary restriction may be based upon individual testing or the empiric removal of foods. A history is obtained from the family and then testing to foods in the child's diet is recommended. Both skin-prick testing (identifying IgE-mediated reactions) and patch testing (identifying non-IgE-mediated reactions) have been helpful in guiding management [67]. Patients then remove all positive foods with repeat endoscopy. Upwards of 75% improve symptomatically and histologically with this approach. We have also found the positive predictive value to be greater than 74% for all foods, and the negative predictive value to be between 88 and 100%, depending on the food (although milk was much lower) [68]. The recent consensus report has recommended allergy testing via prick testing as well as patch testing for evaluation [1]. Empiric removal of seven foods including milk, soy, egg, peanut, tree nuts, wheat and seafood has also been used. Kagalwalla reported success with this approach in 74% of their 35 patients [69]. Although we and others have found that aeroallergens play a role in EE [70], food allergies play the major role. We have reported only one patient whose biopsy worsened in the pollen season and improved out of the pollen season (on the same diet) [71]. However, we have seen approximately 15–25% of patients having aeroallergens playing a smaller role in the pathogenesis of disease. Similarly, Wang and colleagues have observed a seasonality in the diagnosis of EE of 243 patients, with fewer patients diagnosed in the winter, which is suggestive of a role of pollens in their cohort [72]. A similar seasonal variation was seen in 41 adult patients [73]. These studies suggest an important role for aeroallergens in select patients with EE.

The role of food allergies in adults is less convincing. In one paper by Simon and colleagues, they found that the elimination of two particular grains (wheat and rye) had no significant changes in their symptoms upon removal [74]. This one series eliminated only two particular grains, indicating the shortcomings of allergy testing in adults, but did not examine the most common foods that cause EE in pediatrics and does not eliminate the role of food allergies in adult EE. There are other case reports of food elimination working in adults with the removal of milk [75] and a high rate of food sensitization [39], suggesting similarities between adults and pediatrics.

Box 2. Treatment options for eosinophilic esophagitis

- Dietary
 - Elemental diet
 - Six-food elimination diet
 - Selective elimination diet based on allergy testing
- Topical corticosteroids (off-label use)
 - Budesonide
 - Fluticasone
 - Oral steroids
 - Future medications
 - Anti-IL-5
 - Viscous budesonide
- Other biologics

Avoidance strategies

In most cases, EE is thought to be related to an underlying food allergy, and avoidance will lead to an improvement in symptoms and normalization of biopsy. Similarly in patients with asthma, AR, AD and/or food allergy, the avoidance of known allergens or triggers leads to an improvement in symptoms and pathology [76]. While most of these atopic patients require additional medications to manage their disease(s), dietary restrictions alone may be sufficient in EE. In other atopic conditions, patients may recognize a trigger and have symptoms immediately upon exposure. Typically with EE, the underlying trigger is unknown until evaluation. At times, avoidance is either not possible or unsuccessful, or quality of life is too low due to dietary restrictions, and medical management is necessary and is common for many patients with EE.

Corticosteroid therapy

Corticosteroids are the mainstay of therapy for EE and other atopic conditions. Both systemic and ‘topical’ forms of steroids have been used. Corticosteroids are thought to inhibit proinflammatory cell recruitment, downregulate the production of proinflammatory cytokines and induce eosinophil apoptosis [77]. Blanchard *et al.* found that levels of eotaxin-3 and IL-13 mRNA are decreased following steroid therapy in patients with EE [78].

Systemic (oral) steroids have been used to manage asthma exacerbations, treat allergic reactions and manage severe persistent asthmatics [79]. Similarly, systemic steroids are useful in treating severe and acute forms of disease, particularly in patients who may have had long-

standing untreated EE. Similar to their use in acute asthma attacks, systemic steroids in EE have value in the short-term management of patients with severe nutritional restriction by dysphagia, especially in the presence of a stricture. When a dilation is being considered, steroids are sometimes used for a few weeks prior to dilation to soften the stricture and are a useful precaution to reduce the risk of perforation [9,11,80-82]. Oral steroids have a greater rate of histological improvement than topical steroids [80]. However, systemic steroids for any medical condition have an increased side-effect profile up to 40% in a randomized trial [80], and limited use is suggested. With EE, discontinuation of oral steroids leads to the recurrence of both symptoms and abnormal histology [11,80].

Another option is the use of inhaled or topical corticosteroids for both atopic diseases and EE. These medications are commonly used and recommended for the treatment of AR, asthma and AD [27,83,84]. In fact, several investigators have reported success with swallowed steroids both in children and adults with EE [11,85-89]. Both topical fluticasone propionate and budesonide suspensions have been used. However, not all patients respond to swallowed steroids [87,89]. Side effects including oral candidiasis may occur in up to 15% of patients [80,85-89]. Upon discontinuation, patients will often relapse [11,80]. At this time, long-term effects, especially on growth, are unknown. Certainly, further studies regarding the use of swallowed steroids in EE are necessary.

Mast cell stabilizers

Mast cells most probably play a role in EE and other atopic conditions. Mast cell stabilizers, such as cromolyn sodium or nedocromil, have been used in asthma, AR and allergic conjunctivitis. When evaluated in EE, cromolyn sodium was not effective [11]; as such, they are not recommended [1].

Leukotriene receptor antagonists

Eosinophils generate large amounts of leukotrienes and, in turn, leukotrienes attract eosinophils. Leukotriene modifiers have been successful in some patients with asthma and allergic rhinoconjunctivitis. Interestingly, leukotriene levels were equivalent in esophageal tissues in normal healthy patients and patients with EE [46]. As leukotriene antagonists such as montelukast have been shown to have a symptomatic benefit in adults, they demonstrate a similar control of the symptoms of bronchial asthma and the symptoms of EE without a change in histology [90]. The significance of persistence of esophageal eosinophils without symptoms is unclear. Therefore, leukotriene modifiers have not been recommended as a first-line therapy in the treatment of EE in the most recent consensus report [1].

Biologics: anti-IL-5 & anti-TNF

Humanized monoclonal antibody therapy blocking IL-5 (anti-IL-5) is currently under investigation for asthma and EE. Although not all studies revealed an improvement in asthmatics with anti-IL-5, two recent studies did. One revealed a decrease in exacerbations in patients with refractory eosinophilic asthma and the other revealed a decrease in the amount of steroids in steroid-dependent asthmatics [91,92]. Early studies with anti-IL-5 in four patients with EE revealed an improvement [93], and larger clinical controlled trials for reslizumab are underway, including one that was recently completed for mepolizumab.

Increased expression of TNF- α is found on epithelial cells from patients with active EE [45]. TNF- α is a known proinflammatory cytokine that may play a role in atopic disease, including asthma and EE. Preliminary studies have used anti-TNF- α in small numbers of asthmatics with severe refractory disease [94]. In an open-label trial of infliximab (anti-TNF- α), there was no significant improvement in symptoms or histology in three adult patients with EE, although

one had a partial response [95]. Currently, these treatments are expensive and have a potential for side effects, in particular anti-TNF- α when used in the long-term treatment of EE. Their use needs to be carefully balanced against the severity of disease, and they are probably not required for the majority of patients with EE.

Immunosuppressant agents

Azathioprine has been utilized in patients with inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease and chronic active hepatitis), in which immunosuppression is of utmost importance. A recent Cochrane review of azathioprine use in severe steroid-dependent asthmatics recommended further studies [62]. In a small cohort of patients with severe steroid-dependent EE, treatment with azathioprine and 6-mercaptopurine induced clinical and histological remission [63].

Expert commentary

As with other atopic diseases, EE is a chronic disorder. Although we have had success in dietary restrictions or total elimination with the removal of the food allergens, this approach is quite difficult in terms of cost, compliance and taste. In the event that dietary modification is unsuccessful or not an option, alternative therapies are necessary for management. Different patients may respond to different medical therapies. The underlying pathophysiology is similar between atopic diseases and EE. Similar approaches to management have been and will continue to be applied, including topically applied corticosteroids. As we learn more, we will be able to apply our knowledge to newer treatment modalities. Continued research in all areas of atopic disease, including EE, is of utmost importance.

Five-year view

We predict that significant progress in the field of EE will occur in the next 5 years. Three clinical trials with reslizumab, anti-IL-5 (NCT00538434), mepolizumab (NCT00358449) and viscous budesonide (NCT00762073) will be completed, and will probably be the first US FDA-approved medications for the treatment of EE. The establishment of The International Gastrointestinal Esophageal Researchers will start a series of large cohort studies to understand the natural history of the disease. In addition, the first genome-wide association studies for EE will be finishing, and new potential pathways will be identified. Research for noninvasive markers for EE, instead of serial upper endoscopies with biopsies, and improved food allergy testing will help patients' quality of life.

Key issues

- Eosinophilic esophagitis (EE), like other atopic diseases (e.g., asthma and allergic rhinitis), are seen in increased prevalence.
- EE and atopy (asthma, allergic rhinitis and atopic dermatitis) are probable Th2-driven diseases with a predominance of IL-4, IL-5 and IL-13.
- In murine models, both EE and asthma can be induced by epicutaneous sensitization.
- EE and atopic dermatitis can be induced by aeroallergens and food allergens, while aeroallergens only exacerbate asthma and allergic rhinitis. EE is induced by food allergies and histology, and clinical improvement is seen with food avoidance, in particular elemental diet.
- Topical and systemic steroids can help with symptoms and histological findings in asthma, atopic dermatitis and EE.

- Other allergy medications (e.g., cromolyn and leukotriene antagonists) are not beneficial in treating EE.
- Clinical trials for new agents (anti-IL-5 and viscous budesonide) are recently completed/ongoing.

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Figure 1. US prevalence of asthma and atopic dermatitis in the 1990s and 2000s, expressed as a percentage

The prevalence of adult cases of eosinophilic esophagitis in Switzerland is expressed as a number per 100,000.