Eosinophilic esophagitis: treatment in 2005

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Purpose of review

Eosinophilic esophagitis is an isolated, eosinophilic inflammation of the esophagus. The symptoms are often confused for those of gastroesophageal reflux. Over the past few years, there has been a significant increase in the literature surrounding eosinophilic esophagitis as more than two-thirds of the articles written on the subject have been published within the past 3 years. Because the incidence is rising and the condition is easily diagnosed by endoscopy with biopsy, it is important for physicians to understand the pathophysiology, clinical presentation, and treatment options available for patients.

Recent findings

The etiology of eosinophilic esophagitis in children is reported to be associated with an allergic response to food antigens. Because allergy tests are often unable to determine the causative foods, complete elimination of all foods is often required. The diagnosis requires a biopsy of the esophagus, stomach and duodenum. The condition is diagnosed if the patient's esophageal biopsy depicts over 20 eosinophils per high-powered field despite the use of aggressive acid blockade, biopsies of the stomach antrum and duodenum are normal, and the tissue inflammation resolves when dietary antigens are removed from the diet. While the most commonly involved foods causing eosinophilic esophagitis include milk, eggs, nuts, beef, wheat, fish, shellfish, corn and soy, almost all foods have been implicated. Alternative treatments include esophageal dilatation and medical therapy.

Summary

This article reviews the past year's literature, concentrating on the pathophysiology, and treatment of eosinophilic esophagitis in both children and adults.

Keywords

eosinophilia, esophagitis, food allergy

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Abbreviations

EoE eosinophilic esophagitis
HPF high-powered field
IL interleukin

0267-1379

Introduction

Eosinophilic esophagitis (EoE) is an emerging worldwide disease. It has recently been documented to occur in many European countries as well as in Australia, Brazil and Japan [1•–4•]. Recent epidemiologic studies suggest a rising incidence in the United States with at least one case occurring in every 10 000 children [5••]. While pediatric gastroenterologists have been interested in EoE for more than 10 years, the awareness among adult gastroenterologists has recently increased over the past 3 years. This disorder, initially mistaken for gastroesophageal reflux, has been reported to be increasing in incidence in both children and adults. Before 1995, sporadic case reports of adult patients with eosinophilic esophagitis related to dysphagia or vomiting were reported in the literature [6,7]. In 1982, Winter *et al.* [8] correlated the presence of esophageal eosinophils as a marker for reflux esophagitis. EoE was first identified in 1995 when Kelly *et al.* [9] demonstrated that eight patients with a persistent, isolated esophageal eosinophilia, unresponsive to acid blockade, responded instead to a strict amino acid based diet. Since 1995, each year, there has been an increasing number of articles in the medical literature relating to the etiology, clinical presentation and treatment of EoE in both children and adults.

Etiology

The etiology of EoE is not fully understood. The question remains whether or not EoE is based on allergic disorder, the result of an abnormal immunologic response or secondary to severe acid reflux disease. Prior to the 1990s, EoE was simply a descriptive disease. In 1995, Kelly *et al.* [9] demonstrated a relationship between food antigens and EoE. Some investigators, however, continued to argue that food allergy was not the cause of EoE. Several articles have been written regarding other possible immunologic or allergic mechanisms that may contribute to the development of EoE. One potential theory implied that inhaled allergens contribute to the development of esophageal eosinophilia. Others believed that the host's altered immunologic system response is at fault. A final possibility suggests that EoE may be a

subset of eosinophilic gastroenteritis. This past year, several articles have been written which have expanded the knowledge regarding the etiology of EoE.

Environmental antigens have been implicated as a possible contributor to EoE. Fogg *et al.* [10] reported a case of a 21-year-old with asthma and allergic rhinoconjunctivitis. Her EoE became symptomatic with exacerbations during the pollen season, followed by resolution during winter months. A similar finding was shown in an animal model by Mishra *et al.* [11] who determined that the inhalation of a respiratory allergen caused EoE in mice. He found that the allergen-challenged mice developed elevated levels of esophageal eosinophils and epithelial cell hyperplasia similar to that seen in humans who have EoE. The question of respiratory antigens causing an esophageal eosinophilia was further investigated by Mishra and Rothenberg [12]. They utilized a mouse model to evaluate intratracheal interleukin (IL)-13 to induce eosinophilic esophagitis through an IL-5, eotaxin 1 and stat-5 dependant mechanism. Eosinophil levels were monitored and immunohistic chemical standing was performed. The intratracheal delivery of IL-13 induced an eosinophilic accumulation in the esophagus, including epithelial hyperplasia. These findings were abolished in stat-6 deficient mice, almost completely ablated in IL-5 deficient mice, and significantly diminished in eotaxin-1 deficient mice. The authors theorized that an intimate connection between respiratory and esophageal inflammation exists in mice. The issue remains as to whether or not respiratory antigens induce esophageal inflammation or whether intratracheal antigens move into the esophagus through ciliary mechanisms and after being swallowed invoke an esophageal response.

While gastroesophageal reflux is associated with acid-induced tissue damage, the inflammation of EoE involves the mucosa, submucosa and possibly the muscular layer. Fox *et al.* [13] utilized endoscopic ultrasound in order to determine the possible anatomic alterations in children with EoE compared with healthy children. Measurements of the distal esophagus were obtained including the thickness of the total wall, the mucosal and submucosal thickness and the muscularis propria and circular muscle thickness. The study demonstrated that significant expansion of the esophageal wall occurs in patients with EoE, suggesting that more than just the mucosal layer is involved. They theorized that expansion of the mucosa and submucosa was most likely caused by infiltration by inflammatory cells, specifically eosinophils, which cause changes in the extracellular matrix.

Pathophysiology

Several reports this year have discussed the possible pathogenesis of EoE. EoE has been thought to occur when mast cells (in response to allergens) migrate to the esophageal wall where they release histamine, eosinophilic chemotactic factor and platelet activating factor [14••]. Eosinophils are subsequently activated, releasing toxic cationic protein. These authors base their hypothesis on recent evidence that suggests that eosinophils directly damage the gut mucosa and gut wall. Eosinophils contain cationic proteins such as major basic protein eosinophil-derived neurotoxin and eosinophil peroxidase which can injure and damage the intestinal lining. Eosinophils also contain interleukins such as IL-3 and IL-5 which promote tissue inflammation. In specific sensitized people, immunoglobulin (Ig)E interfering with food allergens and aeroallergens may degranulate mass cells thus causing a release of histamine, interleukins and chemokines which attract eosinophils to the affected site. The formation of esophageal rings may be related to histamine which activates acetylcholine causing a contraction of the esophageal muscularis mucosa. Narrowing of these muscle fibers deforms the mucosal layer resulting in the formation of esophageal rings. These rings may be transient and reversible, although continuous contraction of these muscle fibers and hypertrophy and thickening of the muscle layers of the mucosa could contribute to permanent scar formation.

Straumann *et al.* [15••] characterized different eosinophil subpopulations by comparing the expression of certain proinflammatory proteins of tissue-dwelling eosinophils in different parts of the gastrointestinal tract. Various cytokines and interleukins were measured in the esophageal and intestinal tissue as well as blood eosinophils from both controls and patients with EoE. Those patients who had EoE demonstrated strong evidence of eosinophil activation with increased expression of CD-25, IL-4 and IL-13. Straumann *et al.* concluded that tissue-dwelling eosinophils demonstrated different and distinct cytokine expression patterns in patients with EoE when compared with controls.

Genetics

Over the past few years, there has been increased evidence that EoE may have a genetic predisposition. Meyer [16•] suggested the potential hereditary or genetic link to EoE when he reported a father–daughter connection with regard to EoE. Similarly, Patel and Falchuk [17•] described three brothers: a 41-year-old, a 34-year-old, and a 44-year-old, all of whom were diagnosed with EoE. They all presented with either dysphagia or esophageal food impaction. On endoscopy, all had more than 20 eosinophils per high-powered field (HPF). One had a visually normal-looking esophagus and was treated with topical fluticasone which improved his symptoms. After discontinuing therapy his symptoms recurred and therapy was reinstituted. The second brother had linear furrowing on endoscopy. He was treated with topical fluticasone therapy and also symptomatically improved. The final

brother had narrowing in both the proximal and distal esophagus. There was no report regarding his treatment. All of the family members were encouraged to pursue allergy testing.

Clinical

EoE is frequently associated with other atopic diseases as 68% of patients also have another allergic disease such as rhinitis, bronchial asthma and atopic dermatitis [18••]. In addition, other food allergies have been reported, including oral allergy syndrome, urticaria or diarrhea. Many patients also have a high frequency of aero-allergen sensitization and more than 50% have an IgE food allergen sensitization. Allergic airway diseases often precede the development of EoE, suggesting that the initial sensitization might take place in the airways.

Adults with EoE often present with functional esophageal abnormalities. Upon reviewing a computerized database, the radiographs of 14 patients with EoE were examined by separate radiologists to determine whether strictures, esophagitis, a hiatal hernia or other esophageal abnormalities were present [19•]. Seven of the 14 patients had an allergy history, including allergic rhinitis, food allergy or drug allergies; two patients had a peripheral blood serum eosinophilia; 13 had a history of dysphagia with six of these patients having had at least one food impaction; and six patients had reflux symptoms. By barium study, two patients had esophageal strictures in the upper esophagus, two in the middle esophagus, four in the distal esophagus and three at the gastroesophageal junction. The mean length of the stricture was 5.1 cm. Seven patients had a ringed-esophagus with a distinctive ring-like indentation in the region of the stricture formation. Ten patients had a hiatal hernia while nine had spontaneous gastroesophageal reflux during fluoroscopy. During endoscopy, only seven of the 10 patients had distinct evidence of stricture formation. Although esophageal rings were seen in three of the patients during fluoroscopy, they were not seen during endoscopy.

Diagnosis

The definition of EoE requires that the eosinophilic infiltration be limited to the esophagus, that it is unresponsive to acid blockade and that it responds to the removal of dietary antigens. Because esophageal acid exposure has been linked to the presence of esophageal eosinophils, acid reflux disease must be considered. Generally, patients with EoE should initially be treated with a proton pump inhibitor. If still symptomatic an upper endoscopy is performed. Currently, the only accurate method for diagnosing EoE is upper endoscopy with biopsy. Although many reports have commented on specific visual features appreciated on endoscopy, up to 34% of children have a visually normal esophagus [20]. Thus, it is essential that esophageal biopsies be obtained whenever EoE is considered. Furthermore, because the esophageal inflammation may be patchy, multiple biopsies (two distal and two proximal) should be collected [20].

In some cases, a 24 h pH probe is necessary to determine if therapy for acid reflux is adequate. Steiner *et al.* [21••] performed a retrospective study in children correlating histology with pH probe measurements by evaluating the number of esophageal eosinophils with the reflux index. The patients were divided into five groups: group I had no eosinophils per HPF and no histologic changes; group II had no esophageal eosinophils per HPF with mild histologic changes; group III demonstrated 1–5 eosinophils per HPF; group IV had 6–20 eosinophils per HPF; and group V had more than 20 eosinophils per HPF. The study included 305 patients with the following results: group I had a mean reflux index of 2.14 ± 0.18; group III had the highest reflux index of 5.96 ± 1.53; group V patients had a similar reflux index to the group I patients of 2.02 ± 0.53 and 2.14 ± 0.18, respectively. The authors concluded that the presence of large numbers of esophageal eosinophils does not correlate with increased gastroesophageal reflux. In fact, Sant'Anna *et al.* [22•] found that alkalinization of the esophagus was demonstrated in nine pH probe recordings of patients with EoE, which represents a previously unreported pH probe characteristic of this condition.

In two separate reports, Liacouras *et al.* [20] and Markowitz *et al.* [23] demonstrated that the removal of food antigens is related to clinical and histologic improvement of EoE in children. Unfortunately, many patients cannot historically relate the responsible food as their symptoms are often delayed for hours or days after ingestion. Moreover, noninvasive allergy testing typically does not identify the causative food allergens. Spergel *et al.* [24••] recently examined the use of several different allergy tests, including standardized skin prick testing, radioallergosorbent test, and food challenges.

The authors mentioned that these methods are extremely valuable in IgE-mediated disorders, especially in children who have symptoms of urticaria and anaphylaxis. With regard to diagnosing patients who have non-IgE-mediated allergies or a mixed IgE and non-IgE-mediated allergy, however, these tests are often not very useful. They explain that a new technique, skin patch testing, used in combination with skin prick testing is a more useful method for diagnosis and treatment of specific allergic patients, such as those with atopic dermatitis and EoE. Patch testing was originally used in the early 1900s but over the last 10 years it has increased in use mainly to identify non-IgE-mediated food reactions contributing to atopic dermatitis [25]. Although most of the recent studies have been performed in children, patch testing

can also be performed in adults. Spergel *et al.* recommend a combination of skin prick and patch testing in patients with EoE, which often identifies 50–60% of causative foods in these patients.

Treatment: esophageal dilatation

In adults, esophageal dilatation has been the treatment of choice for most adults with functional or mechanical dysphagia secondary to EoE. Dilatation may also be useful in children who have fixed esophageal strictures. Traditional mechanical dilators are more effective than balloon dilators [26•]. Over the past 3 years, however, several reports have suggested that esophageal tears may not only occur during dilatation but also with the simple introduction of the endoscope [27]. Dilation is contraindicated when previous dilatation attempts have resulted in severe significant complications such as mucosal tearing or perforation. Finally, intramucosal steroids and proton pump inhibitors are important associated treatments for resistant strictures and reflux-associated strictures.

Medications

Various medical therapies have been utilized to treat EoE. Before 2000, the mainstay of treatment was the use of either systemic or topical corticosteroids. Over the past 5 years, two other medications, cromolyn sodium and leukotriene receptor antagonists, have been employed to treat EoE [28••]. Because of the underlying esophageal inflammation, secondary acid reflux typically accompanies EoE; thus, proton pump inhibitors have also been used. Between January 2000 and December 2003, Desai *et al.* [29•] evaluated consecutive adult patients with acute esophageal food impaction in a hospital with a practicing primary gastroenterologist. Thirteen of 31 patients had no prior history of using a proton pump inhibitor while 18 patients underwent endoscopy with biopsy 4–8 weeks after treatment with a proton pump inhibitor. Of the 31 patients, 17 demonstrated more than 20 eosinophils per HPF and 13 of the 17 patients in this group were pretreated with a proton pump inhibitor. Eleven of the 17 patients who had more than 20 eosinophils per HPF had more than one food impaction before diagnosis and two separate recurrent food impactions despite treatment with the proton pump inhibitors. These patients required dilatation of the proximal strictures with a Maloney dilator.

Recently, the use of viscous budesonide was reported. Aceves *et al.* [30•] described two pediatric patients with EoE who did not tolerate or comply with topical fluticasone therapy. Because of continued symptoms of vomiting and poor weight gain, the patients were placed on a regime of a twice daily oral budesonide suspension (500 μg) mixed with sucrolose, forming a viscous solution. One patient had complete resolution of abdominal pain and vomiting and normalization of esophageal eosinophils and basal zone hyperplasia. Clinically, the other patient also improved although, histologically, the patient did not normalize.

Dietary therapy

Food allergy has been identified as the main cause of EoE. The possibility of food antigens causing EoE was first considered in 1995 when 10 pediatric patients with persistent gastroesophageal reflux, unresponsive to aggressive acid blockade and antireflux surgery, were placed on a strict diet of an amino acid based formula [9]. Within 6 weeks, these patients who had previously had a marked eosinophilic esophagitis became asymptomatic and their esophageal tissue normalized. Over the next 5 years, sporadic reports emerged in the literature confirming these findings. In 2003, Markowitz *et al.* [23] studied 51 children who were diagnosed with EoE and who were placed on an amino acid based formula. All but two of these patients responded dramatically to an elemental formula with resolution of their disease.

Most recently, Liacouras *et al.* [20] reported his 10-year experience of 381 children with EoE. Of these, 172 were placed strictly on an amino acid based formula, most utilizing nasogastric tubes in order to receive the appropriate amount of calories. Another 75 patients were placed on an elimination diet based on allergy testing using a combination of skin prick and patch testing. The results of this study again demonstrated that food allergens are involved in the tissue inflammation seen in EoE. With the withdrawal of some specific foods or all foods, both clinical symptoms and tissue histology markedly improved. After using an amino acid based formula and achieving resolution of the disease, foods can then be reintroduced slowly in order to determine those specific foods causing the problem. In general, it is usually not just one food that causes EoE, but multiple foods. In general, these patients are placed on an elemental formula for at least 6 months. During that time, reintroduction of food is attempted. This elemental formula appears to have no nutritional disadvantage in that the patient's growth parameters (weight and height), laboratory values, and physical activity levels were not altered. Unfortunately, approximately 15% of children who have EoE are allergic to almost all ingested foods. These patients require prolonged treatment with an amino acid based formula.

Once EoE has been identified, we use a systematic approach to dietary therapy. First of all, patients should be seen by an allergist who should perform a combination of skin prick and patch testing in order to identify possible IgE and non-IgE-mediated food allergies. If specific foods are identified, these foods should be removed from the diet, clinical symptoms should be

followed, and a follow-up endoscopy should take place in approximately 2 months. If the esophagus has normalized and clinical symptoms have improved, then at least one of those identified foods is the culprit. Future investigation would be required to identify if more than one of those foods is the cause of EoE. If, on the other hand, the esophagus does not normalize with withdrawal of selected foods, then we would suggest the strict use of an amino acid based formula. One month later, an upper endoscopy should be performed. If the esophagus has normalized, EoE has been proven and a slow reintroduction of food can be initiated. We generally restart one food at a time every 5–6 days. Obviously, if symptoms recur during this food initiation, then the most recent food should be eliminated. If, however, no symptoms recur, we advocate a repeat upper endoscopy after reintroducing four to five new foods. The endoscopy should be performed 3–4 weeks after the last food is reintroduced. If the endoscopy is normal, then additional foods can be reintroduced. Obviously, if the endoscopy is abnormal, then one or more of the recently added foods are causing EoE. A nutritionist should be involved to be sure that patients are receiving adequate calories, fluid, and other nutritional requirements. Often, we prescribe additional vitamins to be given while patients are on an amino acid based formula.

Currently, it is not known if the etiology of adults with EoE is similar to children with EoE. Although the use of dietary restriction or a strict elemental diet has been shown to be effective in adolescents and young adults, there have been no definitive studies performed in adults. It is quite likely that dietary restriction would prove effective in adults; however, this method of therapy will not be commonplace until studies demonstrate its usefulness.

Conclusion

EoE is a disorder that has become increasingly diagnosed over the past 10 years. EoE should be suspected in any patient who has upper gastrointestinal symptoms, and an isolated eosinophilic esophagitis despite the use of a proton pump inhibitor. Recent literature suggests that food allergy is the most likely cause of EoE. Subsequently, the evaluation of food allergy by an allergist and the elimination of selected foods should be performed in all patients suspected of having EoE. A strict amino acid based diet should be implemented in those patients who continue to have EoE. A repeat endoscopy with biopsy should be performed to prove resolution of the disease. Besides diet, several pharmacologic treatment options have also been utilized, including systemic and topical corticosteroids, cromolyn sodium and leukotriene receptor antagonists. Recently, new literature has suggested that several chemokines, including IL-5, stat-6 and eotaxin, may have specific roles in the activation and recruitment of eosinophils [12,31•,32•]. Future medical therapy may target these pathways.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 183).

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