

Eosinophilic esophagitis

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Purpose of review

Eosinophilic esophagitis (EE) is an isolated, eosinophilic inflammation of the esophagus. In the past, the symptoms of EE were often confused for gastroesophageal reflux (GER). Thus, many physicians unsuccessfully treated patients with EE with medications used for GER. Because the incidence of EE is rising and EE is easily diagnosed by endoscopy with biopsy, it is important for physicians to not only accurately identify patients with EE but also understand the treatment options available.

Recent findings

While patients with acid reflux may have a few eosinophils, patients with EE have high levels of eosinophils in their esophagus as part of an allergic response to food antigens. The inflammation may cause abdominal pain, nausea, or vomiting. If EE persists for years, it may cause a narrowing of the esophagus that leads to dysphagia. In young children, many of the symptoms of EE mimic those of gastroesophageal reflux. Medications used to treat reflux are not effective against EE. Over the past few years, many new reports and retrospective studies have been written on the subject of EE. The focus of these papers concentrated on the etiology and treatment of EE.

Summary

The diagnosis of EE requires a biopsy of the esophagus. Typical allergy tests are not effective for diagnosis of EE because the allergic reaction involved in EE is non-IgE mediated. The most commonly involved foods include milk, eggs, nuts, beef, wheat, fish, shellfish, corn, and soy; however, almost all foods have been implicated. Because allergy tests are often unable to determine the causative foods, complete elimination of all foods is often required. In these cases, patients must be placed on a strict elemental formula for 1 to 3 months to heal the esophagus. Repeat endoscopy with biopsy is often necessary. Several medications have been used including corticosteroids, cromolyn sodium, and leukotriene inhibitors. This review discusses the past year's literature, concentrating on the etiology, diagnosis, and treatment of EE in both children and adults.

Keywords

eosinophilic, esophagitis, allergy

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Introduction

Over the past ten years, eosinophilic esophagitis (EE) has generated a large amount of interest among pediatric gastroenterologists. This disorder, initially mistaken for gastroesophageal reflux, is a problem that appears to be increasing in incidence. In the past, EE went largely unrecognized, especially in the adult literature, as many endoscopists failed to recognize that a severe, isolated eosinophilic esophagitis could occur despite a visually normal- looking esophageal mucosa. Recently, guided by the literature in pediatric gastroenterology demonstrating not only the rise in EE but also displaying that mucosal biopsies play an important role in endoscopy, EE is now being readily recognized in the adult population as well. The following review discusses the past year of information regarding EE in both children and adults.

History

Between 1975 and 1995 sporadic case reports of adult patients with eosinophilic esophagitis related to dysphasia or vomiting appeared in the literature [1–5]. In 1982, Winter *et al.* [6] correlated the presence of esophageal eosinophils as a marker for reflux esophagitis. His study was performed on 46 children utilizing pH probe studies, manometry, and endoscopy with biopsy. He compared these results to a control group of children. He discovered that eosinophils correlated with prolonged esophageal acid clearance and histologic features of esophagitis. Subsequent adult studies by Brown *et al.* [7] and Tumala *et al.* [8] confirmed this result.

Since the mid-eighties, several reports began to appear regarding esophageal eosinophilia unresponsive to acid blockade. Many of these articles were conducted by radiology groups because these patients initially presented with dysphagia accompanied by esophageal strictures requiring dilatation [9,10]. Additionally, some of the ar-

ticles mentioned that treatment with oral corticosteroids could be effective. However, in general, EE was not typically considered by adult gastroenterologists. In 1995, Kelly and Sampson [11] demonstrated that eight patients with persistent EE, unresponsive to acid blockade, responded to an amino acid-based diet. Since that study, many more articles have been published regarding EE. A recent article in the Clinics of North America by Markowitz and Liacouras [12••] provides a detailed summary of the history, possible etiology, diagnosis, clinical presentation, management, and therapy of EE.

Etiology

The etiology of EE is not fully understood. The question remains whether or not EE is based on allergic disorder, an abnormal immunologic response, or as a result of severe acid reflux disease. With regard to reflux, while aggressive acid therapy may improve the symptoms of EE, it does not change the histology of EE. Several studies have documented normal pH probe studies in patients with EE [13,14]. Currently, most authors agree that EE appears to be driven by a combination of an allergic and immunologic response. Prior to 1995, EE was simply a descriptive disease. Subsequently, Kelly and Sampson demonstrated a significant relation between food allergy and EE [11]. However, some investigators continue to argue that food allergy is not the full cause of EE. Several articles have been written regarding other possible immunologic or allergic mechanisms that may contribute to the development of EE. One potential cause implies that inhaled allergens may contribute to subsequent esophageal eosinophilia. Others believe that the host's altered immunologic system response is at fault. Finally, another possible etiology suggests that EE may be a subset of eosinophilic gastroenteropathies. This past year, several articles have expanded the knowledge regarding the etiology of EE.

Environmental antigens have been implicated as a possible contributor to EE. Fogg *et al.* [15] reported a case of a 21-year-old female with asthma and allergic rhinoconjunctivitis. Her EE became symptomatic with exacerbations during the pollen season, followed by resolution during winter months. It was demonstrated that at altering times of the year, the patient had gastrointestinal symptoms, including vomiting, abdominal pain, weight loss, and dysphagia that correlated with histologic abnormalities of the esophagus demonstrating an increase in eosinophils. This was followed by normalization of both her symptoms and esophageal histology during the winter months (off peak for pollen season). This report suggests that EE may be related to pollen exposure. The thought was that the relation between EE and food was unlikely because the diet appeared to remain constant throughout this period. A similar finding was shown in a Murine model by Mishra *et al.* [16] who found that the inhalation of a respiratory allergen caused EE in a mouse

model. They found that the allergen-challenged mice developed elevated levels of esophageal eosinophils and epithelial cell hyperplasia features that mimicked EE.

The question of respiratory antigens causing an esophageal eosinophilia was further investigated by Mishra and Rothenberg [17•]. They used a mouse model to evaluate intratracheal IL-13 to induce eosinophilic esophagitis through an IL-5, eotaxin 1, and stat-5–dependent mechanism. Eosinophil levels and immunohistochemical staining 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 the respiratory antigen exposure induced esophageal inflammation or whether the intratracheal antigen moved into the esophagus through ciliary mechanisms and then was swallowed invoking an esophageal response.

While gastroesophageal reflux is associated with acid-induced mucosal tissue damage, the inflammation of EE involves the mucosa, submucosa, and possibly the muscular layer. Fox *et al.* [18] used endoscopic ultrasound to determine the possible anatomic alterations in children with EE compared with healthy children. High-resolution endoscopic ultrasound was used to delineate the esophageal tissues in 11 patients with documented EE and in eight patients with normal esophageal tissue. 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 EE suggesting that more than just the mucosal layer is involved. Fox *et al.* theorized that expansion of the mucosa and submucosa was most likely caused by infiltration by inflammatory cells specifically including eosinophils as well as changes in the extra cellular matrix.

Diagnosis

Clinically, EE presents in a variety of ways. In young children, EE typically presents with symptoms similar to gastroesophageal reflux including epigastric pain, regurgitation, vomiting, and chest pain. As children become adolescents, symptoms of dysphagia become more prominent. These findings are now being reported to also occur in adults with EE. Typically, most adults with EE present with symptoms of dysphagia and esophageal strictures. In general, patients experience some relief with acid-blocking medication; however, the esophageal histology does not change. Biopsies of patients with EE on aggressive acid blockade continue to demonstrate a

dense EE. Approximately 50% of patients with EE have a strong medical history of allergic symptoms including asthma, rhinitis, and eczema. In addition, 30 to 50% of patients also have a strong family history of another individual in the family with EE or a history of other allergic symptoms. Interestingly, patients with EE often have intermittent symptoms. Some patients may only complain of one or two symptoms each month, whereas others complain daily.

Currently, the diagnosis of EE is made only by endoscopy with biopsy. Pin prick skin testing, RAST testing, and the evaluation of IgE levels or serum eosinophils have been difficult to correlate with the diagnosis of EE. Recent evidence has demonstrated an increased chance of diagnosis with the use of skin patch testing [19]. Often, the endoscopic appearance of patients with EE can be normal. On the other hand, abnormal esophageal findings include a ringed-like ("trachealization") esophagus, longitudinal linear furrows, or multiple small white papules suggestive of *Candida* [20,21••]. These small white patches represent eosinophilic abscess formation. At times, because of the intense eosinophilic infiltration, the esophagus may be extremely narrowed.

Sundaram *et al.* [22] reported on several cases of EE. They reported on 13 children presenting with a variety of gastrointestinal complaints who had white plaques seen visually on upper endoscopy in the esophagus and who had EE documented by biopsy. Other associated visual findings with regard to EE included linear fissuring and furrowing, and to a lesser extent friability, erythema, and edema. The eosinophilic infiltration was present in both the mid and distal esophagus with evidence of micro abscess formation. Elevation of peripheral eosinophils as well as serum IgE levels did not correspond to the level of disease.

Straumann *et al.* [23] also reported on the visual findings of EE with regard to a fragile, inelastic, and delicate esophageal mucosa. He suggested that this was a clinical and endoscopic sign of EE. The paper described a series of patients with EE who presented for dilatation secondary to dysphagia. All five patients had extremely fragile, inelastic, and delicate mucosa, which tore easily, even with minor trauma. The five patients ranged in age from 24 to 52 and had duration of symptoms ranging from 2 years to 40 years. All of the patients had at least 30 eosinophils per high-powered field documented by biopsy. During the dilatation procedure, large esophageal tears were noted in all five patients. Several patients had tears simply by the introduction of the endoscope. While these patients may have had mucosal tearing, it is difficult to determine the etiology of EE without a biopsy. In addition, regardless of etiology, stricture formation often leads to esophageal tearing.

Recently, Nurko and Furuta [24] suggested that an association of Schatzki's ring may occur in adolescents with EE. Their conclusion was that EE may play a role in the pathogenesis of a Schatzki's ring. On the other hand, patients with EE may radiographically appear to have a Schatzki's ring, but in fact, they may instead have tissue inflammation mimicking a ring-like appearance that improves with therapy for EE. The idea of a narrowed esophagus was confirmed by Kaplan who suggested that tearing of the esophagus can occur easily with the simple passage of the endoscope in patients with EE [25].

Several past studies reported that the isolated finding of more than 20 esophageal eosinophils per HPF implied the diagnosis of EE [26,27•,28]. Recently, Kahn *et al.* [29] and Steiner *et al.* [30•] corroborated this finding. Khan *et al.* studied a group of children who had esophageal eosinophilia and who presented with obstructive esophageal features such as stricture impactions or dysphasia. They concluded that two subgroups exist: (1) those patients who likely had gastroesophageal reflux disease and who had less than 20 eosinophils per high-power field (HPF); (2) those patients with allergic eosinophilic esophagitis who had greater than 20 eosinophils. Unfortunately, a number of patients had an indeterminate number of eosinophils, between 5 and 20. As in the previous study conducted by Ruchelli, the etiology for this group is difficult to assess. In an attempt to correlate the degree of acid reflux with the number of esophageal eosinophils, Lim *et al.* recently studied a large number of patients who underwent both upper endoscopy and a 24-hour pH probe on the same day. They subsequently divided the patients into varying groups depending on the number of esophageal eosinophils visualized. They concluded that the presence of a dense esophageal eosinophilic infiltrate did not correlate with increased acid reflux. In addition, patients with EE almost always had a normal pH probe study [21••].

The diagnosis of EE appears to be increasing throughout the major developing countries in the world. Initially, EE seemed to be a disorder that was confined to small, local pockets in the United States. However, as more gastroenterologists have become familiar with the subtle findings of EE and have begun using endoscopy with biopsy more frequently, EE now seems to occur in all parts of the United States. In addition, several recent reports have expanded the location of EE to many countries outside the United States. Cheung *et al.* [31] reported on 21 Australian patients, mean age of 10.1 years, with EE. These patients were more often male, had a history of allergy, and a history of food bolus obstruction requiring endoscopic removal. They performed esophageal pH probe measurements as well as upper endoscopy. The pH probe findings demonstrated that there was no evidence of gastroesophageal reflux. In addition to reports from Canada and Great Britain, Munitiz *et al.*

reported on one patient in Spain while Esposito *et al.* made observations on 7 cases of EE in Italy [13,32–34]. Finally, Cury *et al.* [35] reported on two Brazilian boys, aged eight and seven, who had classic symptoms of gastroesophageal reflux. Subsequent upper endoscopy with biopsy demonstrated marked eosinophilic infiltration of the esophagus. In both cases, the subjects were treated with oral prednisone and both became asymptomatic with normalization of their upper endoscopies.

As mentioned previously, the diagnosis of EE currently rests upon the use of upper endoscopy with biopsy. Histologic evidence of an isolated esophagitis of more than 20 eosinophils per HPF confirms the diagnosis. Unfortunately, some gastroenterologists continue to rely on visual inspection of the esophagus. Attwood *et al.* [32] commented on the difficulty that adult gastroenterologists have in assessing the esophagus visually. Often, biopsies were not performed when the mucosa visually looked normal. Attwood *et al.* reported that there is still a significant problem with the diagnosis of EE in adults. They commented on the lengthy duration of the patient's symptoms prior to the patient's being diagnosed with EE.

Treatment

The treatment of EE continues to be somewhat controversial and widely debated. Medical and surgical treatment for GERD is not effective [12••,36]. Several studies have shown convincing evidence that food allergy is the most common cause of EE [11,37–39]; thus, the removal of the causative food antigens should heal the disease. Despite this proof and because of the difficulty in determining the foods responsible for EE, other treatment options are often used. Anti-inflammatory medications, mast cell stabilizers, and leukotriene receptor antagonists have been reported to be somewhat effective in the treatment of small groups of patients with EE.

In 1995, Kelly and Sampson demonstrated that EE was related to food allergy [11]. They showed a response to a strict elimination diet with an amino acid-based formula. This finding was confirmed by Markowitz and Liacouras [39] in a recent article in 2003. These investigators demonstrated that an elemental diet was an effective treatment for EE in children and adolescents. Three hundred forty-six patients with symptoms of chronic gastroesophageal reflux disease and histologic evidence of isolated esophageal eosinophils were evaluated. Of these, 51 (approximately 15%) were ultimately diagnosed with EE. The patient's average age was 8.3 years of age with a range from 3 years of age to 16 years of age. An elemental diet was instituted using an amino acid-based formula. The number of esophageal eosinophils decreased from 33.7 before the diet to an average of one eosinophil per HPF after the diet. The average time for clinical improvement was 8.5 days. Forty-eight patients required

nasogastric tube feedings. This study demonstrated that food allergy was the cause of EE. Sundaram [22] reported that with regard to treatment, six patients with EE were treated with a strict elemental diet and of these five of the six had dramatic improvement in their symptoms. Several other children underwent elimination diets based on RAST testing with varying results. In this study, they reported that the common allergic antigens included milk, soy, eggs, and wheat. Unfortunately, identifying the specific foods that cause EE remains difficult. Because EE is not an IgE-mediated disease, allergy testing often cannot determine the foods causing EE. Thus, many patients with EE must undergo a strict food elimination diet utilizing an elemental formula. Because this formula is not palatable, many patients often need to be given formula through a nasogastric tube.

Because of the difficulty in initiating an elemental formula, many investigators opt for medical treatment. These types of treatment included the use of systemic corticosteroids, topical ingested steroids, cromolyn sodium, and leukotriene receptor antagonists. While most studies demonstrate an improvement in clinical symptoms and a reduction of the esophageal eosinophilia (not normalization), upon withdrawal of these medications, the patient's symptoms and abnormal histology recur. Finally, the chronic use of these medications has been linked to significant complications and side effects.

With regard to corticosteroids, in 1998, Liacouras *et al.* [40] demonstrated that oral corticosteroids improved EE. However, upon withdrawal of this medication both the symptoms and histologic anomalies recurred. Several investigators have also demonstrated that use of inhaled corticosteroids improved EE. Faubion *et al.* [41] initially demonstrated the effect of ingested steroids. This therapy was recently studied by Arora *et al.* [34] who evaluated the charts of 21 patients with the diagnosis of EE seen in Rochester, Minnesota between 1999 and 2001. The diagnosis was made based on a visual appearance that included a ringed esophagus as well the presence of a dense eosinophilic infiltrate on biopsy (> 20 eosinophils/HPF) with normal stomach and duodenal biopsies. Visually, Arora *et al.* noticed either a ringed esophagus or a smooth tapering in the distal esophagus that was atypical of peptic stricture. Sixteen of the 21 patients had undergone a previous esophageal dilatation. Once diagnosed, patients were placed on swallowed fluticasone propionate 200 micrograms per puff twice a day for six weeks. Almost every patient improved rapidly within days of treatment. Complications included oral candidiasis; three patients developed a relapse with dysphagia within 12 to 18 months of initiating therapy; two patients showed no benefit; and 4 of 17 patients required additional corticosteroid treatment within the first 12 months. The author did not routinely perform follow-up

endoscopy; however, one patient did undergo a repeat endoscopy after therapy and still had evidence of EE and esophageal ring formation.

Unfortunately, these studies have been conducted with small groups of patients and have not adequately assessed the long-term effect or the possibility of recurrence. In general, several of these studies have shown that while patients appeared to be asymptomatic with the use of inhaled corticosteroids, many patients continued to have a modest eosinophilic infiltration of the esophagus. This leads to the question as to whether or not it is best simply to treat patients to improve symptoms or whether or not to treat patients to improve and cure their disease. Medications such as oral cromolyn sodium have not been shown to be effective.

Recently, there has been some literature demonstrating the benefits of leukotriene receptor antagonists, such as Montelukast®. Attwood *et al.* [32] reported on 12 patients who were diagnosed with EE since 1995. These patients subsequently received a leukotriene receptor antagonist. The mean age of these patients was 40 years of age with onset of symptoms somewhere between age 15 and age 62 with mean duration of symptoms of 36 months. The primary symptom was dysphagia, although five patients reported regurgitation and six had heartburn. The median density of the eosinophils was approximately 57 eosinophils per HPF. All patients underwent upper endoscopies with biopsies prior to beginning the medication. Eight patients were begun on up to 100 mg per day of Montelukast. Initially, seven of the eight patients demonstrated complete subjective improvement in dysphagia and were subsequently placed on a maintenance dose of 20 to 40 mg per day. Six of the eight patients had recurrence of symptoms within three weeks of cessation or reduction in medication. No biopsies were performed on medication; thus the degree of esophageal eosinophilia on medication was not known.

The theory behind using Montelukast for symptomatic treatment of EE is that Montelukast selectively blocks the D4 receptor of cysteinyl leukotriene present on the eosinophils. Other properties of leukotrienes include eosinophil attraction and migration, powerful constriction of smooth muscle, airway edema, mucous hypersecretion, and reduction of ciliary motility. Leukotrienes are predominately released by eosinophils, basophils, and mast cells. By blocking the deformed receptor, the inflammatory action of the eosinophil is reduced. Thus, the eosinophil is not removed, but their action is negated.

It has been suggested that the use of a mono-clonal antibody, anti-IL-5, may play a role in patients with severe EE. IL-5 has been found to be a strong eosinophil activator [42]. IL-5 is a cytokine critically involved in regu-

lating aspects of eosinophils including their production, activation, and tissue recruitment. Garrett and Rothenberg [43] reported on the safety and efficacy of using a mono-antibody directed against IL-5 in patients with hypereosinophilic syndrome. They performed an open-labeled trial, using three intravenous doses of anti IL-5 in four patients with hypereosinophilic syndrome. Anti-IL-5 improved symptoms and significantly lowered peripheral blood eosinophil counts in all patients. This decline in eosinophil count was sustained for at least 12 weeks after the last dose of anti-IL-5. The authors suggest that anti-IL-5 is safe, effective, reduces eosinophil counts, and has potential glucocorticoid-sparing effects. Work with this agent has demonstrated the possibility of improvement in patients with EE.

Although it appears that longstanding EE often causes chronic symptoms of reflux and dysphagia and the development of esophageal strictures, several investigators suggest that aggressive treatment is not necessary. Because of the lack of information and long-term follow-up with regard to these patients, it is difficult to absolutely conclude that longstanding eosinophilic infiltration of the esophagus portends significant harm. While studies have demonstrated that EE can be diagnosed and successfully treated by eliminating specific food allergens, there is a group of opponents who remain concerned about the short- and long-term social effects of utilizing these diets. One adult study looked at long-term follow-up of patients with EE and observed that without treatment these patients continued to lead reasonably normal lives [44]. Several questions remain. Should patients not be treated but instead endure chronic symptoms? What is the long-term effect on a chronically inflamed esophagus?

Adult versus pediatric eosinophilic esophagitis

Although EE was first identified by case reports in adult literature, the major advances in etiology, diagnosis, and treatment have come from the pediatric literature. Between 1995 and 2002, many papers were published by different pediatric investigators revealing the importance of EE. The literature demonstrated that esophageal biopsies were especially important in these patients, despite the lack of visual findings. Recently, there has been a significant increase in the adult literature regarding EE. EE is currently one of the most discussed topics in both the pediatric and adult gastrointestinal literature. This disorder has now become widely accepted as a significant cause of dysphagia in adolescents and adults and should be considered in all patients who present with symptoms of gastroesophageal reflux symptoms unresponsive to acid blockade.

A recent article by Katzka [45•] discussed the emergence of EE in adults over the past few years. In this article,

EE should be considered if greater than 15 esophageal eosinophils were present; the diagnosis of reflux was assumed when three or fewer esophageal eosinophils were seen per HPF; and an indeterminate esophagitis was identified when patients had 3 to 15 eosinophils. The discussion centered on the need for a more strict definition. He further discussed the etiology of EE with his main focus on the possibility of EE being an allergy-mediated disorder. In general, he reported that many EE patients have other associated extra-esophageal allergic disorders; that the elimination of specific food products can effectively treat the disease; and that response to medications effective in allergic disorders, such as steroids, often improve the disease. The role of aeroallergens was also entertained. With regard to diagnosis, he mentioned that if a strong suspicion of EE is present, endoscopy with biopsy is critical to make the diagnosis. Often, visual findings do not yield the degree of disease severity. Possible treatment options include identification and elimination of underlying allergens, anti-allergy or immunosuppression therapy, and third, endoscopy treatment for stricture complications.

In adults, the common treatment regimen for EE is esophageal dilatation. Because adult patients with EE often go undiagnosed for years, strictures frequently develop. Esophageal dilatation can be a painful procedure and is usually accompanied with acid suppression therapy. However, most patients with EE do not show an improvement in their histologic eosinophilia; thus this disease continues. These patients subsequently require long-term acid-suppression therapy and repeated esophageal dilatation. In the Attwood study, the patients reported no symptoms as young children and the disease appeared later in life [32].

Croese *et al.* [46] authored one of several recent papers highlighting the fact that EE occurs in adults and adult gastroenterologists are becoming more aware of its presence. This Australian paper reviewed patients who had unexplained eosinophilic inflammation of the squamous mucosa of the esophagus (greater than 30 eosinophils per high-powered field) in a retrospective review. The diagnosis of EE was made in 31 patients (21 men) with an average age of 34 years who ranged from 14 to 77 years. Visually, 97% of patients had esophageal mucosal furrows while 89% had dysphagia. Symptoms of this disorder were present for an average of 54 months with a maximum of 15 years prior to diagnosis. In addition, they mention that diagnosis was delayed in seven patients for an average of almost seven years with a range of 1 to 10 years because the sentinel features were overlooked and during initial endoscopy, biopsies were not taken. Strictures were present in 57% of these patients and esophageal dilatation was performed. Esophageal dilatations consistently relieved symptoms; however, often repeated dilatations were required. Esophageal tears were re-

ported in 87% of these patients, 90% of patients had an allergic history, 36% had peripheral eosinophilia, and 58% had a total IgE level that was abnormal.

Recently, Potter *et al.* [47•] reported one of the largest adult series of patients with EE. Over a three-year period between 1999 and 2002, 29 adult patients (21 men) with documented EE (greater than 50 eosinophils per HPF) were evaluated. Up to 48% had a history of asthma, environmental allergy, or atrophy. Greater than 90% had abnormal endoscopic findings that included a uniform, small caliber esophagus, single or multiple corrugations or ring-like formations, a proximal esophageal stenosis or small, papular, whitish lesions. Almost 25% of patients had a history of chronic heartburn, while 83% had dysphagia. The mean age of these patients was 35 years of age. Esophageal dilatation was performed in 13 patients. A transient improvement in swallowing was noted in 3 of 13 patients after dilatation; however, in most patients symptoms recurred.

With regard to long-term follow-up, Straumann *et al.* reported on the natural history of EE of 30 adult patients observed for up to 11 years [48•]. During the period of observation, while an esophageal eosinophilic infiltration persisted in all symptomatic patients, the cell numbers decreased (but did not normalize) over time. No inflammatory process was seen in the stomach or duodenum, and no patient evolved into a hypereosinophilic syndrome. Almost 60% of patients demonstrated no change or no worsening of the severity of dysphagia. The authors theorize that EE is a primary and chronic disease restricted to the esophagus, which leads to persistent dysphagia and structural esophageal alterations. In addition, there appeared to be no impact on the patient's nutritional state. The authors suggest that EE is a chronic condition and that once established follows a chronic course in almost all patients. However, this report does not address the possibility of dietary or allergic induced esophagitis. They mention that the density of eosinophils and changes in esophageal epithelium seem to decrease over time. Unfortunately the esophageal changes are still quite significant with the authors documenting that more than 40 eosinophils per high-powered still existed at a later date in some patients.

Conclusion

Eosinophilic esophagitis is a disorder that has become increasingly diagnosed over the past 10 years. While most of the literature suggests that food antigens are most likely responsible for the development of EE, some believe that environmental antigens, such as aeroallergens, may also play a key role in the pathogenesis of EE. Several treatment options exist including the removal of specific food antigens and the use of several medications such as corticosteroids and leukotriene antagonists. Recently, new literature has suggested that several chemo-

kines including IL-5, stat-6, and eotaxin have specific roles in the activation and recruitment of eosinophils. Currently, the treatment of EE remains in its infancy. While it has been well documented that the strict avoidance of those foods responsible for the disease is curative, future therapy may involve the development of antichemokine products that impact directly on eosinophil function.

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