Eosinophilic Esophagitis

INTRODUCTION

Eosinophils can be found in biopsies of the distal esophagus in patients with gastroesophageal reflux disease (GERD). For this reason many physicians believed that the cause of the ringed esophagus was GERD (1). However many of these patients have no GERD symptoms (2,3), others have negative 24 hour pH studies (4) and only a small minority have responded to proton pump inhibitor therapy (2).

Eosinophilic esophagitis (EE), also described as idiopathic or primary eosinophilic esophagitis, is emerging as a more well-defined clinical syndrome. It is relatively underdiagnosed in adults and most of the information we have has been garnered from case reports and case series in children. Kelly and Frazier in 1966 described dysphagia in patients with mid-esophageal rings (5). EE was later described in 1978 by Landres, et al (6) followed by more detailed information in adults provided by Attwood, et al in 1993 (7).

Since then, there has been growing interest in establishing more selective criteria to better delineate EE from gastroesophageal reflux disease (GERD) as a distinct and separate entity. This paper will focus mostly on the disease in adults.

EE is an inflammatory disorder of the esophagus diagnosed pathologically by a dense infiltrate of >15–25 eosinophils per high power field, usually in the mucosa. This criterion is not agreed upon with most experts requiring >20 eosinophils per high power field. No eosinophils are present in normal esophageal tissue and reflux disease has been associated with 5–10 eosinophils per high power field, usually in the distal esophagus although there is no consensus on the maximum numbers of eosinophils seen with reflux. Findings of eosinophils in the proximal esophagus should prompt one to consider EE in the differential diagnosis. It is also important to rule out other causes of eosinophilic infiltration such as parasitic and fungal infections.

EPIDEMIOLOGY

Cases of EE have been reported from Switzerland, England, Spain, and Japan but primarily in the United States. As more cases are diagnosed, perhaps epidemi-
Eosinophilic Esophagitis

GERD IN THE 21ST CENTURY, SERIES #14

ology could allude to a predisposing factor as the etiology of EE is still unknown.

Since eosinophils are not natural residents of the esophageal mucosa, many hypotheses for the recruitment of eosinophils to the esophagus have been investigated. One hypothesis is that EE may be a delayed hypersensitivity reaction to food allergens. In 1995, Kelly, et al proposed that EE developed as a response to dietary protein(8). They conducted a study of 10 pediatric patients with symptoms attributed to GERD refractory to antisecretory medications. These patients were found to have eosinophilic infiltration limited to the esophagus (no evidence of eosinophilic gastroenteritis). The patients completed 6 weeks of a diet with an elemental formula (consisting of free amino-acids, median chain triglyceride oil and corn syrup) as well as clear liquids. Older patients were allowed to have corn and apples as these foods have been found to have extremely low likelihood of inducing a hypersensitivity reaction. After the 6 weeks, patients underwent repeat endoscopy and biopsy. Eight out of 10 patients had a resolution of their symptoms and 2 had marked improvement. All patients had a reduction in the number of eosinophils on their repeat biopsies and five of 10 patients had none. Eight of 10 patients were able to stop their antireflux medications. Markowitz, et al (9) in a larger study found similar findings. In their study, 51 patients who had symptoms refractory to medications and had negative tests for reflux disease had improvement in their symptoms and biopsies after one month of an elemental diet (9).

Another interesting hypothesis is that EE is an immunologic response to allergens outside of the gastrointestinal tract, in particular the respiratory system. It is thought that there may be a connection between the T helper cell immune response in the lung and in the esophagus. T helper cells secrete cytokines such as IL-5, the most potent and specific activator of eosinophil activation and recruitment. Other important cytokines include IL-4 and IL-13 which are found in elevated levels in the asthmatic lung. Dysregulation of IL-13 has been reported in asthma, atopic dermatitis, and allergic rhinitis. Mishra, et al proposed that the overexpression of IL-13 in the lung may contribute to the development of EE (10). They conducted a study in IL-5 deficient mice as well as wild type mice, in which IL-13, IL-4, IL-9, IL-10 or saline were delivered intratracheally. The esophagus and bronchoalveolar lavage (BAL) fluid were examined. When doses of 1.0 and 10 µg of IL-13 were delivered, there was a significant increase in the number of eosinophils detected in the esophagus and the BAL fluid but not in the stomach of these mice. None of the other cytokines produced the same effect. Also, EE did not develop in IL-5 deficient mice demonstrating that IL-5 is crucial in priming and activating eosinophils after IL-13 delivery.

HISTORY

Symptoms can range from nausea, vomiting, abdominal pain, heartburn, chest pain, globus sensation, or regurgitation to dysphagia to solids leading to food impaction. In children, the symptoms may be more subtle such as poor growth, abdominal pain, irritability, nighttime cough, slower rate of eating, or even a lack of interest in eating. The classic historical feature in an older child or adolescent is that they have learned to eat so slowly and chew their food so well that they are always the last member of the family to leave the table after a meal.

There is a male predominance among adult patients. Pediatric patients have a stronger association with atopic disease with a personal or family history of seasonal allergies, eczema, rhinitis, conjunctivitis, dermatitis, or asthma. In 2001, the Cincinnati Childrens Hospital Medical Center launched a world-wide-web based registry (www.cincinnatichildrens.org/eosinophils) for eosinophilic gastrointestinal disorders and in 4 months, 107 surveys were completed by patients through the website (11). Of these, 51 patients identified themselves as having eosinophilic esophagitis. Sixty-four percent reported a history of allergic conjunctivitis, 38% with asthma, and 26% with eczema. However, the history of atopy is not necessary to make the diagnosis.

PHYSICAL EXAM

There are no distinctive physical findings in patients with EE that distinguishes EE from other diseases.

(continued on page 47)
DIAGNOSIS

As many patients are misdiagnosed as having severe GERD refractory to the conventional antacid medications, Markowitz, et al has proposed using lack of response to a proton pump inhibitor drug as a criterion for the diagnosis of EE (9).

EE is a spotty disease. Consequently if the diagnosis is suspected, multiple biopsies (up to five) should be taken not only in the lower and upper portions of the esophagus but also in the stomach to eliminate the rare condition of eosinophilic gastroenteritis. Biopsies should be placed in formalin, not Bouin’s fixative, as eosinophils are less likely to be identified in tissue fixed with Bouin’s (2). Whitish patches are seen more often in the pediatric age group than in older patients. These represent microabscesses of eosinophils and should be biopsied if seen (2).

A growing number of endoscopic findings have been associated with EE. Endoscopic features include normal endoscopy, small caliber esophagus, strictures both proximally and distally, corrugated ringed appearance, trachealization (2), “crepe-paper” mucosa (17), “feline esophagus” as it resembles esophageal structure in cats, furrowing with irregular, linear grooves, and exudates which can appear as white vesicles and papules. These whitish patches may suggest candida infection but the microscopic evaluation will reveal fungal elements if present. Signs of erosive esophagitis from reflux disease should be ruled out during endoscopy.

It is important to solidify the diagnosis by excluding GERD with a 24 hour pH study. Manometry can be normal or may show ineffective peristalsis, simultaneous contractions, diffuse spasm, or high amplitude contractions (12).

Endoscopic ultrasound has shown significant thickening in the total wall including mucosa, submucosa and muscularis propria as compared to normal controls (13).

Radiographic studies such as an upper GI series may be incorporated to rule out any abnormal anatomy. Nurko suggested that EE may play a role in the development of Schatzki’s rings in adolescents (13). However, Liacouras proposed that patients with EE who were previously diagnosed with Schatzki’s ring may in fact have tissue inflammation causing a ring-like appearance which improves with appropriate therapy (14).

TREATMENT

Treatment for EE has been challenging. Most patients have already failed a course of proton pump inhibitors but, if not, an empiric trial is warranted as acid exposure may worsen the symptoms. Since GERD is so common it is possible to have both entities at the same time. As demonstrated in pediatric studies, an elemental diet can help improve symptoms and histologic findings but the formula is generally not palatable and requires nasogastric tube administration in some patients. However, the formula is more successful than attempting to avoid all food allergens as most patients have multiple allergens (8). Also, not all patients have an association with a food allergen for their disease.

Use of topical corticosteroids has been effective without the risk of significant systemic absorption. Arora and colleagues evaluated the use of swallowed topical fluticasone propionate inhaler twice daily for six weeks in 21 patients with solid food dysphagia and findings of EE on histologic and endoscopic examination (15).

All patients had a resolution of their dysphagia up to 12 months after their 6 week trial with fluticasone and there were no cases of oral candidiasis. We have seen two people who after periods of being asymptomatic have discontinued their inhaled steroids and after several months developed recurrent dysphagia. Resuming inhaled steroids rendered them both asymptomatic after several weeks.

Specific instructions must be given to patients to explain how to take the topical steroids as the pharmacist will often tell the patients to inhale the steroids believing the patients are taking them for asthma. We use fluticasone dipropionate; we ask the patient to spray the material into the mouth. Some physicians ask the patient to rinse the mouth with water and swallow the water. Others tell the patient not to eat or drink for 30 minutes after application. There is no standardized way to use this medication. Both methods seem to work. We like to start with 2 puffs of 220 mcgm per puff twice daily. Because others seem to have recur-
references after short treatment periods we have tended to taper the dose from 2 puffs bid to 1 puff bid after 6 months then 1 puff daily for a while. There is no proven best way.

Systemic corticosteroids have been used with success, usually in resistant patients; however, long term use is not advised due to potential side effects including stunted growth in children and candidiasis.

Other treatments include disodium cromoglycate, a mast cell stabilizer, and leukotriene inhibitors such as montelukast. We have seen one patient who was unable to take inhaled steroids who took oral disodium cromoglycate. She has remained asymptomatic for several months and her esophageal eosinophilia is gone. There are rare patients who must be placed on immunomodulators such as azathioprine. Straumann has rarely had to treat chronic patients with EE with azathioprine alone (Straumann A., personal communication). A pilot study has been conducted with mepolizumab, a humanized monoclonal antibody against IL-5 which suggests improvement in the degree of eosinophilia in the tissue but these results need to be further investigated (16).

**TREATMENT (ESOPHAGEAL DILATION)**

Straumann first described the “crepe paper” mucosa as fragile with loss of elasticity thought to be pathognomonic for EE, causing large lacerations after passing the endoscope despite a lack of narrowing or resistance (17).

Langdon suggested dilation for strictures from EE should be done cautiously because of the risk of tear and perforation due to the delicate nature of the mucosa and recommended inspection of the esophagus after each dilator has been passed (18).

Kaplan, et al recommended a minimum of 8 weeks of medical therapy with proton pump inhibitors, histamine antagonists, or immunosuppressants before attempting dilation as patients with EE are more prone to developing mucosal rents, even with passage of the endoscope and perforation after dilation (3). We encourage careful dilation, waiting several weeks after steroids have been introduced, if possible. Often the steroids will render the patient’s dysphagia asymptomatic and dilation need not be performed.

**CONCLUSION**

Eosinophilic esophagitis is now better recognized by both gastroenterologists and pathologists. Hopefully through more expeditious and accurate diagnosis of this specific disease entity, more information can be obtained to improve patient care and the relief of their symptoms with medical therapy and minimizing the development of strictures.

**References**