Eosinophilic Esophagitis in a Patient with Gastroesophageal Reflux Symptoms

Suresh G. Jayatilaka, MD
Robert Spira, MD, FACG, FACP

Eosinophilic esophagitis (EE) is a distinct disease that is presenting with increasing frequency in both adult and pediatric patients. The typical presentation in adults is solid food dysphagia in young men who have an atopic predisposition. EE should be suspected in patients with unexplained dysphagia or those with symptoms of gastroesophageal reflux disease (GERD) who do not respond to proton pump inhibitor therapy. Endoscopic examination of the esophagus may reveal furrows, corrugations, rings, whitish plaques, crepe-paper–like appearance, and a small-caliber esophagus. Demonstration of marked eosinophilic infiltration in the esophageal epithelia is diagnostic for this condition. This article presents the case of a man who presented with GERD-like symptoms refractory to conventional medications in whom endoscopy and subsequent biopsy demonstrated EE. The presenting features, diagnosis, and treatment of EE are also briefly reviewed.

CASE PRESENTATION

Initial Presentation and History

A 71-year-old-man was referred to a gastroenterologist by his primary care physician for evaluation of localized epigastric pain, early satiety, heartburn, and reflux which he had been experiencing for approximately 1 year. Past medical history was significant for GERD. The patient was taking lansoprazole 30 mg once a day for the previous 3 months without any relief of his symptoms. He denied nausea, vomiting, dysphagia, melena, and weight loss. He had no complaints of chest pain, shortness of breath, or cough. He had never undergone an upper endoscopy examination. He did not smoke or drink alcohol. His family history was significant for colon cancer in his father at age 74 years. His medications consisted only of lansoprazole.

Physical Examination

On physical examination, the patient's vital signs were stable and he was afebrile. Examination of his abdomen revealed a soft, nontender, nondistended abdomen with bowel sounds in all 4 quadrants. The remainder of the physical examination was benign. The patient was scheduled for an elective outpatient upper endoscopy.

Upper Endoscopy and Diagnosis

The endoscope was passed with ease under direct visualization to the third portion of the duodenum. Significant nodularity and a corrugated appearance affecting the entire esophagus were noted (**Figure 1**). Multiple random biopsy specimens were obtained from the mid esophagus. The gastroesophageal junction appeared normal. There was evidence of nonerosive gastritis and mild duodenitis. Examination of the esophageal biopsy specimens revealed more than 20 eosinophils per high-power field (HPF) (**Figure 2**), a finding diagnostic of EE. The patient was seen in follow-up 3 weeks after endoscopy. At that time, he declined further treatment because his symptoms had resolved.

DISCUSSION

A number of conditions can predispose the esophagus to eosinophilic infiltration, including GERD, parasitic infections, systemic eosinophilic syndromes, and the entity known as EE.[1–7] First described by Landres et al[8] in 1978, EE is now emerging as an important differential diagnosis in patients with esophageal symptoms. Over the past 5 years, there has been an increase in the number of publications related to EE.[9,10]

Pathophysiology

The pathophysiology of EE remains controversial. The peptide eotaxin is thought to play a key role in antigen-mediated eosinophil recruitment in the gastrointestinal tract.[11] A popular hypothesis suggests that

Dr. Jayatilaka is a gastroenterology fellow, and Dr. Spira is a professor of medicine; both are at Seton Hall School of Postgraduate Medicine, South Orange, NJ.

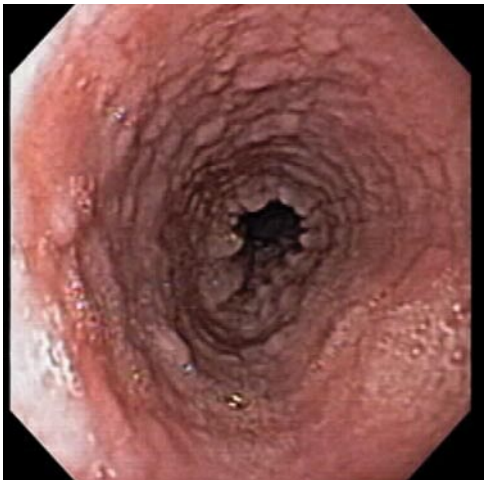

Figure 1. Corrugated, nodular-appearing esophagus visualized on upper endoscopy evaluation of patient.

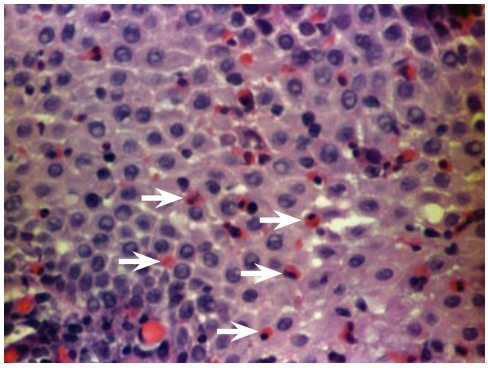

Figure 2. Esophageal biopsy specimen demonstrating more than 20 eosinophils (*arrows*) per high-power field (hematoxylin-eosin stain).

eosinophil recruitment in EE may be triggered by environmental antigens. This hypothesis is supported by a study in which esophageal eosinophilia developed in mice exposed to respiratory allergens but did not develop in mice exposed to oral or intragastric allergens.[12] This study also highlighted the importance of eotaxin and interleukin (IL)-5 in eosinophil recruitment in the esophagus. In the absence of eotaxin, eosinophil recruitment was attenuated, whereas in the absence of IL-5 it was ablated. Another hypothesis favors the recruitment of eosinophils in the esophagus in the aftermath of an acute infectious process.[5,13] A role of food additives or pesticides also has been hypothesized.[5,13]

After migrating to the esophagus, eosinophils release additional chemoattractants such as IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor.[14] Eosinophils can cause local inflammation by release of eosinophil-derived major basic protein, a cytotoxic cationic protein.[15] This persistent inflammatory response is likely responsible for the development of dysphagia. Because of its clinical and immunologic characteristics, the term "asthma of the esophagus" has been applied to EE.[16]

Epidemiology

A high prevalence of EE has been reported in children with reflux symptoms who are unresponsive to proton pump inhibitors (68%–94%).[17,18] The prevalence in adults with reflux symptoms remains unknown, which may be attributed to poor disease awareness and the lack of well-established diagnostic criteria. Studies have shown a male predominance in pediatric and adult patients with EE, with boys accounting for 73% of pediatric patients with EE[17–20] and men accounting for 75% of adults with EE.[16,21–23] The majority of pediatric patients had atopic conditions, including asthma, atopic dermatitis, and food allergy (51%–84%). Adult patients also had an atopic predisposition (29%–60%). Blood eosinophilia was seen in approximately 60% of pediatric patients and in 5% to 50% of adult patients. Increased serum immunoglobulin E levels, positive skin prick test, and positive radioallergosorbent test were found in a number of patients (40%–73%).

Diagnosis

The clinical presentation of EE is different in children and adults. In children, the predominant features can suggest GERD: vomiting, dysphagia, and abdominal pain.[17,24] In adults, dysphagia is often accompanied by solid food impaction. Desai et al[25] demonstrated an increased association of EE among adults with food impaction (17 of 31 patients). Upper endoscopic findings include furrows, vertical lines in esophageal mucosa, corrugations, rings, adherent white plaques, and a crepe-paper–like mucosa in the mid to distal esophagus. GERD lesions are mostly limited to the distal esophagus, whereas EE appears to affect the proximal and mid esophagus. Abnormal endoscopic findings are present in approximately 90% of patients.[9]

The diagnostic hallmark of EE is a marked eosinophilic infiltration of the esophagus demonstrated on esophageal biopsy. This histologic finding is diagnostic if the eosinophilic infiltration exceeds 20 eosinophils per HPF in the squamous epithelium.[2,3,23,24] A lesser degree of eosinophilic infiltration is also seen with GERD (5–10 eosinophils/HPF).[2,3] EE seems to affect the esophagus specifically, with infiltration in the stomach or intestine found in only 4% to 13% of patients with EE.[21,24]

Treatment

Elimination and elemental diets, systemic and topical corticosteroids, and leukotriene receptor antagonists have been used to treat EE. The hypothesis that food allergens are the stimulus for the inflammatory response in EE is the premise for using dietary therapies to treat EE. With an elimination diet, foods are restricted based on skin prick and atopy patch testing results. Spergel et al[26] have demonstrated that in more than 75% of patients with EE, both symptoms and esophageal inflammation can be significantly improved with dietary elimination of foods. Another dietary therapy that has been used to treat EE is an elemental diet, which consists of ingesting free amino acids, corn syrup solids, and medium-chain triglyceride oil followed by gradual reintroduction of single foods.[3,18] However, the practicality of an elemental diet is unclear given its expense and poor palatability and questions around its long-term effectiveness.

Topical corticosteroids have been shown to provide relief of symptoms in patients with EE. Arora et al[23] used topical steroids to treat 21 adult patients with EE who had solid food dysphagia for at least 6 years. The standard protocol was fluticasone propionate (220 μg/puff) 4 puffs twice daily without a spacer for a total of 6 weeks. The patients were instructed to swallow rather than inhale and to rinse their mouths with water. Therapy resulted in complete relief of dysphagia in all patients for a minimum of 4 months. The only adverse effect noted was dry mouth. However, the authors noted that symptoms recurred in 50% to 60% of adult patients after 12 to 18 months. Following recurrence, treatment with a shorter course of topical corticosteroid is recommended.

The efficacy of topical versus systemic steroids was evaluated in a controlled trial that included 50 children randomized to receive oral prednisone (1 mg/kg twice daily) or swallowed fluticasone (220 μg/puff 4 times daily) for 8 weeks.[27] Patients underwent upper endoscopy with biopsy at baseline and after 4 weeks of treatment. Overall histologic improvement and symptom resolution were slightly better with the prednisone group. Although the data suggest that oral prednisone may be slightly more effective than topical fluticasone, the degree of benefit may not justify routine use of systemic steroids in patients in light of their side effects.

Montelukast is a selective inhibitor of the leukotriene D4 receptor that is used in the treatment of asthma. Symptomatic improvement was observed in 7 of 8 adults with EE who were treated with montelukast.[22] Treatment was begun with 10 mg daily but increased to a total dose of 100 mg daily based on symptoms. Side effects observed included nausea and myalgia during the 14-month treatment. Mepolizumab is a humanized monoclonal antibody against IL-5, which has a central role in eosinophil recruitment. Beneficial effects of anti-IL-5 treatment using mepolizumab have been reported in 4 patients with various hypereosinophilic syndromes.[28]

Patients with esophageal rings or strictures may require dilation. However, esophageal dilation should be performed carefully as it has been associated with deep mucosal tears and esophageal perforation. Kaplan et al[29] recommend considering dilation only in patients with EE who do not respond to medical therapy and have rings that appear to be obstructing the lumen.

CONCLUSION

EE, primarily reported as rare in children, is emerging as a prevalent adult disease. It should be considered in the differential diagnosis of patients who present with dysphagia, especially young men with atopic predispositions who have solid food dysphagia and food impaction. In this setting, the finding of more than 20 eosinophils per HPF on esophageal biopsy is diagnostic of this entity and would justify treatment with topical corticosteroids. **HP**

REFERENCES

1. Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. Gastrointest Endosc 2002;56:260–70.
2. Liacouras CA. Eosinophilic esophagitis in children and adults. J Pediatr Gastroenterol Nutr 2003;37 Suppl 1: S23–8.
3. Markowitz JE, Liacouras CA. Eosinophilic esophagitis. Gastroenterol Clin North Am 2003;32:949–66.
4. Munitiz V, Martinez de Haro LF, Ortiz A, et al. Primary eosinophilic esophagitis. Dis Esophagus 2003;16:165–8.
5. Rothenberg ME, Mishra A, Collins MH, Putnam PE. Pathogenesis and clinical features of eosinophilic esophagitis [editorial]. J Allergy Clin Immunol 2001;108:891–4.
6. Rothenberg ME, Mishra A, Brandt EB, Hogan SP. Gastrointestinal eosinophils. Immunol Rev 2001;179: 139–55.
7. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol 2004;113:11–29.
8. Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. Gastroenterology 1978;74:1298–1301.
9. Potter JW, Saeian K, Staff D, et al. Eosinophilic esophagitis in adults: an emerging problem with unique esophageal features. Gastrointest Endosc 2004;59:355–61.
10. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med 2004;351:940–1.
11. Hogan SP, Mishra A, Brandt EB, et al. A critical role for eotaxin in experimental oral antigen-induced

eosinophilic gastrointestinal allergy. Proc Natl Acad Sci U S A 2000;97:6681–6.
12. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. J Clin Invest 2001;107:83–90.
13. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? Clin Gastroenterol Hepatol 2004;2: 523–30.
14. Desreumaux P, Bloget F, Seguy D, et al. Interleukin 3, granulocyte-macrophage colony-stimulating factor, and interleukin 5 in eosinophilic gastroenteritis. Gastroenterology 1996;110:768–74.
15. Talley NJ, Kephart GM, McGovern TW, et al. Deposition of eosinophil granule major basic protein in eosinophilic gastroenteritis and celiac disease. Gastroenterology 1992;103:137–45.
16. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660–9.
17. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. Gastroenterology 2002;122:1216–25.
18. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003;98:777–82.
19. Cheung KM, Oliver MR, Cameron DJ, et al. Esophageal eosinophilia in children with dysphagia. J Pediatr Gastroenterol Nutr 2003;37:498–503.
20. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol 2002;109:363–8.
21. Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. Gastrointest Endosc 2003;58:516–22.
22. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic oesophagitis: a novel treatment using Montelukast. Gut 2003;52:181–5.
23. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. Mayo Clin Proc 2003;78:830–5.
24. Orenstein SR, Shalaby TM, Di Lorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children [published erratum appears in Am J Gastroenterol 2001;96:2290]. Am J Gastroenterol 2000;95:1422–30.
25. Desai TK, Stecevic V, Chang CH, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. Gastrointest Endosc 2005;61:795–801.
26. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. Ann Allergy Asthma Immunol 2005; 95:336–43.
27. Gupta SK, Fitzgerald JF. Treatment of allergic eosinophilic esophagitis with oral prednisone and swallowed fluticasone: a randomized, prospective study in children [abstract]. Gastroenterology 2003;124:A-19.
28. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 2004;113: 115–9.
29. Kaplan M, Mutlu EA, Jakate S, et al. Endoscopy in eosinophilic esophagitis: "feline" esophagus and perforation risk. Clin Gastroenterol Hepatol 2003;1:433–7.

Copyright 2006 by Turner White Communications Inc., Wayne, PA. All rights reserved.