Invited Review

Eosinophilic esophagitis

A. Ntailianas, I. Danielides

SUMMARY

Eosinophilic esophagitis (EE) is an allergic or idiopathic disease of the esophagus. The most characteristic symptom of EE is dysphagia, which may be accompanied by food impaction. Eosinophilic infiltration of the esophagus is the main marker for the disease and endoscopic biopsy of the distal and proximal esophagus and histology is the only way to establish the diagnosis of EE. Endoscopic findings include concentric rings or web like strictures, an appearance resembling feline esophagus, longer strictures and small caliber esophagus, corrugation, vertical furrows, patchy whitish exudates or tiny white papules. Treatment of EE with proton pump inhibitors has been found to be ineffective. Elimination diets or anti-inflammatory medications (corticosteroids) are helpful to induce remission in patients with EE. An attractive alternative to systemic corticosteroids is the administration of topical corticosteroids. For patients with strictures or rings unresponsive to medical treatment, in whom dysphagia persists, endoscopic dilatation should be performed but this involves high risk for deep mucosal tears and esophageal perforation. More studies, especially in adults, are needed to determine the long term management and the best treatment strategy.

INTRODUCTION

Eosinophilic esophagitis (EE) is an underdiagnosed disorder of children and adults, previously confused with esophageal inflammation due to gastroesophageal reflux (GERD). It is an allergic or idiopathic disease of the esophagus characterized clinically by symptoms of dysphagia and at times heartburn, unresponsive to antisecretory therapy and histologically by the presense of eosinophils within the squamous epithelium or deeper tissue of the esophagus.

Gastroenterology Department "Hygeia" Hospital, Athens, Greece

Author for correspondence:

A. Ntailianas, Hygeia Hospital, Erythrou Stavrou 4, 151 23 Athens, Greece, tel.: +2106867474, Fax: +2106867036, e-mail: apntailianas@yahoo.gr

Etiology of EE / Pathophysiology

Eosinophilic esophagitis, also called allergic esophagitis, primary or idiopathic eosinophilic esophagitis, is a disease of unknown etiology. Small numbers of eosinophils may be seen in normal stomach or bowel but not in the esophagus. Eosinophils infiltrate into the esophagus in GERD, infections, collagen vascular diseases and eosinophilic gastroenteritis. EE may represent a subset of idiopathic eosinophilic gastroenteritis, but the role of food allergy has been lately emphasized[1]. EE is a result of food hypersensitivity.[2] A type IV allergic reaction (cell-mediated) and not a type I (IgE mediated) is most likely involved. In patients with type IV food hypersensitivity symptoms may occur hours to days after ingestion of a causative food. Although skin prick tests or radioallergosorbent tests (RAST tests) for IgE antibodies are often negative, delayed reaction skin testing (skin patch testing) may identify the offending food.[3]

There is speculation that EE is a disease related to urban environment, possibly air pollutants or other factors unique to large cities, since most patients were referred to tertiary centers in large North American cities, but this may represent an observational bias.[4] Noel et al found a familial pattern suggesting either a genetic predisposition or a cause related to an unknown environmental exposure.[5]

Eosinophilic infiltration of the esophagus, which is the main marker for the disease, is related to the release of proinflammatory mediators, such as prostaglandins, leucotrienes, interleukin (IL)-5 and IL-13.[6] Oxygen free radicals and peroxidase have been implicated in the pathophysiology of the disease as well.

Acid reflux is not related to EE. Steiner et al found

that patients with more than 20 eosinophilis per HPF in histology have normal pH studies.[7] Eight studies including 64 patients with EE (adults and children), showed normal pH study of the distal esophagus.[8]

Motility disturbance has been noted by several investigators in EE. Tertiary contractions, aperistalsis, diffuse spasm, nutcracker esophagus and simultaneous contractions has been demonstrated in affected patients. However stationary manometry has been reported normal in other studies. Nurko et al performed ambulatory 24 hour manometry and found that EE patients had ineffective peristalsis after meals more often than controls and high amplitude contractions.[9] In these patients dysphagia correlated with abnormal esophageal manometric findings.

Esophageal wall thickness has been measured by using EUS and both submucosal and muscular thickening has been found. Fox et al, using a 20 MHz high-resolution catheter probe, detected significantly more thick total wall, mucosa/submucosa and muscularis propria in 11 children with EE, compared to normal controls.[10] The involvement of the muscular layer leads to muscle dysfunction which explains clinical features such as dysphagia and food impaction.

Epidemiology of EE

The epidemiology and the prevalence of EE are not well defined. In children the diagnosis is made after infancy and through adolescence. In adults it is typically made in the third or fourth decades of life, but older patients have been described as well. There appears to be a gender predilection and over three quarters of cases reported were male.[8]

Studies are needed to assess the prevalence of EE in adults. The number of cases reported is increasing. A large study describing 103 children with EE from a single centre[5], showed that only 2.8% of cases had been identified prior to 2000, suggesting that the disease is increasing in frequency. The overall incidence per 10,000 population was estimated to be 0.909 in 2000 and increased to 1.281 in 2003. It is unclear whether this reflects a real increase in the prevalence of the disease or if the diagnosis has gone unrecognized for many years, or both. Because the incidence of asthma is rising in the developed world, it is reasonable to speculate that there is also a rising incidence in allergic diseases of the GI tract, like EE. On the other hand, clinicians consider alternative diagnoses for patients with GERD unresponsive to proton pump inhibitors or surgical fundoplication. Thus patients considered to have atypical or refractory GERD are now increasingly recognized as having EE.

Diagnosis

a) Clinical features

The most characteristic symptom of EE is dysphagia, which may be accompanied by food impaction. Dysphagia is longstanding and resistant to anti-acid treatment. This is usually related to esophageal dysmotility, but strictures, small-caliber esophagus and rings may be the cause in a subset of patients.[8]

Food impaction is a common presenting symptom. A study evaluating 12 adults with food impaction, without heartburn, who had repeated episodes despite proton pump inhibitor treatment, showed in biopsy specimens from both distal and proximal esophagus, more than 20 eosinophils/HPF (high power field).[11] In primary gastroenterology practice histology features of EE were seen in more than half (54%) of patients presenting with esophageal food impaction.[12] This raises a high index of suspicion for EE when evaluating patients with food impaction, especially repeated episodes.

Other symptoms related to EE in adults are vomiting and chest pain. In children obstructive symptoms are not so common (1/3 of cases), while EE may present with vomiting, nausea, regurgitation, water brush, heartburn, chest pain, epigastric abdominal pain, feeding refusal, slow growth and respiratory symptoms such as cough, wheezing, sinusitis, choking and pneumonia.[13]

Peripheral eosinophilia and increased IgE levels have been reported in 20-60% of patients. Eosinophilic gastroenteritis should be excluded. Food allergy is found in most patients and many have asthma or chronic respiratory disease.[14] A family history of allergic diseases, such as asthma, rhinitis, conjunctivitis, eczema and food allergies is often noted in patients with EE (62-85%). Patients should be asked about personal and family history of allergy since this may be a clue to diagnosis.

b) Endoscopy

The endoscopic findings are subtle, so the endoscopist should keep the diagnosis of EE in his mind and inspect the esophagus carefully. The new generation video endoscopes with their greater resolution are helpful in most situations.

The main endoscopic findings include concentric rings or web-like strictures, an appearance resembling feline esophagus. Esophageal rings are intermittent contractions of the circular muscle of the esophagus evoked by esophageal inflammation, or fibrous web-like strictures and although they can be seen in barium studies, they are best viewed endoscopically. Esophageal rings

have been reported as a manifestation of gastroesophageal reflux, but they should always raise the suspicion of a missed EE.[15]

Another endoscopic finding is longer strictures and small caliber esophagus which is in fact a long segment esophageal stricture as a complication of chronic inflammation. In one study of 5 male adults, 4 of whom had histologically confirmed EE, all of them had narrow esophagus. In 2 patients this finding escaped detection and was appreciated only after a long linear shearing was noticed after dilatation.[16] This has been also noticed by others and a history of esophageal perforation or severe pain after dilation of a stricture may serve as a diagnostic criterion. It is also remarkable that extensive changes occur in the absence of mucosal lesions like erosions or ulcers. This is another difference from GERD.

Corrugation, vertical furrows, a linear pattern of alternating furrows and folds, caused by thickening of mucosa and submucosa may be visible and they are characteristic endoscopic appearances. Patchy whitish exudates or tiny white papules, which may resemble mild esophageal candidiasis, is a recently described characteristic feature. In fact it represents aggregates of eosinophils.[17]

c) 24 hours pH study-manometry

EE may exist in a patient with prominent heartburn and intermediate numbers of eosinophils. This patient may be thought to have refractory reflux and should be verified by esophageal pH monitoring. Normal pH monitoring results eliminates gastroesophageal reflux as a cause of eosinophilic inflammation.The test may be confusing sometimes in patients having both EE and GERD and in patients with active EE who may have abnormal pH study because of esophageal inflammation, muscular dysfunction and ineffective esophageal peristaltic clearance.

Manometry may be useful in the evaluation of a patient with dysphagia, without stictures, and non-diagnostic histology. A correlation of dysphagia with abnormal esophageal manometric findings has been noted in patients with EE.

d) Histology

Currently endoscopic biopsy of the distal and proximal esophagus and histology is the only way to establish the diagnosis of EE. A review of studies over the last 10 years suggests that the majority of patients with EE have more than 20 eosinophils per HPF, although some may not have extensive esophageal eosinophilic infiltration in the initial endoscopy.[18] Ruchelli showed that children with EE had more than 20 eosinophils per HPF, while children with gastroesophageal reflux disease had less than 5 eosinophils per HPF.[19]

There seems to be no difference in the number of eosinophils identified in distal or mid esophagus, but in some studies the distal esophagus was found to have a greater number of eosinophils per HPF. In another study, comparing 64 patients with EE to 45 with GERD, the latter had a mean of 2.3 eosinophils per HPF in the distal esophagus and 1.8 eosinophils per HPF in the proximal esophagus. In contrast patients with EE had a mean of 38.6 and 25 eosinophils per HPF in the distal and proximal esophagus.[20] In this study not all had proximal involvement in both groups, especially for patients with GERD. So the absence of eosinophils in the proximal esophagus does not rule out the diagnosis of EE.

Temporal variation in eosinophilic infiltration, inadequate tissue sampling and histopathologic oversight, may delay the diagnosis of EE in 56% of patients.[21] Significant variability exists in eosinophil concentration in individual patients and 5 biopsies are needed to achieve 95% sensitivity (using a diagnostic threshold of >25 eosinophils per HPF).[22]

There is no cutoff value to establish the diagnosis of EE, but a recent retrospective study of children with endoscopy, biopsies and pH study concluded that the presence of more than 20 eosinophils per HPF is likely associated with a nonacid-related cause of esophagitis.[7] If there is suspicion of a more generalized eosinophilic gastroenteritis, other sites of the gastrointestinal tube should be biopsied.

Prognosis

The long term prognosis of EE is unknown. Strictures can occur early in the course of the disease. Untreated patients may remain symptomatic or have frequent episodic symptoms. These patients have usually progressed to the fibrostenotic stage. Attacks of dysphagia are more common in patients with blood eosinophilia. In EE the eosinophilic infiltration remains confined to the esophagus and does not extend to the stomach or the duodenum. The esophageal eosinophilia persists to all symptomatic patients but cell numbers may decrease spontaneously.

To date no malignant potential has been associated with the disease.[21]

Treatment

Treatment of EE with aggressive acid blockade with proton pump inhibitors has been found to be ineffective in several reports[1]. While acid suppression may improve symptoms by lowering acid reflux secondary to the underlying esophageal inflammation and motility disturbance of the esophagus, it does not reverse the esophageal histologic abnormality. Anti-reflux surgery should obviously be ineffective. In one report of 2 patients, unresponsive to medical treatment, Nissen fundoplication failed to improve symptoms or esophageal eosinophilic infiltration.[22]

The optimal treatment of EE has not yet been defined since experience is small and controlled trials are rare. Treatment should be individualized and patients should be best treated, whenever possible, as part of clinical studies. There are essentially two basic approaches to the treatment of EE: elimination diets or anti-inflammatory medications.

Elimination diets involves the removal of allergic food which is the antigenic stimulus that triggers inflammation. The elimination of the offending foods can reverse the inflammation of the esophagus, but the isolation of these foods may be extremely difficult. The cause of EE is a delayed hypersensitivity response and it takes several days for symptoms to recur after eating the offending food. Besides when a particular offending food has been removed from the diet, it may take days or weeks for symptoms to resolve and endoscopic biopsy is the only diagnostic test to confirm resolution of the disease. In addition, although one food may be identified, other foods, not easily identified may contribute to the disease.

Kelly et al treated 10 children with EE and increased numbers of eosinophils on endoscopic biopsy (median 41 eosinophils per HPF) with an aminoacid based elemental formula for a minimum of 6 weeks. Eight patients had complete resolution of symptoms and the other 2 improved. Endoscopic biopsies showed significant improvement (median 0.5 eosinophils per HPF). Following food challenge symptoms recurred. Avoidance of the offending foods allowed 8 of the 10 patients to remain asymptomatic without acid-suppression medications.[23]

In another large study 51 patients (children and adults) were put on elemental diet containing free amino acids, corn syrup solids and medium-chain triglyceride oil, orally or by nasogastric tube. Within 8 days on average 49 of 51 patients improved. A repeat endoscopy and biopsies after one month confirmed marked reduction in the number of eosinophils. Foods were reintroduced every 5-7 days and each patient was given an individualized diet to keep them symptom free.[24]

These results are promising but aminoacid formulas are unpalatable and the administration especially to children is difficult. Nasogastric intubation is often necessary to maintain the body weight and this is undesirable for the patient and family. These formulas are also expensive and may not be covered by insurance. Still elimination diet is a non-pharmacologic solution that avoids potential side effects of medical therapies.

Another report showed resolution of symptoms in 18 of 26 children who underwent skin prick testing and patch testing. Six more patients had partial improvement and 2 were lost to follow up[3]. Esophageal eosinophil counts improved from 55.8 to 8.4 eosinophils per HPF. The most common foods incriminated, using skin prick testing were milk and eggs, while with patch testing wheat was the most common food. However these results are not easy to interpret since many of the patients were also taking medications for allergies or asthma.

Immunosuppression with systemic corticosteroids has been tried with success. Liacouras et al treated 20 patients with oral methylprednisolone at a dose of 1.5 mg/Kg twice daily for 4 weeks and then a weaning dose over 6 more weeks. The average time for initial clinical improvement was 8 days. After 4 weeks 13 patients became asymptomatic and 6 more had clinical improvement. All 20 patients had also histologic improvement and decreased eosinophils per HPF. After 12 months of follow up 10 patients remained asymptomatic and 9 relapsed[25]. Although systemic corticosteroids are effective, the serious adverse effects coupled with the relapsing nature of EE restrict their wide use.

An attractive alternative to systemic corticosteroids is the administration of topical corticosteroids. In a large series of adults, 21 patients were treated with fluticasone propionate, 220μg/puff, twice daily, for 6 weeks. Patients were instructed to swallow (and not inhale) and then rinse their mouth with water. All patients had relief of dysphagia which started the first few days of treatment and lasted for at least 4 months.[26] Other studies have confirmed these good results. Dry mouth and esophageal candidiasis are the adverse events described. Larger doses, which when inhaled may cause dysphonia, growth inhibition and adrenal suppression, are believed to be relatively safe, since fluticasone is swallowed and not inhaled, undergoing first pass metabolism by the liver.

One controlled study compared topical versus systemic corticosteroids. 22 patients received fluticasone and

20 prednisolone for 8 weeks. After 4 weeks of treatment histologic improvement was observed in 19 patients in each group, but the degree of improvement was better in the prednisolone group. Twenty weeks after stopping treatment 8 patients in the fluticasone group and 7 patients in the prednisolone group remained asymptomatic.[27] These data suggest that prednisolone may be slightly more effective, but the degree of benefit does not justify its routine use if the serious potential adverse events of systemic corticosteroids are taken into account. Besides EE is a relapsing disease and chronic or repeated treatment should be considered.

Oral cromolyn has been tried in occasional patients who responded.

Montelucast, a selective leucotriene antagonist, has been given in 8 adults with EE. Symptomatic improvement was observed in 7 patients with doses up to 100mg daily, depending upon symptoms. Most patients continued the medication for a median of 14 months. Side effects like nausea and myalgia were noted.[28] The overall safety of high doses used remains questionable.

Mepolizumab, a humanized monoclonal antibody against IL-5, was given in 4 patients with a variety of hypereosinophilic syndromes, one of which had EE. Treatment resulted in 10-fold reduction of tissue eosinophil levels.[29]

Probiotics have not been tried yet in patients with EE. They will likely be used in the future for the treatment and prevention of gastrointestinal food allergy[14] and may play a role in EE as well.

For patients with strictures or rings unresponsive to medical treatment, in whom dysphagia persists, endoscopic dilatation should be performed. This involves high risk and should be done cautiously since it has been associated with deep mucosal tears and esophageal perforation.[30] Tears and perforation can occur without resistance, so the esophagus should be inspected after passing each dilator.

In summary, both diet and corticosteroids are helpful to induce remission in patients with EE. More studies, especially in adults, are needed to determine the long term management and the best treatment strategy.

REFERENCES

1. Markowitz JE, Liakouras CA. Eosinophilic esophagitis. Gastroenterol Clin N Am 2003; 32: 949-966.
2. Bock SA, Lee WY, Remigio LK, et al. Studies of hypersensitivity reactions to foods in infants and children. J Allergy Clin Immunol 1978; 62:327-334.
3. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol 2002; 109:363-368.
4. Elitsur Y. Eosinophilic esophagitis-is it in the air? J Pediatr Gastroenterol Nutr 2002; 34:325-326.
5. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. N Engl J Med 2004; 351 :940-941.
6. Schmid-Grendelmeier P, Altznauer F, Fischer, et al. Eosinophils express functional IL-13 in eosinophilic inflammatory diseases. J Immunol 2002; 169:1021-1027.
7. Steiner SJ, Gupta SK, Croffie JM, et al. Correlation between number of eosinophils andreflux index on same day esophageal biopsy and 24 hour esophageal pH monitoring. Am J Gastroenterol 2004; 99:801-805.
8. Fox VL, Nurko S, Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. Gastrointest Endosc 2002; 56:260-270.
9. Nurko S, Fox V, Fortunato C, et al. Esophageal motor abnormalities in patients with allergic esophagitis. A study with prolonged esophageal pH/manometry [abstract]. J Pediatr Gastroenterol Nutr 2001; 33:417.
10. Fox V, Nurko S, Teitelbaum J, et al. Abnormalities of the esophageal wall detected by high-resolution probe endosonography in patients with allergic esophagitis [abstract]. J Pediatr Gastroenterol Nutr 2000; 31:S285.
11. Desai T, Goldstein N, Stecevic V, et al. Esophageal eosinophilia is common among adults with esophageal food impaction [abstract]. Gastroenterology 2002; 122:M1723.
12. Desai T, Stecevic V, Chang CH, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. Gastrointest Endosc 2005; 61:795-801.
13. Orenstein S, Shalaby T, Lorenzo CD, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. Am J Gastroenterol 2000; 95:1422-1430.
14. Bischoff S, Crowe SE. Gastrointestinal food allergy: new insights into pathophysiology and clinical perspectives. Gastroenterology 2005; 128:1089-1113.
15. Siafakas C, Ryan C, Brown M, et al. Multiple esophageal rings : an association with eosinophilic esophagitis. Case report and review of the literature. Am J Gastroenterol 2000; 95:1572-1575.
16. Vasilopoulos S, Murphy P, Auerbach A, et al. The small-caliber esophagus : an unappreciated cause of dysphagia for solids in patients with eosinophilic esophagitis. Gastrointest Endosc 2002; 55:99-106.
17. Lim J, Gupta S, Fitzgerald J, et al. White specks in esophageal mucosa (WSEM): a true endoscopic manifestation of severe eosinophilic esophagitis (EE) in children [abstract]. J Pediatr Gastroenterol Nutr 2001; 33:411.
18. Liacouras C. Eosinophilic esophagitis: a subset of eosinophilic gastroenteritis. Curr Gastroenterol Rep 1999; 1:253-258.
19. Ruchelli E, Wenner W, Voytek T, et al. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. Pediatr Dev Pathol 1999;

2:15-18.
20. Liacouras CA, Wenner WJ. The quantity of esophageal eosinophils, not the location, is diagnostic of eosinophilic esophagitis in children [abstract]. Gastrointest Endosc 2000; 51:AB133.
21. Sanjeevi A, Komorowski RA, Shaker S et al. Eosinophilic esophagitis: Potential sources for diagnostic error in the histopathologic detection. Gastroenterology 2005; 128:41.
22. Gonsalves N, Policarpio-Nicolas M, Zhang Q et al. Histopathologic variability in eosinophil concentrations in eosinophilic esophagitis necessitates multiple biopsy sampling. Gastroenterology 2005; 128:40.
23. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patient for up to 11.5 years. Gastroenterology 2003; 125:1660-1669.
24. Liacouras CA. Failed Nissen fundoplication in two patients who had persistent vomiting and eosinophilic esophagitis. J Pediatr Surg 1997; 32:1504-1506.
25. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterol 1995; 109:1503-1512.
26. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol 2003; 98:777-782.
27. Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. J Pediatr Gastroenterol Nutr 1998; 26:380-385.
28. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. Mayo Clin Proc 2003; 78:830-835.
29. Gupta SK, Fitzgeralg JF, Davis MM. Treatment of allergic eosinophilic esophagitis with oral prednisolone and swallowed fluticasone: a randomized prospective study in children [abstract]. Gastroenterology 2003; Abstract ID101884.
30. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic esophagitis: a novel treatment using Montelukast. Gut 2003; 52:181-185.
31. Garrett JK, Jameson SC, Thompson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. J Allergy Clin Immunol 2004 ; 113 :115-119.
32. Kaplan M, Mutlu EA, Jakate S, et al. Endoscopy in eosinophilic esophagitis : feline esophagus and perforation risk. Clin Gastroenterol Hepatol 2003; 1:433-437.