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Pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis

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Disclosures

INTRODUCTION — Esophageal eosinophils were once considered to be a hallmark of gastroesophageal reflux disease [1]. However, it has become apparent that the esophagus, which is normally devoid of eosinophils, is an immunologically active organ that is capable of recruiting eosinophils in response to a variety of stimuli [2,3].

Esophageal eosinophilia has been described in association with eosinophilic gastroenteritis, an uncommon condition that can cause a range of symptoms, including malabsorption, dysmotility, and ascites, depending upon the layer of the intestinal tract that is involved [4,5]. When the gastrointestinal eosinophilia is limited to the esophagus, is accompanied by characteristic symptoms, and other causes of eosinophilia have been ruled out, it is termed eosinophilic esophagitis. In the past, eosinophilic esophagitis was abbreviated as "EE" but, because of confusion with erosive esophagitis, many prefer the abbreviation "EoE".

A panel of experts defined eosinophilic esophagitis as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" [6]. It is important to differentiate between eosinophilic esophagitis, which is a clinicopathologic diagnosis, and esophageal eosinophilia in the absence of characteristic symptoms, which can be seen in association with multiple conditions. (See 'Differential diagnosis' below.)

This topic will review the pathogenesis, clinical manifestations, and diagnosis of eosinophilic esophagitis in adults and children. Eosinophilic gastroenteritis, other diseases with eosinophilic involvement of specific organs, and the treatment of eosinophilic esophagitis are discussed separately. (See "Eosinophilic gastroenteritis" and "Diseases with eosinophilic involvement of specific organs" and "Treatment of eosinophilic esophagitis".)

EPIDEMIOLOGY — Eosinophilic esophagitis has been reported in several countries in North and South America, Europe, Asia, and Australia, but there have been no published reports from countries in Africa. A study of a pathology database from the United States found that the disease has been detected in most states that reported data [7]. The results of one survey suggested there may be regional variation, with a higher prevalence in northeastern states and lower prevalence in western states [8]. The diagnosis also appears to be more common in urban as opposed to rural settings. Prevalence within the United States may also differ between climate zones with a higher prevalence in cold and arid zones as compared with the tropical zones [9].

The first cases of probable eosinophilic esophagitis were reported in the late 1960s to 1970s [10-12]. Early reports (mostly from the 1990s) described patients with multiple esophageal rings, which were attributed to gastroesophageal reflux disease or a congenital origin [10,13-18]. The assumed association with gastroesophageal reflux disease (GERD) was based upon the observation that biopsies from patients with a ringed esophagus had basal zone hyperplasia, papillary lengthening, and intraepithelial eosinophils, findings that are seen in patients with documented reflux disease. However, careful review of these reports has raised questions about the association with GERD, since many of the patients did not respond to antisecretory therapy or have objective evidence of reflux on a 24-hour pH study [13,19]. In addition, esophageal dilation in some of these patients was associated with deep mucosal tears and esophageal perforation, complications also seen in patients with eosinophilic esophagitis who undergo dilation [14-16,18,20-24].

The incidence of eosinophilic esophagitis appears to be increasing [25-27]. Some of the increase may be due to increased recognition of the disorder, but increased recognition is unlikely to fully account for the rising incidence.

One reason that increased recognition is unlikely to be the sole explanation is that gastrointestinal barium radiography has been practiced for many decades and it is likely that the characteristic ringed pattern in the esophagus would have been described earlier. While studies evaluating the prevalence of eosinophilic esophagitis in biopsy samples from patients undergoing endoscopy have not detected an increase since at least the late 1980s [28,29], population-based studies have supported an increasing incidence:

- A population-based study evaluated the incidence of eosinophilic esophagitis in Olmsted County Minnesota over thirty years [30]. The incidence increased significantly during the last three of the five-year intervals examined (from 0.35 per 100,000 population between 1991 and 1995 to 9.45 per 100,000 between 2001 and 2005). The prevalence was estimated to be 55 per 100,000 in 2006.

- Two population-based studies from Switzerland concluded that the incidence of eosinophilic esophagitis was increasing and, in one study, the incidence was approaching that of inflammatory bowel disease [26,31].

- A population-based study in children focused on 103 patients who had been identified from a single institution's pathology database in Hamilton County, Ohio [25]. The overall incidence per 10,000 population was estimated to be 1.28 in 2003, an increase from 0.91 in 2000. The authors noted that the most recent incidence rates exceed those of inflammatory bowel disease in children.

The majority of affected adults have been men in their 20s or 30s, although later presentations have been described [20,32]. In a series of 31 adults (24 men and 7 women), the mean age at diagnosis was 34 years (range 14 to 77 years) [32]. Symptoms (predominantly dysphagia) had been present for an average of 4.5 years prior to diagnosis. The male predominance may be related to variations in a gene located on the X-chromosome that have been associated with eosinophilic esophagitis. (See 'Pathogenesis' below.)

Among children, the disease is also more common in boys (71 percent in the series described above) [25]. In another population-based study, children with eosinophilic esophagitis were significantly more likely to be Caucasian (84 percent compared with 73 percent of the surrounding community as a whole) [33]. Patients were also more likely to be male (76 versus 48 percent).

PATHOGENESIS — The pathogenesis of eosinophilic esophagitis is incompletely understood but includes environmental and genetic factors. Adaptive T-cell immunity driven by type 2 T-helper (Th2) cells, involving interleukin (IL)-13, IL-5, and IL-15 expression appears to play a major role in the pathogenesis of eosinophilic esophagitis [34-39]. (See "T helper subsets: Differentiation and role in disease".)

Eosinophils establish themselves as permanent residents of the gastrointestinal tract early during embryonic development, although they are not normally found in the esophagus. The process is regulated in part by the peptide eotaxin [40], which has a central role in antigen-mediated eosinophil recruitment [41]. The recruitment of eosinophils is observed in a variety of inflammatory or infectious conditions such as inflammatory bowel disease, gastroesophageal reflux, and exposure to food allergens [42-44]. Pathogenetic factors that distinguish eosinophilic esophagitis from other causes of esophageal eosinophilia are not yet certain but some studies suggest variations in molecular signatures. (See 'Distinction from GERD' below.)

Environmental factors and T-cell immunity — Many patients with eosinophilic esophagitis have a history of allergies and peripheral eosinophilia (see 'Associations with other disorders' below) [5,45-48].

The association of eosinophilic esophagitis with allergies suggests that eosinophil recruitment to the esophagus may be an immune response to environmental antigens in genetically predisposed individuals. This hypothesis is supported by a few observations. First, feeding children with eosinophilic esophagitis an elemental diet (thus avoiding food allergens) results in clinical and histologic improvement [49]. Second, a group has demonstrated that priming with epicutaneous exposure to antigens can result in esophageal eosinophil recruitment in a mouse model [50]. Finally, there is seasonal variation in presentation, with fewer cases being diagnosed in the winter months (when outdoor aeroallergens are relatively low) [30,51,52].

The immune response involves numerous cytokines, some of which have been implicated in the pathogenesis of eosinophilic esophagitis. Once in the esophagus, eosinophils appear capable of persistence through release of known eosinophil chemoattractants such as eotaxin, IL-3, IL-5, and granulocyte macrophage-colony stimulating factor (GM-CSF) [53]. The recognition of key modulators of eosinophil recruitment and function has important

clinical implications. In addition to being potential targets for drug development, they may also have a role in the diagnosis and monitoring of the disease [54]. (See "Role of cytokines in the immune system".)

Studies of cytokines in eosinophilic esophagitis have shown the following:

- IL-5 and eotaxin – A murine model of eosinophilic esophagitis provided evidence that eotaxin and IL-5 play important roles in the pathogenesis of esophageal eosinophilia [55]. In the absence of eotaxin, eosinophil recruitment was attenuated, and in the absence of IL-5 it was ablated. Furthermore, mice engineered to be deficient in IL-5 were resistant to esophagitis [56]. IL-5 appears to mediate eosinophil induced esophageal remodeling and collagen deposition [57]. Other studies have demonstrated that the immunologic changes responsible for eosinophil recruitment in affected patients appear to be confined to the esophagus [38] and are driven mainly by an IL-5 selective Th2 response [58].

  In another report, patients with eosinophilic esophagitis had a striking increase in expression of eotaxin-3 (also known as CCL26) and mice that were deficient in the eotaxin-3 receptor were protected from experimental eosinophilic esophagitis [59]. In addition, another study demonstrated that treatment with topical glucocorticoids in patients with eosinophilic esophagitis down-regulated esophageal eotaxin-3 levels (as well as other cytokines implicated in eosinophilic esophagitis) [60].

- IL-13 – Intratracheal delivery of IL-13 induces esophageal eosinophilic inflammation by mechanisms that are dependent upon IL-5, eotaxin, and STAT6 (a signal transducer and activator of transcription) [61]. In addition, keratinocyte stimulation with IL-13 results in eotaxin-3 expression, a process that is reversible with glucocorticoids [62].

- IL-15 – IL-15 activates T cells to produce cytokines that act on eosinophils. In a study of patients with eosinophilic esophagitis, IL-15 levels were increased sixfold in tissue samples and twofold in serum compared with controls [37].

- Fibroblast growth factor 9 – Increased expression of fibroblast growth factor 9 (FGF9) and other profibrogenic cytokine genes (IL-5 and CCL18) in the subepithelial layer of the esophagus has been noted in eosinophilic esophagitis, suggesting that they may have a role in the fibrogenic response [63,64]. Prolonged treatment with fluticasone propionate has been associated with a downregulation of profibrogenic cytokine gene expression [64].

Once in the esophagus, eosinophils may cause local inflammation by release of eosinophil major basic protein, a cytotoxic cationic protein [65]. The ongoing inflammatory response may be responsible for the development of dysphagia. A preliminary study suggested that the presence of intraepithelial eosinophils in the esophagus was associated with dysphagia, independent of the caliber of the esophageal lumen or the presence of a mechanical narrowing [66]. By contrast, dysphagia was associated with decreased esophageal distensibility that was not predicted by the eosinophil count in another report [67].

Genetic factors — A genetic predisposition to eosinophilic esophagitis is supported by evidence of familial clustering. In addition, a possible susceptibility locus has been identified on chromosome 5q22 [68].

A family history of eosinophilic esophagitis has been noted in some patients [25,26,69-71]:

- In a study of 103 children with eosinophilic esophagitis, a positive family history was observed in 7 percent [25]. This included three sibling pairs and the mother of one of the pairs of siblings. In addition, a family history of atopic disease was seen in 74 percent. (See 'Associations with other disorders' below.)

- A case report documented three brothers with eosinophilic esophagitis [69], while another documented an affected father and daughter [70].

- Another report described 17 patients from seven families who had dysphagia and eosinophilia, although not all had eosinophilic esophagitis (some had Schatzki's ring while others had eosinophilic gastroenteritis) [71].

Clinical and pathological characteristics of patients with a familial form of eosinophilic esophagitis are similar to those with sporadic disease [72].

Genetic defects that may predispose to eosinophilic esophagitis have been identified. One study detected an eosinophilic esophagitis gene cluster that included a defect in filaggrin, a barrier protective molecule typically found in the skin [35]. Another genome wide study of children found an association of eosinophilic esophagitis with defects in thymic stromal lymphopoietin (TSLP, a cytokine involved in Th2 cell determination) [68]. Finally, a genetic variant of the TSLP receptor, which is encoded on a pseudoautosomal region of the X-chromosome, has been associated with eosinophilic esophagitis in male (but not female) patients [73].

CLINICAL MANIFESTATIONS — The clinical manifestations of eosinophilic esophagitis vary with age. Adults and teenagers frequently present with dysphagia and food impactions, whereas in younger children symptoms often include feeding difficulties and abdominal pain.

Clinical manifestations in adults — Common clinical manifestations seen in adults include [7,20,24,30,74-98]:

- Dysphagia
- Food impaction
- Chest pain that is often centrally located and does not respond to antacids
- Gastroesophageal reflux disease-like symptoms/refractory heartburn
- Upper abdominal pain

Dysphagia to solid foods is the most common symptom [7,74-78]. Up to 15 percent of patients being evaluated for dysphagia with endoscopy are found to have eosinophilic esophagitis [76,78,99]. A history of food impaction is present in up to 54 percent of patients [24,79,80] and esophageal strictures have been noted in up to 31 percent of patients [30,81-86]. In one community-based series, 17 of 31 patients presenting with food impaction over a three-year period were diagnosed with eosinophilic esophagitis [79].

Esophageal dysmotility may also be observed, suggesting possible involvement of the muscular layers of the esophagus [87-89,100]. High resolution endoscopic ultrasonography in affected children and adults has shown expansion of the esophageal wall and all individual tissue layers [90-92].

Eosinophilic esophagitis has been noted in 1 to 4 percent of patients with refractory reflux in prospective studies [77,101]. However, cost-effectiveness models suggest that evaluating for eosinophilic esophagitis in patients with refractory reflux is only cost-effective when the prevalence of eosinophilic esophagitis is greater than 8 percent [102].

Finally, spontaneous esophageal perforation (Boerhaave's syndrome), esophageal perforation following endoscopy, and mucosal tears associated with endoscopy have been reported [20,23,24,93-95]. (See "Boerhaave's syndrome: Effort rupture of the esophagus" and "Complications of endoscopic esophageal stricture dilation", section on 'Risk factors'.)

Clinical manifestations in children — Symptoms in children vary depending in part upon their age [25,103-106]. In one series, the most common presenting symptoms included [25]:

- Feeding dysfunction (median age 2.0 years)
- Vomiting (median age 8.1 years)
- Abdominal pain (median age 12.0 years)
- Dysphagia (median age 13.4 years)
- Food impaction (median age 16.8 years)

The possibility of disease progression was supported in a case-control study that suggested an increased rate of dysphagia (49 versus 6 percent) and food impaction (40 versus 3 percent) in children with esophageal eosinophilia who had been followed for an average of 15 years [107].

Feeding dysfunction continues to be defined, but is an increasingly recognized presentation of eosinophilic esophagitis [108]. It includes failure to develop normal eating patterns (eg, not advancing past liquids) and adopting coping strategies (eg, refusing to eat solids after previously eating them).

Similar findings were described in a single center report involving a total of 381 children. The mean age was 9 years and 66 percent were male. Patients most commonly presented with symptoms suggestive of gastroesophageal reflux (85 percent) or dysphagia (18 percent) [104]. The esophageal mucosa was abnormal by endoscopy in 68 percent, whereas in 32 percent it appeared normal despite severe histologic eosinophilia.

ASSOCIATIONS WITH OTHER DISORDERS — There is a strong association of eosinophilic esophagitis with allergic conditions such as food allergies, environmental allergies, asthma, and atopic dermatitis. It has been estimated that 28 to 86 percent of adults and 42 to 93 percent of children with eosinophilic esophagitis have another allergic disease [25,30,48,52,109-114]:

- In one series, 10 of 13 patients (77 percent) had a history of an allergic disorder defined as asthma, allergic rhinitis, urticaria, hay fever, atopic dermatitis, food allergy, or medicine allergy, and/or positive radioallergosorbent test (RAST) or positive allergic skin tests [110]. Twelve of 13 patients (92 percent) had an absolute peripheral eosinophilia and 9 of 12 patients (75 percent) had concurrent eosinophilic gastroenteritis.

- In another report, 13 of 19 children (68 percent) had positive skin or RAST testing to a median of seven foods [109].

- In a third series, 18 of 23 adults (78 percent) had an atopic diathesis (most commonly allergic rhinitis) [48]. Most patients were sensitized to several environmental allergens. Among the foods tested, allergies to wheat, tomato, carrot, and onion were the most common.

An association with celiac disease (and response to a gluten free diet) was described in a case series [115]. In addition, an association with Schatzki ring has also been described [116], although the strength of the association is unclear [117,118].

DIAGNOSIS — The diagnosis of eosinophilic esophagitis should be based upon symptoms, endoscopic appearance, and histological findings. In patients suspected of having eosinophilic esophagitis, the first diagnostic test is typically an upper endoscopy with esophageal biopsies following one to two months of treatment with a proton pump inhibitor, though radiographic and laboratory findings may support the diagnosis. In addition, other disorders that can cause esophageal eosinophilia, such as gastroesophageal reflux disease (GERD), should be ruled out. (See 'Differential diagnosis' below.)

Endoscopy — A variety of morphologic features in the esophagus have been described in patients with eosinophilic esophagitis [4,21,32,45,110,119-125]. A 2012 meta-analysis that compared 4678 patients with eosinophilic esophagitis and 2742 controls estimated the frequency of the following endoscopic features [126]:

- Stacked circular rings ("feline" esophagus) (picture 1): 44 percent

- Strictures (particularly proximal strictures) (picture 2): 21 percent

- Attenuation of the subepithelial vascular pattern: 41 percent

- Linear furrows (picture 3): 48 percent

- Whitish papules (representing eosinophil microabscesses) (picture 1): 27 percent

- Small caliber esophagus: 9 percent

Individual endoscopic features suggestive of eosinophilic esophagitis had low sensitivity ranging from 15 to 48 percent but high specificity ranging from 90 to 95 percent. Positive and negative predictive values ranged from 51 to 73 percent and 74 to 83 percent, respectively. Given the low sensitivity of endoscopic findings for eosinophilic esophagitis and variable positive predictive value, histology remains important in making a diagnosis of eosinophilic esophagitis, regardless of the endoscopic appearance (see 'Histology' below).

Complications associated with endoscopy in patients with eosinophilic esophagitis (even in the absence of esophageal dilation) include esophageal perforation and mucosal tears [23,93-95].

Histology — Esophageal biopsies from patients with eosinophilic esophagitis show an increased number of eosinophils. The vast majority of patients have at least 15 eosinophils per high power field (peak value) in at least one biopsy specimen after taking a proton pump inhibitor [127]. Esophageal eosinophilia in the absence of clinical features is not sufficient to make a diagnosis of eosinophilic esophagitis.

During endoscopy biopsies should be obtained from the distal esophagus as well as either the mid or proximal

esophagus [128]. The sensitivity of biopsies for diagnosing eosinophilic esophagitis depends upon the number of biopsies obtained:

- In a report of 66 adults, the sensitivity was 100 percent after obtaining five biopsies compared with 55 percent with one biopsy [81].

- A second study found that the sensitivities for two, three, and six biopsies were 84, 97, and 100 percent, respectively [129].

We suggest that, at a minimum, two to four biopsies be obtained from the distal esophagus, as well as another two to four from the mid or proximal esophagus.

Biopsy specimens should be fixed in formalin or paraformaldehyde rather than Bouin's fixative since formalin is more effective at preserving the integrity of eosinophils. Immunohistochemical studies have demonstrated that the number of eosinophils and amount of degranulation are underestimated by standard (hematoxylin and eosin) staining, although the clinical relevance for making a diagnosis is unclear [130].

As noted above, a threshold of 15 eosinophils per high power (400x) field (HPF) is generally required for the diagnosis (picture 4) [131]. Biopsies should be obtained after one to two months of treatment with a proton pump inhibitor or a negative pH study. Acid suppression is critical since a subset of patients with large numbers of eosinophils may achieve complete histological resolution after treatment with a proton pump inhibitor [132-134].

Other histologic findings suggestive of eosinophilic esophagitis include [5,21,131,135-143]:

- Eosinophil microabscesses

- Superficial layering of eosinophils

- Sheets of eosinophils

- Extracellular eosinophil granules

- Subepithelial and lamina propria fibrosis and inflammation

- Basal cell hyperplasia

- Papillary lengthening

- Increased numbers of mast cells, B cells, and IgE bearing cells

While some studies suggest that histologic findings correlate with symptom severity [7,144-146], others do not [76,83,103,147].

Adults with symptoms suggestive of eosinophilic gastroenteritis (eg, abdominal pain, nausea, vomiting, diarrhea, ascites), as well as all children, should also have gastric and duodenal mucosal biopsies obtained, since the approach to patients with eosinophilic gastroenteritis varies from that for patients with eosinophilic esophagitis. However, at least one report found that a subset of patients has incidental gastric eosinophils, but a similar clinical presentation and response to treatment as patients without gastric involvement [148]. (See "Eosinophilic gastroenteritis".)

Radiology — Barium studies are not sensitive for diagnosing eosinophilic esophagitis, but can help characterize anatomic abnormalities and provide information on the length and diameter of strictures [149]. Findings described in patients with eosinophilic esophagitis undergoing barium studies include strictures and a ringed esophagus (picture 5) [125]. In addition, other causes for symptoms can be ruled out (ie, malrotation) as a cause for vomiting.

Laboratory tests — There are no diagnostic serum markers for eosinophilic esophagitis. However, 50 to 60 percent of patients with eosinophilic esophagitis will have elevated serum IgE levels (>114,000 units/L) [48,113]. Peripheral eosinophilia is seen in 40 to 50 percent of patients but is generally mild [82,105,150,151]. It decreases with topical glucocorticoid therapy [152].

Evaluation for allergies — Because of the strong association of eosinophilic esophagitis with allergies, we

suggest that patients with eosinophilic esophagitis undergo evaluation by an allergist or immunologist. Children are often treated with dietary therapy and uncontrolled data suggest that the information gained from allergy testing may help guide therapy. In addition, dietary therapy is sometimes used in the treatment of motivated adults. Allergy testing may also help with the management of concomitant atopic disease, which is common in patients with eosinophilic esophagitis. (See "Treatment of eosinophilic esophagitis", section on 'Dietary therapy' and "Overview of skin testing for allergic disease" and "Diagnostic evaluation of food allergy".)

Therapeutic trial — Patients with eosinophilic esophagitis should improve with appropriate therapy. (See "Treatment of eosinophilic esophagitis".)

Other diagnostic tests — Other diagnostic tests that have been evaluated but that are not routinely used include endoscopic ultrasound [153,154], impedance planimetry to measure esophageal pressures [67,155], esophageal manometry [89,156,157], and endoscopic confocal laser microscopy [158].

Findings on standard esophageal manometry in patients with eosinophilic esophagitis are nonspecific.

DIFFERENTIAL DIAGNOSIS — The differential diagnosis includes a variety of conditions that can cause morphologic or histologic findings that resemble eosinophilic esophagitis. These include gastroesophageal reflux disease (GERD), recurrent vomiting due to other causes, parasitic and fungal infections, congenital rings, Crohn's disease, periarteritis, allergic vasculitis, drug injury, connective tissue diseases, bullous pemphigoid, pemphigoid vegetans, graft versus host disease, achalasia, drug hypersensitivity, celiac disease, vasculitis, carcinoma, and a number of causes of peripheral eosinophilia in which the esophagus (along with other organ systems) may become involved. (See "Diseases with eosinophilic involvement of specific organs".)

There are occasional patients who have characteristic findings of esophageal rings but do not have esophageal eosinophilia. In addition to considering the diagnoses above, it is important to ensure that adequate biopsies were obtained. In our clinical experience, some of these patients have responded to dietary elimination therapy used to treat eosinophilic esophagitis. Whether such patients have eosinophilia in deeper layers of the esophagus not sampled by standard biopsies is unknown.

Distinction from GERD — The most common consideration in the differential diagnosis of eosinophilic esophagitis is GERD. As noted above, large numbers of eosinophils (>100/HPF) may be seen in association with GERD. (See 'Histology' above.)

Case reports have described children with a dense eosinophilic infiltrate that resolved after treatment with a PPI alone [159], suggesting that the histologic findings may have been due to GERD:

- In a series of 36 children with ≥15 eosinophils/HPF, 14 (39 percent) responded histologically to high-dose PPIs alone [136].

- In a study of 712 patients with upper gastrointestinal symptoms undergoing endoscopy, 35 (5 percent) had ≥15 eosinophils/HPF on biopsies obtained from the upper-middle esophagus [160]. Twenty-six patients (75 percent) had a clinicopathologic remission on treatment with a PPI, including half of the patients with a typical eosinophilic esophagitis phenotype. Based upon these findings, the authors concluded that using histologic criteria alone to diagnose eosinophilic esophagitis may lead to an overestimation of the prevalence of the disorder.

Because of the association of GERD with esophageal eosinophilia, biopsies for eosinophilic esophagitis should be obtained after one to two months of treatment with a PPI or after an esophageal pH study has excluded reflux. In one study, 712 patients who were not on PPIs and were undergoing upper endoscopy for upper GI symptoms were examined [160]. Thirty-five (5 percent) had ≥15 eosinophils/HPF on initial examination. However, after treatment with a PPI, only 9 of the 35 (26 percent) met diagnostic criteria for eosinophilic esophagitis.

A number of clinical and histologic features have been identified that may help distinguish eosinophilic esophagitis from GERD. Clinically, patients with eosinophilic esophagitis are more likely to be male and younger than 45 years of age. They are more likely to have dysphagia, esophageal morphological abnormalities (such as rings, furrows, or exudates), and food allergies, and are less likely to have a hiatal hernia or heartburn [82,161].

Histologic features suggestive of eosinophilic esophagitis rather than GERD include:

- Large numbers of intraepithelial eosinophils on histologic examination [139,161-163]. In two reports, the presence of more than 20 eosinophils/HPF was typically associated with non-acid-related causes of esophagitis [163] and patients with eosinophilic esophagitis had significantly more eosinophils than patients who responded to therapy for GERD (28 to 31 versus 5 per HPF overall, and 19 to 32 versus 1 per HPF with biopsies from the proximal esophagus) [162]. Patients with eosinophilic esophagitis are also more likely to have ≥15 eosinophils/HPF in three or more biopsies taken at different levels [136].

- Other histologic findings favoring eosinophilic esophagitis include proximal esophageal involvement, subepithelial and lamina propria fibrosis [138], eosinophilic abscesses [105,161], more severe basal cell hyperplasia [164], activated mucosal mast cells/increased epithelial tryptase density [140,143,165,166], and degranulating eosinophils [82].

- Assessment of eotaxin-3 and major basic protein (MBP) levels in esophageal biopsy specimens (by immunohistochemistry or real-time PCR) has been suggested to help differentiate GERD from eosinophilic esophagitis, but further studies are needed [139,167,168]. (See 'Environmental factors and T-cell immunity' above.)

Proton pump inhibitor-responsive esophageal eosinophilia — Increasingly, it is being recognized that there is a group of patients who have typical symptoms of eosinophilic esophagitis and have had GERD diagnostically excluded, but who have a clinical and histologic response to proton pump inhibitors [136,144,169-172]. The mechanisms involved in such a response are not well understood.

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- Basics topics (see "Patient information: Upper endoscopy (The Basics)" and "Patient information: Eosinophilic esophagitis (The Basics)")

- Beyond the Basics topic (see "Patient information: Upper endoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Eosinophilic esophagitis should be considered in adults with a history of food impaction, with persistent dysphagia, or with gastroesophageal reflux disease (GERD) that fails to respond to medical therapy. In children, symptoms that may be associated with eosinophilic esophagitis vary by age and include feeding disorders, vomiting, abdominal pain, dysphagia, and food impaction. (See 'Clinical manifestations' above.)

   In particular, the diagnosis should be considered in young men or boys, and in those with a history of food or environmental allergies, asthma, or atopy. A history of esophageal perforation or severe pain after dilation of a stricture should also raise suspicion of this disorder.

- Making a diagnosis of eosinophilic esophagitis requires the presence of both symptoms and histologic findings. In addition, other disorders that can cause esophageal eosinophilia, such as GERD, should be ruled out. (See 'Differential diagnosis' above.)

- In patients suspected of having eosinophilic esophagitis, the first diagnostic test is typically an upper endoscopy with esophageal biopsies, though radiographic and laboratory findings may support the

diagnosis. We suggest that, at a minimum, two to four biopsies be obtained from the distal esophagus, as well as another two to four from the mid or proximal esophagus. (See 'Diagnosis' above.)

- A variety of morphologic features in the esophagus have been described in patients with eosinophilic esophagitis. Endoscopic findings include:

  - Stacked circular rings ("feline" esophagus) (picture 1)
  - Strictures (particularly proximal strictures) (picture 2)
  - Attenuation of the subepithelial vascular pattern
  - Linear furrowing that may extend the entire length of the esophagus (picture 3)
  - Whitish papules (representing eosinophil microabscesses) (picture 1)
  - Small caliber esophagus

- Histologic findings suggestive of eosinophilic esophagitis include:

  - Peak eosinophil count of ≥15 eosinophils per high powered (400x) field (picture 4) despite acid suppression with a PPI for one to two months or a negative pH study
  - Eosinophil microabscesses
  - Superficial layering of eosinophils
  - Sheets of eosinophils
  - Extracellular eosinophil granules
  - Subepithelial and lamina propria fibrosis and inflammation
  - Basal cell hyperplasia
  - Papillary lengthening

- Because of the strong association of eosinophilic esophagitis with allergies, we suggest that patients with eosinophilic esophagitis undergo evaluation by an allergist or immunologist. In children the results of the evaluation may have treatment implications (eg, elimination diets) though in adults the results usually do not influence the initial treatment decisions. (See "Overview of skin testing for allergic disease" and "Diagnostic evaluation of food allergy" and "Treatment of eosinophilic esophagitis", section on 'Elimination diets'.)

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GRAPHICS

Eosinophilic esophagitis
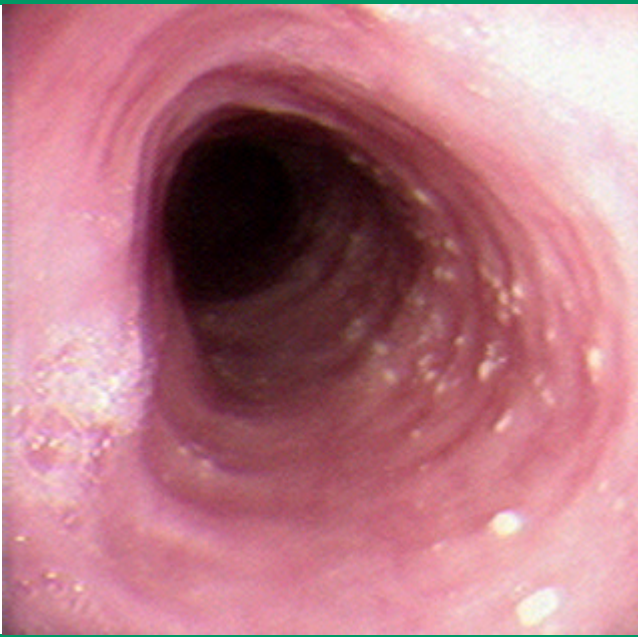
Upper endoscopy in a 36-year-old man with dysphagia. Multiple rings are present in the proximal to mid esophagus giving it the appearance of a trachea. Small whitish papules are also visible representing eosinophilic abscesses on histology. The patient's symptoms responded to oral fluticasone.
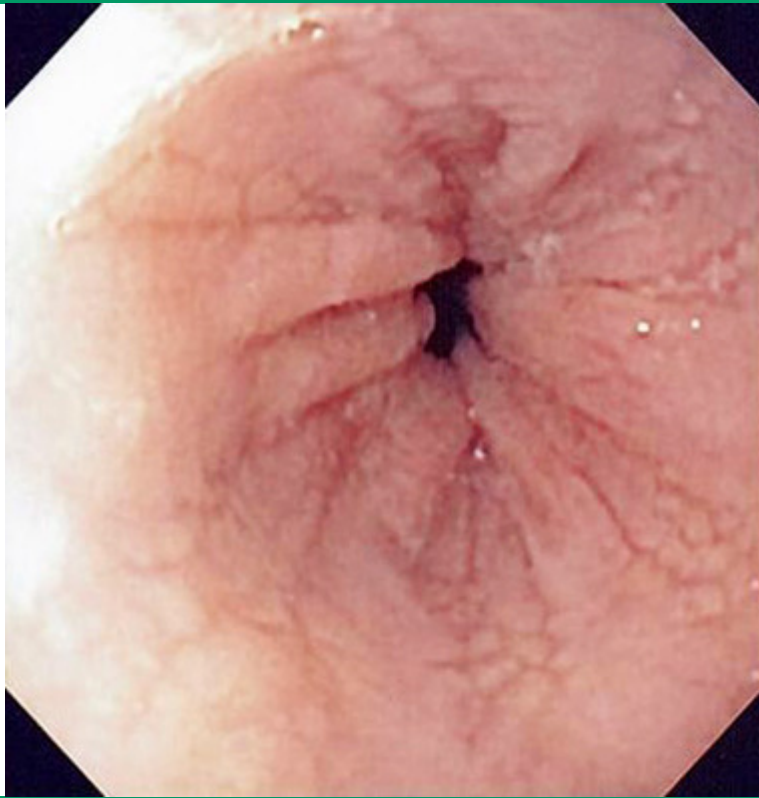*Courtesy of Eric D Libby, MD.*

Eosinophilic esophagitis
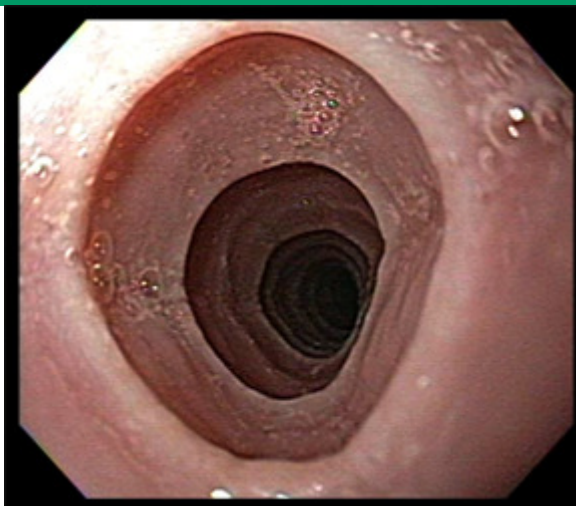
Endoscopic view of the proximal and mid esophagus showing
multiple ring-like structures.
*Courtesy of Andres Gelrud, MD and Anthony Lembo, MD.*

Eosinophilic esophagitis

A 14-month-old with failure to thrive and loose stools. Endoscopy demonstrates a thickened furrowed esophagus consistent with eosinophilic esophagitis. These patients commonly have dysphagia with, as well as without, evidence of stricture. Eosinophilic esophagitis is also a common cause of dysphagic in atopic school-aged children. Histology would demonstrate sheets of eosinophils in the lamina propria.
Courtesy of Karen Murray, MD.

Eosinophilic esophagitis
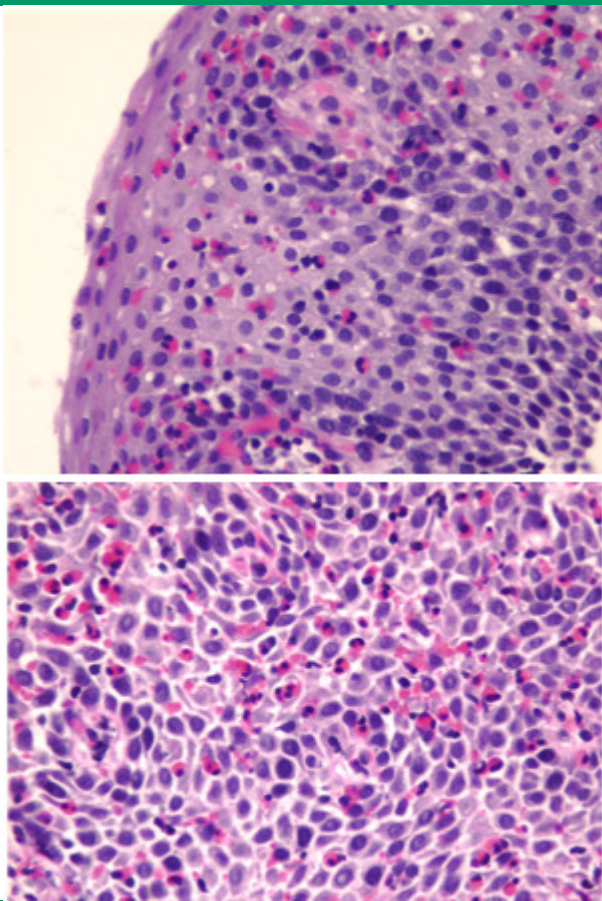
Esophageal biopsies from a patient with eosinophilic esophagitis. There is severe active esophagitis characterized by marked basal zone hyperplasia (top panel) and large numbers of eosinophils (greater than 40 per high power field, bottom panel). Biopsies obtained from the proximal, mid and distal esophagus showed similar findings. The long linear extent of the esophagitis plus the large numbers of eosinophils are characteristic pathologic features of eosinophilic esophagitis.
Courtesy of Maria Botero, MD and Donald Antonioli, MD.

Eosinophilic esophagitis

Barium swallow in a patient with eosinophilic esopahgitis showing mild segmental ring-like areas of narrowing in the proximal and mid esophagus representing "trachealization" of the esophagus.
Courtesy of Norman Joffe, MD.