A 52-year-old woman presented with dysphagia, which started when she was 30 years old. Initially, the dysphagia was intermittent but had progressed to daily occurrences during the past 2 years. She had progressively more difficulty in swallowing solids, but not liquids. The patient described a spasmlike sensation in her chest, which occurred as soon as she started eating; this had become more prominent during the past 6 months. Almost once a week, food would “get stuck” in her esophagus, and she had to regurgitate it to relieve the discomfort. Bread and meat were the usual offenders. The oropharyngeal swallowing mechanism was not compromised. The patient had “heartburn” every week for the past 2 years, which she described as a burning sensation radiating from the lower to the midsternal level; it was relieved with antacids. She denied aspiration, halitosis, a sensation radiating from the lower to the midsternal level; it was not compromised. The patient had “heartburn” every week for the past 2 years, which she described as a burning sensation radiating from the lower to the midsternal level; it was relieved with antacids.

Besides the dysphagia, the patient had experienced progressive dyspnea for 4 years, which had been attributed to asthma. The dyspnea was episodic and mostly exertional, but occasionally occurred at rest. There was no clear relationship to environmental allergen exposure. She denied seasonal or food allergies, hay fever, eczema, or dermatitis. The patient had a history of irregular heartbeats associated with benign premature ventricular contractions, but she denied exertional chest pain, diaphoresis, light-headedness, or syncope. Chronic medical issues included megaloblastic anemia due to vitamin B12 deficiency, obesity, hyperlipidemia, migraines, and depression. Surgical history was notable for tonsillectomy, appendectomy, and hysterectomy. She had had a 30-pack-year smoking history but had abstained for the past 8 years and had stopped drinking alcohol 20 years ago. Scheduled medications were nadolol, lovastatin, fluoxetine, and vitamin B12. Medications taken on an as-needed basis were butalbital-aspirin-caffeine, sumatriptan, and carisoprodol. 

On physical examination, the patient was obese (body mass index, 31.2 kg/m² [calculated as weight in kilograms divided by height in meters squared]). Vital signs were as follows: blood pressure, 105/67 mm Hg; heart rate, 63 beats/min; and respiratory rate, 18 breaths/min. Findings on cardiac, pulmonary, abdominal, and neurologic examinations were unremarkable. On the patient health questionnaire, she scored a 7 on a maximum of 27 points, suggesting mild depression.

1. Which one of the following is the best initial test to evaluate this patient’s dysphagia?
   a. Ambulatory pH monitoring
   b. Breath test for Helicobacter pylori
   c. Esophagogastroduodenoscopy (EGD)
   d. Barium swallow study
   e. Video swallow study

Ambulatory pH monitoring is not helpful in evaluating solid-food dysphagia. It can confirm gastroesophageal reflux disease (GERD) and monitor adequacy of treatment in patients with persistent symptoms despite treatment with acid-suppressing medications. Helicobacter pylori infection causes heartburn and peptic ulcer disease but does not explain the dysphagia. Esophagogastroduodenoscopy is useful for evaluating dysphagia and is the test of choice in this case because it visualizes the esophageal mucosa, allows evaluation of structural and anatomic defects, and obtains biopsy specimens if clinically indicated. However, subtle lesions such as a small ring or diverticulum may be missed. A barium swallow study might be useful to evaluate oropharyngeal dysphagia, esophageal dysmotility, and structural abnormalities that cause progressive solid-food and liquid-dysphagia. A video swallow study allows visualization of the swallowing mechanism, making it useful for evaluation of oropharyngeal dysphagia.

On EGD, mucosal changes were consistent with a ringed appearance and longitudinal furrowing. No hiatal hernia or reflux injury was evident at the gastroesophageal junction. The stomach, duodenal bulb, and postbulbar duodenum were normal.

2. On the basis of the symptoms and endoscopic findings, which one of the following is the most likely diagnosis?
   a. Pill-induced esophageal injury
   b. Esophageal carcinoma
   c. Eosinophilic esophagitis (EE)
   d. Barrett esophagitis
   e. Achalasia
The characteristic endoscopic appearance of pill-induced esophageal injury is 1 or more discrete ulcers that range from 1 mm to several centimeters, with a relatively normal surrounding mucosa.1 No ulcers were seen on endoscopy in our patient. There were no infiltrating, ulcerating, excavating, or fungating lesions suggestive of a malignancy. Our patient had longitudinal furrowing with a ringed appearance of the esophagus, which is suggestive of EE. Other endoscopic findings of EE include a diminished vascular pattern with mucosal shearing. The mucosa can be thickened yet friable with exudates, described as crêpe paper mucosa, and associated with specks, mucosal nodules, and granularity. In severe cases, mucosal rings and esophageal strictures can be present.2,3 In patients with EE, the esophagus can appear to be completely normal on endoscopy.2,3 None of these features are pathognomonic of EE; however, in the appropriate clinical context, the presence of more than 1 of these endoscopic findings is strongly suggestive of EE. The gastroesophageal junction was normal with no signs of ulceration or irregular mucosal margins suggestive of columnar lined esophagus4; thus, Barrett esophagitis is a less likely diagnosis. Endoscopic findings in patients with achalasia include a dilated esophagus that often contains residual food material.

During EGD, a diagnosis of EE was entertained.

3. Which one of the following would be the most helpful in diagnosing EE in our patient?
   a. Multiple esophageal biopsies
   b. White blood cell count with differential
   c. Serum IgE level
   d. Allergy testing
   e. Patient history and EGD appearance are adequate

Performing esophageal biopsy is the next step. The sensitivity of finding eosinophilic infiltration can be substantially increased by obtaining several biopsy specimens (at least 6) from the upper two-thirds of the esophagus and fixing the specimens in formalin or paraformaldehyde instead of Bouin fixative.5,6 Peripheral eosinophilia and elevated serum IgE levels are not helpful in the diagnosis of EE because they are insensitive and nonspecific.7 Although EE can be associated with atopic allergies, rhinitis, and asthma, formal allergy testing is not needed to establish the diagnosis. Patient history and EGD appearance are suggestive of but not enough to establish a diagnosis of EE.

Multiple biopsy specimens obtained from the upper two-thirds of the esophagus demonstrated hyperplastic squamous esophageal mucosa with greater than 35 intraepithelial eosinophils per high-power field (HPF).

4. Which of one the following is the next best step in management of this patient?
   a. Proton pump inhibitor (PPI)
   b. Swallowed aerosolized fluticasone
   c. Esophageal dilation
   d. Oral prednisone
   e. Anti-interleukin (IL) 5 antibody treatment

Treatment with a PPI is the next step because some patients have clinical and histologic resolution with PPI therapy alone.8 This suggests that GERD may be the underlying cause or exacerbating factor of EE.9,10 GERD may mimic, cause, coexist with, or be exacerbated by EE.11-13 High-dose swallowed aerosolized fluticasone is usually the first line of treatment of EE after a trial of PPI to exclude GERD. Esophageal dilation would not be recommended at this time because it is reserved for patients in whom swallowed fluticasone fails and who have persistent dysphagia that leads to weight loss or who present with food impaction. Oral prednisone is not recommended for mild disease but should be considered in patients with severe refractory disease unresponsive to esophageal dilation. Animal studies have demonstrated the role of IL-5 in the pathogenesis of EE; however, currently, clinical evidence is insufficient to recommend therapy with the humanized monoclonal antibody mepolizumab.14,15

We provided our patient with education on reflux disease. She had not been treated previously with a PPI. Therapy with omeprazole, twice-daily before meals, was initiated; the heartburn resolved completely, and the dysphagia improved substantially. In a 4-week period, the patient had just two 30-second episodes of “meat sticking.” She was able to eat an unlimited diet.

5. Which one of the following is true regarding the natural disease course of and risks associated with EE?
   a. Increased risk of esophageal carcinoma
   b. Increased risk of eosinophilic gastritis
   c. Increased risk of ulcerative colitis
   d. Increased risk of recurrent dysphagia
   e. Increased risk of esophageal Crohn disease

Data on the natural history of EE are scarce. It is not known to be associated with development of esophageal carcinoma, eosinophilic gastritis, ulcerative colitis, or Crohn disease. However, patients with EE are known to have recurrent episodes after treatment and can present with dysphagia, food impaction, or even esophageal strictures that require endoscopic treatment and esophageal dilation.7

At 8 weeks after initiation of oral PPI therapy, our patient reported no solid-food dysphagia and was eating an unlimited diet. We suspect that she has EE with GERD. Because her symptoms completely resolved with PPI therapy, EGD was not repeated and specific therapy for EE was not instituted.
Eosinophilic esophagitis is characterized by esophageal inflammation with prominent mucosal eosinophilia and epithelial proliferative changes. The epidemiology of EE has not been extensively studied. The first cases of EE were reported in the 1970s. About 70% of the adult patients are men. Eosinophilic esophagitis has been reported in all ethnicities and in all regions worldwide. The incidence of EE in Olmsted County, MN, increased from 0.86 cases per 100,000 population from 1976-1985 to 8.78 cases per 100,000 population from 1996-2006. The prevalence of EE was 104.7 cases per 100,000 population as of January 1, 2007, in Olmsted County.

The pathogenesis of EE has not been clearly defined. Eosinophils are recruited to the gastrointestinal tract early during embryonic development, although the esophagus is normally devoid of eosinophils. In patients with EE, IL-5 and eotaxin-3 mediate and regulate recruitment of eosinophils to the esophagus. The absence of eotaxin-3 or IL-5 in mice decreased the recruitment of eosinophils to the gut. Eosinophil recruitment in patients with EE may also be a response to environmental allergens. The different mechanisms for antigen sensitization in EE include exposure to intraesophageal and respiratory allergens. The development of EE appears to correlate with a Th2-type immune response and increased levels of Th2 cytokines, such as IL-4, IL-5, and IL-13. Mast cells have also been described in the pathogenesis of EE.

The diagnostic criteria for EE were reviewed at the First International Gastrointestinal Eosinophilic Research Symposium in 2006, and the consensus statement for the diagnosis of EE included the following: (1) symptoms including but not restricted to food impaction and dysphagia in adults, and feeding intolerance and GERD symptoms in children; (2) 15 or more eosinophils per HPF on esophageal biopsy specimen; and (3) exclusion of other disorders associated with similar clinical, histologic, or endoscopic features, especially GERD.

Endoscopy with biopsies is undoubtedly the initial diagnostic test when the clinical suspicion for EE is high. The major histopathologic diagnostic criterion for EE is increased intraepithelial eosinophils. Common methods used to count eosinophils include peak eosinophil count (the highest number of eosinophils within a HPF) or a mean number of eosinophils per HPF; counting eosinophils in several representative HPFs is another option. A peak count of 15 or more intraepithelial eosinophils per HPF is essential to diagnose EE in the presence of suggestive clinical symptoms. Some experts say that, to distinguish EE from eosinophilic gastroenteritis, mucosal biopsy specimens from the stomach and duodenum must be normal. However, stomach and duodenal biopsies are not needed in the usual patient presentation. Other histologic features include a thickened epithelium with basal zone hyperplasia, superficial layering of the eosinophils, and eosinophilic microabscesses. Eosinophilic microabscesses are defined as aggregates of 4 or more eosinophils in a cluster that occur in patients with EE but not in those with GERD. There can be associated inflammation and fibrosis of the lamina propria, papillary lengthening, and increased major basic protein. Apart from EE, other differential diagnoses for eosinophilic infiltration in the esophagus include GERD, Crohn disease, collagen vascular disease, infectious esophagitis (herpes, Candida), drug-associated esophagitis, hypereosinophilic syndrome, and eosinophilic gastroenteritis.

If the diagnosis of EE is not distinguishable from GERD on endoscopy and biopsy, further testing including intraesophageal pH monitoring may be useful in delineating acid reflux as a cause of esophageal eosinophilia. Intraesophageal pH testing has shown normal results in most patients. Also, expert opinion recommendations are that an upper endoscopy with biopsy should be repeated 4 to 8 weeks after high-dose PPI treatment to determine the etiology of esophageal eosinophilia.

Eosinophilic esophagitis is associated with diseases like allergic rhinitis, asthma, and atopic dermatitis; however, complete allergy testing is not helpful in establishing the diagnosis of EE. Systemic markers of an allergic response, including a peripheral eosinophil count and eosinophil granule proteins, serum IgE levels, aeroallergen-specific IgE, food-specific IgE, and peripheral cytokine levels, are insensitive and nonspecific for the diagnosis of EE. Serum eotaxin-3 levels have been shown to correlate with the diagnosis of EE. Additional tests including skin prick testing and atopy patch testing are useful in determining food that should be eliminated and then reintroduced in patients with EE. Details of an allergy evaluation are beyond the scope of this discussion.

The various treatment modalities for patients with EE consist of pharmacological, dietary, and endoscopic interventions, and these can be used either singly or in combination. Unfortunately, no evidence-based guidelines exist for the management of EE. Thus, the goals of treatment are unclear; whether resolution of symptoms alone is sufficient or whether resolution of the eosinophilic inflammation on histopathology is required. Treatment of EE could result in symptomatic improvement or complete resolution of mucosal inflammation. Because EE is a chronic and recurring inflammatory disorder associated with complications including esophageal strictures and esophageal motility disorders, a therapeutic goal of mucosal healing might be appropriate.

Both systemic and local corticosteroid therapy have been effective in managing EE. The proposed mechanisms of corticosteroid action in EE include induction of apoptosis and...
down-regulation of cytokines and chemokines involved in Th-2 responses. Topical corticosteroids are usually effective in inducing EE remission; however, their use as maintenance therapy has not been studied. Oral fluticasone and budesonide are typically used as first-line corticosteroid therapy. Patients should be instructed to administer the corticosteroid with a metered dose inhaler without use of a spacer. The device should be inserted into the mouth and sprayed with lips sealed. The liquid should be swallowed; then patients should rinse and spit to prevent oral candida infection. After administration, the patient should not eat or drink for at least 30 minutes. This regimen is continued for 6 to 8 weeks for induction of remission. Systemic corticosteroids are not recommended for long-term use; however, they can be used in emergent cases of dysphagia that lead to hospitalization. Symptoms usually recur after use of corticosteroids is discontinued.

Leukotriene inhibitors at high doses have been shown to induce symptomatic relief from EE; however, no evidence is available to suggest complete resolution.

Dietary therapies for EE including specific food elimination or use of amino acid–based diet formulas have been useful in children; however, evidence for their use in adults is minimal. Initial studies reported successful treatment of EE with endoscopic dilation alone; however, an increased risk of esophageal perforation was subsequently realized, possibly because of mucosal friability and deep mucosal tears. Current clinical practice for patients with symptoms suggestive of EE is diagnostic endoscopy with biopsies, followed by medical treatment before endoscopic dilation. Endoscopic dilation is reserved for patients whose condition is refractory to medical management, who present with food impaction, or who develop esophageal strictures. Radiographic evaluation should generally precede endoscopic dilation when possible. No evidence-based guidelines are available for monitoring and follow-up of patients with EE. The disease recurs in up to 91% patients after completion of treatment. Untreated EE can lead to strictures, perforation, and dysmotility. No studies with long-term follow-up have been performed to predict the risk of esophageal carcinoma.

In summary, obtaining a detailed history from a patient presenting with dysphagia is important. Clinicians must be aware of EE, its symptoms, and its association with and distinction from GERD. It is essential to identify the symptoms from the patient’s history, establish a diagnosis with endoscopy, and treat early to avoid possible complications.

REFERENCES


Correct answers: 1, c, 2, c, 3, a, 4, a, 5, d