

Endoscopy in Eosinophilic Esophagitis: “Feline” Esophagus and Perforation Risk

MITCHELL KAPLAN,* ECE A. MUTLU,* SHRIRAM JAKATE,* KEITH BRUNINGA,* JOHN LOSURDO,* JOSEPH LOSURDO,† and ALI KESHAVARZIAN*

*Section of Gastroenterology and Nutrition, Department of Internal Medicine, Rush University, Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois; and †Division of Gastroenterology, Hepatology, and Nutrition, Loyola University Medical Center, Maywood, Illinois

Background & Aims: Idiopathic eosinophilic esophagitis is an underdiagnosed disease with typical endoscopic findings, which have not been well described. **Methods:** Charts and pathology reports at two tertiary care centers from June 1993 to April 2002 were reviewed to describe the endoscopic findings of this disease and to correlate them with clinical characteristics. Eight patients were identified as having eosinophilic esophagitis based on clinical symptoms and pathology reports. **Results:** Soft and subtle ring(s) in the esophagus were found in 7 of 8 patients. In 3 of 8 patients, the esophagus appeared rigid. Mucosal rents occurred with simple passage of the endoscope in 5 of 8 patients. One patient developed a perforation after simple passage of the endoscope. Endoscopic findings can be normal or very subtle in these patients, and the findings can easily be missed during endoscopy. Tearing of the esophagus can occur with simple passage of the endoscope or biopsy even in the absence of overt rings. A minimum of 8 weeks of medical therapy (proton pump inhibitor, histamine antagonists, immunosuppressants) should be undertaken before considering dilation because of the high risk involved with the procedure and the good response to medical therapy. **Conclusions:** We recommend considering dilation only in patients with eosinophilic esophagitis who do not respond to medical therapy and have rings that appear to be obstructing the lumen.

Primary or idiopathic eosinophilic esophagitis (IEE) is an underdiagnosed disease characterized by diffuse eosinophilic infiltration, involving both the proximal and distal esophagus. Adult patients with IEE are usually men, have a high rate of atopy, and typically present with dysphagia and food impaction. The purpose of this retrospective review is to describe the typically subtle endoscopic findings and the clinical characteristics in a relatively large series of adult patients with IEE. Our goal is to alert clinicians to consider this diagnosis in young patients with dysphagia and to be aware of the risk of esophageal perforation in this disorder.

Patients and Methods

We reviewed charts and pathology reports at 2 tertiary care centers from June 1993–April 2002 after approval by the respective Institutional Review Boards. Patients with causes of eosinophilic infiltration other than IEE, such as those with pill esophagitis, caustic ingestion, esophageal trauma or irradiation, parasitic infestation, or patients with extraintestinal organ involvement with eosinophils were excluded. Eight patients (6 men, 2 women; mean age, 27 years; range, 20–38 years) were identified as having IEE on the basis of longstanding symptoms unresponsive to proton pump inhibitors (PPIs) and diffuse infiltration of the esophageal mucosa with sheets or large clusters of eosinophils (>25 per high-power field). All patients had undergone a complete blood count with differential white blood count, and some patients also had additional tests including 24-hour esophageal pH studies, upper gastrointestinal barium radiographs, and esophageal motility testing.

Results

The presenting symptom in all 8 patients was dysphagia with an average duration of 4.9 years (range, 0.5–20 years). All patients had a history of atopy (Table 1). Additional symptoms and type of allergy are shown in Table 1.

At endoscopy, the most common finding was subtle and soft ring(s) in the esophagus in 7 of 8 patients (Table 1 and Figure 1). In 1 case the esophagus appeared normal. In most patients, the presence of multiple rings made the esophagus resemble that of a cat,¹ which we have previously termed *feline esophagus*.² In 3 of 8 patients, the esophagus dilation with air insufflation was limited, and there was some resistance to the passage of the scope, even when the diameter of the esophagus appeared normal. In 5 of 8 patients, mucosal rents oc-

Abbreviations used in this paper: IEE, idiopathic eosinophilic esophagitis; PPI, proton pump inhibitor.

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Table 1. Demographics, Symptoms, and Endoscopy in Patients with IEE

Age (yr) Gender	Duration of symptoms	Additional symptoms	Allergy	Endoscopic findings-EGD	Esophageal dilation	Motility
20/F	2 yr	Chest pain, nausea, vomiting, weight loss	Hay fever	Normal	No	Normal
26/M	2 yr	—	Hay fever, asthma	Rings, rent, stiff	Yes	Normal
38/M	9 mo	—	Hay fever	Ring	Yes	Normal
23/M	4 yr	—	Hay fever	Ring, rent, ulcer	No	Normal
22/M	20+ yr	Diarrhea	Hay fever, asthma, shellfish, peanuts	Ring, rent	No	Abnormal
24/F	4 mo	—	Hay fever	Rings	Yes	Not done
30/M	6 mo	—	Hay fever, asthma	Rings, rent, stiff	No	Not done
34/M	10+ yr	Nausea, vomiting	Hay fever, shellfish, peanuts	Rings, rent, stiff	No	Not done

curred with simple passage of the endoscope (Figure 2). In 2 of these patients, the mucosal rents were long; in 1 patient, an esophageal perforation occurred after simple passage of the endoscope and resulted in development of chest pain and fever within hours of endoscopy. Computed tomography showed intramural air in the esophagus compatible with a sealed perforation. The patient was treated conservatively with total parenteral nutrition and antibiotics with complete sealing of the perforation in 2 weeks.

Esophageal biopsy specimens from all patients demonstrated sheets or clusters of eosinophils (Figure 3). The differentiating features between IEE and gastroesophageal reflux disease (Figure 4) were (1) prominence of eosinophilic infiltration toward the luminal surface, (2) higher number of eosinophils in IEE (>25 per high-power field) compared to gastroesophageal reflux disease (<10 per high-power field) with formation of clusters and exudates containing eosinophils in IEE, and (3) similar distribution of eosinophilic infiltration in the mid and distal esophagus in IEE, in contrast to the predominance of eosinophils in the lower esophagus in reflux esophagitis.

Four of 5 patients had a normal esophageal motility study. The remaining patient had an increased number of simultaneous contractions (Table 1). Upper gastrointestinal barium study showed multiple rings in the upper esophagus in 1 patient. A 24-hour pH study was normal in 1 patient.

We assessed efficacy of treatment by the improvement of dysphagia during follow up, which ranged between 2 and 10 years. All patients had an unsuccessful trial of PPIs before referral. After diagnosis, all patients were initially treated with H₁ and H₂ receptor antagonists. All patients improved on this regimen. Two patients responded completely to these medications alone. Two patients who continued to be treated with PPIs also achieved a complete response. Three patients required the addition of prednisone to achieve complete symp-

tomatic response. One of these patients became prednisone dependent with recurrence of dysphagia on steroid withdrawal. Prednisone was successfully discontinued with the introduction of low-dose azathioprine (50 mg). The remaining patient was given a trial of a low histamine diet that was not effective, but there was a complete response to budesonide respules. Dilation was performed in 3 patients during their initial endoscopy before the diagnosis of IEE.

Discussion

Our case series highlights the importance of considering the diagnosis of IEE in young patients with long-standing dysphagia and atopy. Our observations demonstrate that endoscopic findings can be normal or very subtle in these patients, and the findings can easily be missed during endoscopy. Indeed, 6 of 8 patients in our case series had been seen by other gastroenterologists and had a prior endoscopy that was reported normal. It is not surprising that the diagnosis was missed and delayed; the mean duration of symptoms before IEE diagnosis in our case series was 4.9 years, confirming the underrecognition of the disorder by gastroenterologists.

Endoscopic findings in patients with IEE have been reported in the literature as normal,^{3,4} proximal strictures,⁵⁻⁷ distal strictures,⁷ diffuse esophageal polyps,⁵ multiple concentric rings,⁸ small caliber,⁴ and feline esophagus.⁴ Langdon⁹ reported on 11 adult patients with non-cartilaginous "trachealized" esophagi he described as "corrugated ringed esophagus." In their review article, Fox et al.¹⁰ mentioned other gross abnormalities including granularity, absent vascular markings, and vertical furrowing in addition to feline-like rings, corrugation, concentric rings, and strictures. They attributed these findings to mucosal inflammation. In our patients, the "rings" in the esophagus were single or multiple and often subtle. Consequently, they could easily be mistaken as contractions or missed. We have elected to use the



Figure 1. Endoscopic appearance of feline esophagus demonstrating multiple rings throughout the esophagus.

term *feline esophagus* to describe this ringed appearance because of its similarity to the normal endoscopic findings in a cat's esophagus, which looks like the trachea with multiple rings.¹ We do not favor the term *ringed esophagus* because the majority of these patients do not have a true ring. Rather, the esophagus appears more like a "soft" trachea with subtle indentations.

Because endoscopic and radiologic findings can be subtle or normal, the diagnosis of IEE should be made histologically by using random biopsy specimens from both the proximal and distal esophagus. All our patients

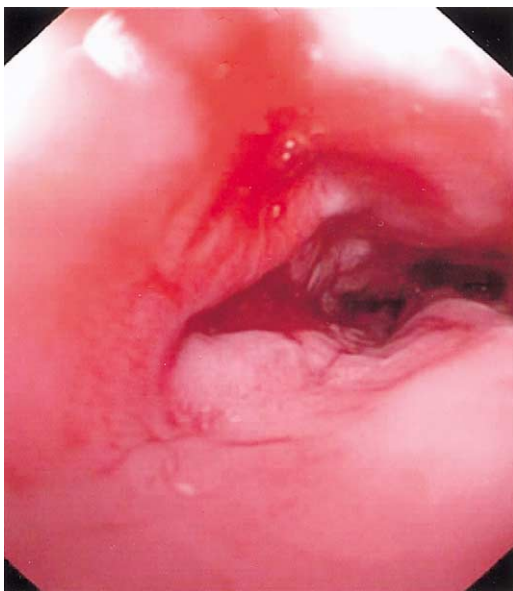


Figure 2. Mucosal rents seen after passage of the endoscope.

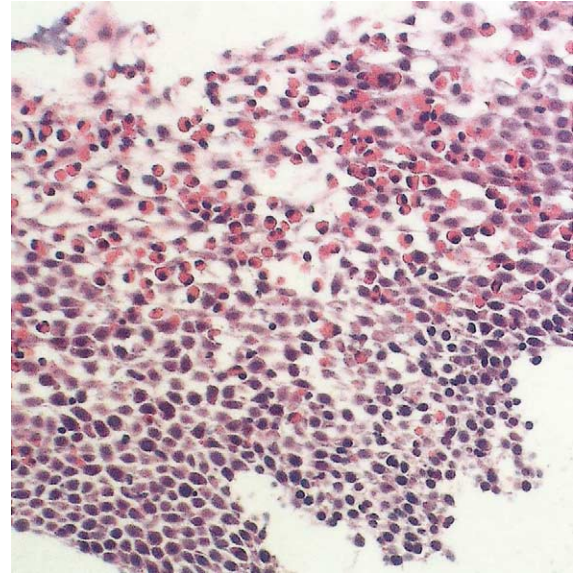


Figure 3. Microscopic changes of IEE in esophageal squamous mucosa. There is basal zone hyperplasia similar to gastroesophageal reflux disease, but the extravasated eosinophils are numerous (>25/high-power field) and more concentrated toward the luminal aspect (H&E stain, original magnification 100 \times).

had their diagnosis confirmed by biopsy. Our experience demonstrates that the pattern (such as prominence of eosinophils toward the luminal side of the biopsy) and extent of eosinophilic infiltration (in sheets and clusters) are important pathologic features that can aid in the diagnosis of IEE and differentiation from reflux itself.

Most notably, there is a lack of response to PPIs in IEE in our case series, similar to the findings of others.¹¹⁻¹³ Previous reports of 24-hour pH testing in these patients have been normal. These observations suggest that simple gastroesophageal reflux disease is unlikely to explain

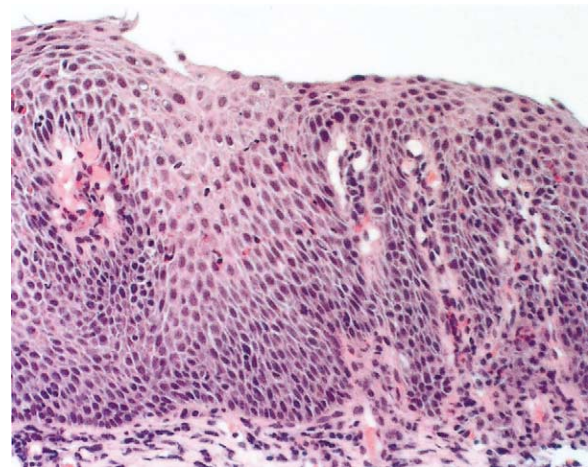


Figure 4. Microscopic changes of gastroesophageal reflux disease in esophageal squamous mucosa. There are basal zone hyperplasia, tall vascular pegs, and a modest number of extravasated lymphocytes and eosinophils (H&E stain, original magnification 100 \times).

the observed eosinophilic infiltration. In contrast to PPI therapy, treatment with histamine receptor blockade resulted in significant improvement of symptoms in many patients, supporting the role of an inflammatory, histamine-mediated response in the etiology of IEE. Our rationale for using combined H₁ and H₂ antagonists was not only to abort the histamine-mediated inflammatory cascade caused by allergy but also to inhibit mast cell activation¹⁴ and release of chemotactic factors for eosinophils.^{15,16} Several second-generation antihistamines can inhibit the influx of eosinophils to the site of allergen challenge in sensitized individuals.^{17,18} Finally, studies have demonstrated that antihistamines can alter eosinophil activation and release of their granules.¹⁹ The observation of a good therapeutic response with H₁ and H₂ blockers needs to be confirmed by a double-blinded, placebo-controlled study.

Swallowed inhaled steroids have also been shown to be effective in treating IEE and reducing intramucosal eosinophilia.²⁰ In this study, fluticasone MDI (metered dose inhaler) was swallowed and not inhaled for a 4–6-week period. The biopsy specimens in all the patients showed dramatic improvement in intramucosal eosinophilia, but only 1 patient had improvement of symptoms. Another series of 15 patients confirmed the efficacy of topical steroids.²¹ Faubion et al.²² and Teitelbaum et al.²³ reported improvement in symptoms and reduction of esophageal eosinophilia in 4 and 11 pediatric patients with IEE, respectively, treated by using swallowed metered doses of fluticasone propionate. Dietary restriction was an ineffective treatment.²³ Budesonide respules resulted in symptomatic improvement and resolution of dysphagia in 1 of our patients with dysphagia not fully controlled with H₁/H₂ antagonists.

Patients with IEE are at increased risk of mucosal renting and perforation after dilation. In our experience, fragility of the esophagus and renting of the esophagus can occur with simple passage of the endoscope or biopsy instrument even in the absence of overt rings. The patient who developed a perforation in our series had no overt ring and developed this complication without dilation. Langdon^{24,25} has emphasized that dilation should be undertaken with great caution. He recommended inspection of the esophagus after passage of each dilator because tearing can occur without the operator feeling any resistance. Vasilopoulos et al.⁴ stressed the importance of endoscopic reinspection immediately after dilation to look for esophageal mucosal trauma. Our experience also highlights the high frequency of esophageal fragility in IEE even in the absence of overt rings. Therefore, gastroenterologists must perform a delicate

endoscopic examination in patients with IEE or suspected IEE. Using a regular adult thin endoscope has been safe in our experience. The role of endoscopic dilation should be questioned. Dilation was done in 3 of our patients at the beginning of our experience, and all patients were dilated during their initial endoscopy before starting medical therapy. Symptoms recurred in all patients after dilation and subsequently resolved with medical therapy. We strongly recommend a minimum of 8 weeks of medical therapy before considering dilation because of the high risk involved with the procedure in this patient population and the good response to medical therapy. We recommend considering dilation only in patients who do not respond to medical therapy and have rings that appear to be obstructing the lumen.

In summary, IEE should be considered in any patient with dysphagia and a history of atopy. Subtle findings of feline esophagus should be searched at endoscopy, which should be performed more carefully because of an increased risk of perforation. Biopsy sampling of the esophageal mucosa is indicated if IEE is suspected even in those with a normal-appearing esophagus to aid early diagnosis of IEE, to avoid unnecessary endoscopic dilation, and to select medical therapy. Further studies are needed to define optimal medical therapy.

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- Address requests for reprints to: Mitchell Kaplan, M.D., Section of Gastroenterology and Nutrition, Department of Internal Medicine, Rush University, Rush Presbyterian St. Luke's Medical Center, 1725 West Harrison Street, Suite 206, Chicago, Illinois 60612-3824. e-mail: Mitchell_S_Kaplan@rush.edu; fax: (312) 563-3883.
- Dr. Joseph Losurdo's current affiliation is Elgin Gastroenterology, 1425 N. McLean Boulevard, Elgin, Illinois.