

CASE STUDY IN GASTROENTEROLOGY & HEPATOLOGY

Ringed Esophagus Secondary to Lymphocytic Esophagitis

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Lymphocytic esophagitis (LE) is a recently described clinicopathologic entity that is poorly characterized and understood. This diagnosis was first characterized as a novel histologic phenotype by Rubio and colleagues when the authors described 20 patients with esophageal biopsies showing a peripapillary distribution of infiltrating CD3-positive T lymphocytes that expressed CD4 or CD8.^{1,2} The exact pathogenesis of lymphocytic esophageal inflammation remains unknown. Previous reports suggest a possible association with Crohn's disease in pediatric patients but not adult patients.^{1,3} However, in a review of 42 patients, a variety of disorders were noted with LE, and the authors could not find a specific association with any chronic conditions, irrespective of age groups.⁴ A review of 129,252 esophageal biopsies found that 0.1% have LE, which appeared to be more common in older women than eosinophilic esophagitis (EoE).⁵

The clinical and endoscopic findings of LE and EoE overlap significantly. Patients with LE commonly present with dysphagia, odynophagia, abdominal pain, and gastroesophageal reflux symptoms.^{5,6} Most patients have a benign clinical course with lower rates of food impaction than patients with EoE.⁶ Although many LE patients have endoscopies that are normal or only show mild esophagitis, some reports suggest that LE patients have a similar rate of esophageal rings but a lower rate of esophageal stricturing.⁶⁻⁸

Overall, no consistent clinical correlations have emerged regarding LE, and the clinical significance of this condition remains unclear. However, increasing awareness of this diagnosis could help in better understanding its etiology, associations, and possible treatment modalities.

Case Report

A 66-year-old woman presented with several months of intermittent solid food dysphagia and upper abdominal

discomfort. She reported having an occasional choking sensation with food stuck at the suprasternal notch, which gradually resolved each time. The patient also reported having occasional upper abdominal discomfort, but denied having chronic heartburn. She denied having any nausea, vomiting, hematemesis, melena, rectal bleeding, or caustic ingestions. She had a history of bipolar disorder and opioid overdose. Her surgical history included a cholecystectomy, and her medications included clonazepam, ziprasidone, buprenorphine, and naloxone. She did not have medication allergies. The patient had a 75 pack/year smoking history and drank 2 to 4 cups of coffee daily. There was no family history of inflammatory bowel disease (IBD) or other gastrointestinal disorders.

A physical examination revealed a woman in no acute distress, with a hoarse voice. Her vital signs and complete physical examination were normal, including a benign abdominal examination, and her stools were guaiac-negative. Her complete blood count with differential, electrolytes, albumin, aminotransferases, bilirubin, and alkaline phosphatase were all within normal limits.

An esophagogastroduodenoscopy (EGD) revealed multiple concentric rings in the middle and lower third of the esophagus (Figure 1). Multiple biopsies were taken from the esophagus and stomach. The stomach biopsy was negative for *Helicobacter pylori* infection and showed no signs of lymphocytic or eosinophilic gastritis. Multiple biopsies obtained from the distal and midesophagus showed mild basal cell hyperplasia and increased intraepithelial lymphocytes without any accompanying neutrophils and eosinophils (Figure 2). Immunostaining revealed that the majority of cells were CD3- and CD5-positive lymphocytes (T-cell markers) that expressed either CD4 or CD8. Immunostaining for CD20 (B-cell marker) failed to reveal any abnormal intraepithelial B-cell infiltrates. Staining for CD1a revealed a normal population of mucosal dendritic cells. Staining for mast cell tryptase revealed a few scattered intraepithelial mast cells. A diagnosis of LE was made. The patient was started

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Figure 1. An esophagogastroduodenoscopy showing concentric rings throughout the esophagus, including the middle third.

on omeprazole 40 mg twice daily, and her symptoms improved after a few days.

Discussion

Traditionally, the endoscopic finding of a ringed esophagus, also called a feline esophagus or trachealization of the esophagus, suggests a diagnosis of EoE. LE has only recently emerged as a clinicopathologic entity, and studies have revealed that sometimes it has overlapping features with EoE, as shown by our patient.¹ Our report also illustrates that an EGD finding of esophageal rings does not always imply a diagnosis of EoE and that biopsies are essential in establishing a correct diagnosis. In this patient, although both the presentation and endoscopic findings were highly suggestive of EoE, histology showed lymphocytic rather than eosinophilic infiltration, confirming a diagnosis of LE.^{7,8} Thus, it is important to recognize that an endoscopic finding of esophageal rings is not pathognomonic for EoE.

The mechanism of esophageal ring formation is not well understood. In the setting of EoE, a commonly accepted hypothesis includes the role of histamine and cationic proteins released by mast cells and eosinophils. In sensitized people, immunoglobulin E interactions with allergens cause mast cells to release histamine, eosinophilic chemotactic factor, platelet-activating factor, and leukotriene B₄. These inflammatory molecules recruit and activate eosinophils, which then release cationic proteins, including major basic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase. Cationic proteins cause tissue damage through the synthesis of leukotrienes. Eosinophils also release interleukins 3 and 5, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor- α , which all promote inflammation.

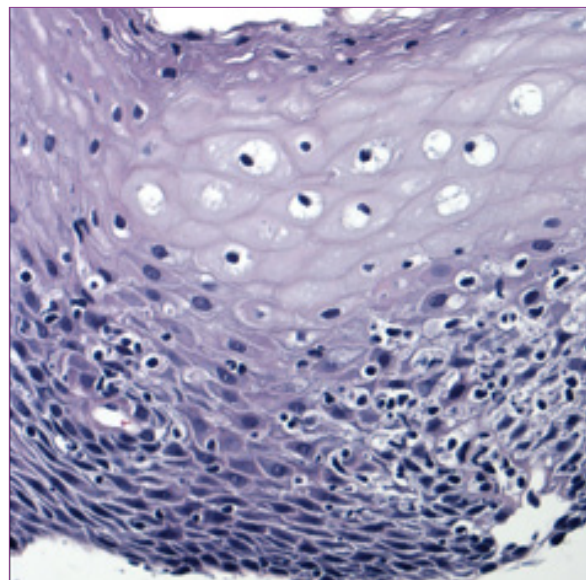


Figure 2. A hematoxylin and eosin stain of esophageal mucosa showing mild basal cell hyperplasia and increased intraepithelial lymphocytes in the peripapillary areas without any eosinophils or neutrophils (300 \times magnification).

Histamine causes activation of acetylcholine, which leads to muscle contraction in the muscularis mucosae, deforming the mucosal layer and possibly resulting in the formation of esophageal rings.⁹ This hypothesis is supported by the improvement of symptoms in patients with EoE who were treated with histamine receptor blockers.¹⁰ The formation of esophageal rings in LE may have a similar etiology. Inflammation of the esophageal mucosa leads to muscularis contraction and thickening of the esophageal wall. In our patient, mast cells were also identified on histology with mast cell-specific immunostains, which suggests that histamine may also play a role in ring formation in LE.

The pathogenesis of LE is poorly understood. What is known is that a significant portion of patients present with dysphagia, such as our patient, and an EGD often shows esophageal rings similar to those found in EoE. The cause for this lymphocyte-dominant inflammation is unknown, although underlying IBD, hypersensitivity reactions, and even celiac disease have been speculated to play a role.¹

It is important for gastroenterologists to consider LE in patients with dysphagia and a ringed esophagus. It is also important for pathologists to recognize this entity and understand its clinical associations. Although treatment modalities have not been studied for LE, a trial of proton pump inhibitors and/or topical corticosteroids may help.⁸ If the esophageal rings appear to cause esophageal narrowing, dilatation (as needed) can be therapeutic.⁷

The authors have no relevant conflicts of interest to disclose.

(continued on page 268)

(continued from page 238)

References

1. Rubio CA, Sjö Dahl K, Lagergren J. Lymphocytic esophagitis: a histologic subset of chronic esophagitis. *Am J Clin Pathol.* 2006;125(3):432-437.
2. Rubio CA, Dick EJ, Orrego A, Hubbard GB. The frequency of lymphocytic and reflux esophagitis in non-human primates. *Int J Clin Exp Pathol.* 2008;1(6):531-535.
3. Ebach DR, Vanderheyden AD, Ellison JM, Jensen CS. Lymphocytic esophagitis: a possible manifestation of pediatric upper gastrointestinal Crohn's disease. *Inflamm Bowel Dis.* 2011;17(1):45-49.
4. Purdy JK, Appelman HD, Golembeski CP, McKenna BJ. Lymphocytic esophagitis: a chronic or recurring pattern of esophagitis resembling allergic contact dermatitis. *Am J Clin Pathol.* 2008;130(4):508-513.
5. Haque S, Genta RM. Lymphocytic oesophagitis: clinicopathological aspects of an emerging condition. *Gut.* 2012;61(8):1108-1114.
6. Cohen S, Saxena A, Waljee AK, et al. Lymphocytic esophagitis: a diagnosis of increasing frequency. *J Clin Gastroenterol.* 2012;46(10):828-832.
7. Mandaliya R, Dimarino AJ, Cohen S. Lymphocytic esophagitis mimicking eosinophilic esophagitis. *Ann Gastroenterol.* 2012;25(4):355-357.
8. Kasirye Y, John A, Rall C, Resnick J. Lymphocytic esophagitis presenting as chronic dysphagia. *Clin Med Res.* 2012;10(2):83-84.
9. Mann NS, Leung JW. Pathogenesis of esophageal rings in eosinophilic esophagitis. *Med Hypotheses.* 2005;64(3):520-523.
10. Kaplan M, Mutlu EA, Jakate S, et al. Endoscopy in eosinophilic esophagitis: "feline" esophagus and perforation risk. *Clin Gastroenterol Hepatol.* 2003;1(6):433-437.