

Lymphocytic Esophagitis

A Chronic or Recurring Pattern of Esophagitis Resembling Allergic Contact Dermatitis

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Key Words: Lymphocytosis; Esophagitis; Spongiosis; Crohn disease; Allergy

DOI: 10.1309/D3PCF6D6YYMQRX9A

Upon completion of this activity you will be able to:

- define the range of situations in which intraepithelial lymphocytes may be observed in the esophagus.
- provide wording for the pathology reports of esophageal biopsies in which the major histologic finding is increased intraepithelial lymphocytes.
- provide a brief summary of the literature regarding the significance of intraepithelial lymphocytes.

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The authors of this article and the planning committee members and staff have no relevant financial relationships with commercial interests to disclose. Questions appear on p 642. Exam is located at www.ascp.org/ajcpme.

Abstract

Lymphocytic esophagitis (LE) is characterized by intraepithelial lymphocytes (IELs) and spongiosis, resembling contact dermatitis. LE has been defined as high numbers of IELs and no or rare granulocytes and was found in young patients and in association with Crohn disease (CD). We reviewed the medical records of 42 LE cases. Cases were divided into severe (IELs in interpapillary and peripapillary fields) and mild (IELs in peripapillary fields) LE. The control group included specimens from 34 consecutive esophageal biopsy cases. Mean ages were similar (LE, 44 years; control subjects, 43 years). CD was present in 5 LE cases (12%) and 1 control case, an insignificant difference. Of patients with LE, 14 (33%) had an allergy; 11 (26%), gastroesophageal reflux disease (GERD); 4 (10%), Helicobacter pylori gastritis; and 18 (43%), dysphagia. No differences were found in clinical features between LE and control cases, except GERD was less common in severe LE (6/30 [20%]) than in control cases (17 [50%]). No patient with LE had celiac disease. No medications were common among LE cases. Patients with LE are statistically no more likely than control subjects to have CD. We found no association between LE and any clinical condition or symptom. Based on sequential biopsies in 7 patients, LE seems to be a chronic disease.

Intraepithelial lymphocytosis of the esophagus has been studied to a limited extent in the context of specific diseases. Wang et al¹ found that numbers of intraepithelial lymphocytes (IELs) were increased in patients with reflux esophagitis compared with patients with normal esophageal biopsy findings, but the increase was not statistically significant. Thus, they concluded that IELs could not be used as an independent marker of reflux esophagitis.¹ Resnick et al² examined the cytotoxic potential of intraepithelial T lymphocytes in the esophagus and found that numbers of cytotoxic T cells were significantly increased in esophageal biopsy specimens with reflux or *Candida* esophagitis.

Rubio et al³ were the first to examine IELs in the esophagus more generally. Their study included 20 patients whose esophageal biopsy specimens had increased numbers of IELs in peripapillary fields and no more than rare granulocytes. Clinical histories and endoscopic findings of these patients were compared with those of a control population consisting of 61 patients with biopsies revealing some form of esophagitis (the majority with reflux esophagitis, but a few with *Candida* or postradiation esophagitis) with both IELs and granulocytes. Of the 20 patients with lymphocytic esophagitis (LE), 11 (55%) were 17 years or younger. Of these 11 pediatric patients, 7 (64%) had Crohn disease. Of the 9 adult patients with LE, only 1 had Crohn disease. Twenty percent had symptoms of gastroesophageal reflux disease (GERD), and 10% had celiac disease. Based on these findings, Rubio et al³ raised the possibility that LE might be a manifestation of Crohn disease.

Esophageal biopsy specimens with significant intraepithelial lymphocytosis are often also spongiotic, resembling acute spongiotic dermatitis, such as allergic contact dermatitis, irritant contact dermatitis, and atopic dermatitis. In these dermatitides, the epidermis is of normal thickness and spongiotic, with exocytosis of lymphocytes, and sometimes other inflammatory cells, into spongiotic foci. Papillary edema and superficial perivascular lymphohistiocytic infiltrates are also found in spongiotic dermatitis.^{4,5} It is not known if LE has lamina propria edema that corresponds to the dermal edema present in spongiotic dermatitis because there is usually little lamina propria present in esophageal biopsy specimens. The resemblance of LE to spongiotic dermatitis raises the possibility that there may be an allergic or irritant cause for some cases.

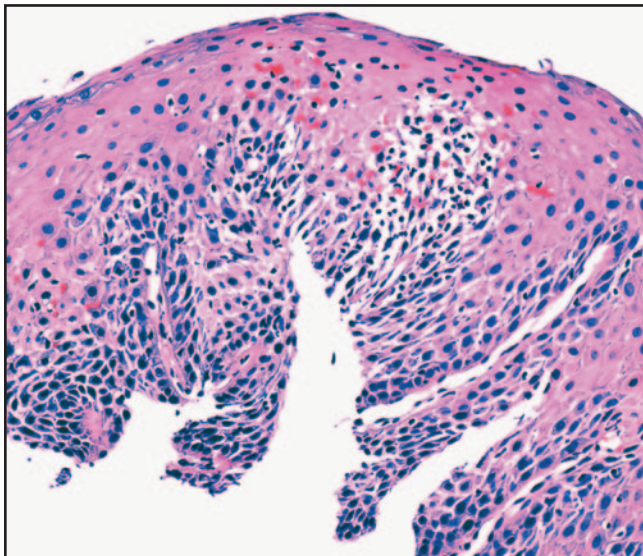
Materials and Methods

Esophageal biopsy specimens from 42 patients that satisfied the Rubio criteria³ for LE were identified and set aside by one of us (H.D.A.). These criteria include high numbers of IELs and no more than rare granulocytes. The cases were part of our general gastrointestinal signout service, which comes from a variety of clinics and includes pediatric patients. We compared the data for these patients with a control group of 34 consecutive patients having esophageal biopsies for

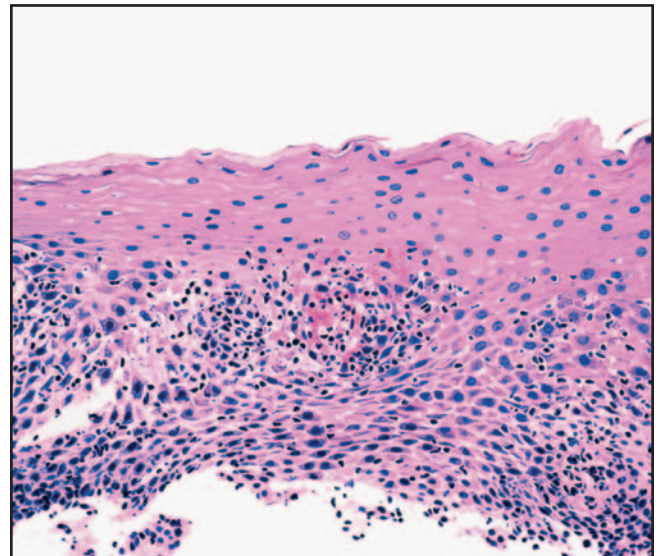
any reason other than Barrett surveillance. We reviewed the medical records of both groups of patients, noting symptoms leading to endoscopy and the endoscopic appearance. Any concurrent, previous, or subsequent gastrointestinal biopsy specimens were retrieved and reviewed. We recorded any history of Crohn disease, symptoms of GERD (defined as having esophageal symptoms such as heartburn or noncardiac chest pain), and *Helicobacter pylori* gastritis identified by biopsy or serologic assay. We noted medications the patients were reported to be taking and sought any history of allergy, including seasonal, food, drug, and dermatologic types, and history of asthma.

Similar to the methods of Rubio et al,³ IELs were counted in the most densely infiltrated peripapillary and interpapillary fields using high-power examination ($\times 400$). Peripapillary was defined as the first 5 layers of squamous epithelium surrounding the esophageal papillae. The cases were coded and counted independently by 3 of us (J.K.P., H.D.A., and B.J.M.) without knowledge of patient symptoms or clinical history. Biopsy specimens with LE were classified as mild if the intraepithelial lymphocytosis was predominantly peripapillary and severe if the lymphocytosis involved both peripapillary and interpapillary areas of the squamous epithelium ■ **Image 1** and ■ **Image 2**.

Comparisons between LE and control groups were performed by using the Fisher exact test.



■ **Image 1** Mild lymphocytic esophagitis has increased intraepithelial lymphocytes aggregated around the papillae, with the normal few, scattered lymphocytes in the interpapillary zones. Intercellular edema (spongiosis) is evident in the region of lymphocytosis. Eosinophils and neutrophils are absent (H&E, $\times 200$).



■ **Image 2** In severe lymphocytic esophagitis, there is a diffuse increase in intraepithelial lymphocytes affecting the peripapillary and interpapillary zones (H&E, $\times 200$).

Results

There was a wide age distribution in the LE and control cases (LE, 2-81 years; control, 10-70 years) with mean ages of 44 and 43 years and median ages of 45 and 43 years, respectively, and no significant age differences between the groups.

The specific location of the esophageal biopsies was known for 22 (52%) of 42 LE cases and for 24 (71%) of 34 control cases. Biopsy specimens from LE cases were from the proximal (3/22 [14%]), mid (6/22 [27%]), and distal (16/22 [73%]) esophagus, compared with 0 (0%), 12 (50%), and 18 (75%) of 24 control cases, respectively. If multiple biopsy specimens were obtained from more than 1 location in the esophagus and submitted in the same specimen jar, the location was deemed unknown because the exact location of the biopsy could not be determined. There was no significant difference between LE and control cases in esophageal biopsy location.

More than two thirds of LE cases (30/42 [71%]) were the severe form, with both peripapillary and interpapillary intra-epithelial lymphocytosis. LE cases had a mean and median of 70.3 and 69 IELs in peripapillary fields, respectively (range, 23-133 IELs), and a mean and median of 36.9 and 30.5 IELs in interpapillary fields, respectively (range, 3-105 IELs).

Severe LE cases had a mean and median of 69.3 and 69 IELs in peripapillary fields, respectively (range, 23-133 IELs), and a mean and median of 43.6 and 36 IELs in interpapillary fields, respectively (range, 17-105 IELs). Mild LE cases had a mean and median of 72.9 and 73 IELs in peripapillary fields, respectively (range, 48-130 IELs), and a mean and median of 20.1 and 16.5 IELs in interpapillary fields, respectively (range, 3-44 IELs). There was a significant difference between the number of IELs in peripapillary and interpapillary fields for all LE cases, similar to the findings of Rubio et al,³ and a significant difference in the number of IELs in interpapillary fields between severe LE and mild LE cases.

Of the 34 control subjects, 26 had normal esophageal biopsy findings. Of the remaining 8, 1 had Barrett esophagus, 3 had eosinophilic esophagitis, 2 had reflux-type changes, 1 had a focus of acute inflammation, and 1 had an ulcer.

Initial symptoms and endoscopic appearances for patients with LE and control subjects are listed in **Table 1**. For none of the symptoms or endoscopic features was there a significant difference between patients with LE and control subjects, except that GERD symptoms were almost twice as common in control subjects (17/34 [50%]) as in patients with LE (11/42 [26%]). Specifically, there was no significant difference between patients with LE (severe, mild, and total) and control subjects (normal results and total) with respect to dysphagia or for any endoscopic appearance, including normal, esophagitis, Barrett esophagus, hiatal hernia, rings, and furrows. In fact, endoscopic rings, a common feature of eosinophilic esophagitis, were present in 3 (10%) of 30 patients with severe LE and 2 (8%) of 26 control subjects with normal biopsy results, not a significant difference, illustrating the nonspecificity of esophageal rings on endoscopy.

There were no significant differences between patients with LE and control subjects in the prevalence of allergies, Crohn disease, or *H pylori* gastritis **Table 2**. Of 42 patients with LE, 5 (12%) had Crohn disease, and, of these, 3 were pediatric patients, ages 8, 11, and 16 years. Of all patients with LE, 8 were younger than 18 years. Thus, in our study, pediatric LE was associated with Crohn disease in 3 (38%) of 8 patients. One patient in the control group had Crohn disease, and this patient was an adult. Differences between patients with LE and control subjects with respect to Crohn disease were not statistically significant, even when only pediatric patients were considered. Among control subjects, 14 (41%) had some form of allergy, excluding drug allergies; 5 (15%) had drug allergies; and no patient had *H pylori*. Of the patients with LE, 14 (33%) had some form of allergy (eg, seasonal

Table 1
Initial Symptoms and Endoscopic Findings in Patients With LE and Control Subjects*

	All Patients With LE (n = 42)	Patients With Severe LE (n = 30)	All Control Subjects (n = 34)	Control Subjects With Normal Biopsy Results (n = 26)
All esophageal symptoms [†]	24 (57)	17 (57)	20 (59)	15 (58)
Dysphagia	18 (43)	13 (43)	12 (35)	10 (38)
GERD symptoms [‡]	11 (26)	6 (20)	17 (50)	13 (50)
Endoscopic appearance				
Normal	13 (31)	9 (30)	11 (32)	10 (38)
Esophagitis	10 (24)	8 (27)	11 (32)	8 (31)
Barrett esophagus	0 (0)	0 (0)	1 (3)	0 (0)
Hiatal hernia	4 (10)	2 (7)	4 (12)	3 (12)
Rings	5 (12)	3 (10)	3 (9)	2 (8)
Furrows	0 (0)	0 (0)	3 (9)	1 (4)

GERD, gastroesophageal reflux disease; LE, lymphocytic esophagitis.

* Data are given as number (percentage).

[†] Includes dysphagia, odynophagia, reflux/heartburn, and noncardiac chest pain.

[‡] Includes reflux/heartburn and noncardiac chest pain.

Table 2
Prevalence of Selected Medical Conditions in Patients With LE and Control Subjects

	All Patients With LE (n = 42)	Patients With Severe LE (n = 30)	All Control Subjects (n = 34)	Control Subjects With Normal Biopsy Results (n = 26)
Allergies (nondrug)	14 (33)	11 (37)	14 (41)	12 (46)
Drug allergy	11 (26)	8 (27)	5 (15)	4 (15)
<i>Helicobacter pylori</i> gastritis	4 (10)	2 (7)	0 (0)	0 (0)
Crohn disease	5 (12)	4 (13)	1 (3)	1 (4)

LE, lymphocytic esophagitis.

allergies, asthma, allergic skin conditions, food allergy); 11 (26%) reported a drug allergy; and 4 (10%) had *H pylori* gastritis. No patient with LE had celiac disease, and review of the records disclosed no medications in common among them.

Concurrent Gastrointestinal Biopsies

For 30 (71%) of 42 patients with LE, additional biopsy or cytologic specimens from the gastrointestinal tract were obtained at the time of esophageal biopsy. Biopsies from the stomach (23 cases), small bowel (15 cases), and colon (6 cases) had a variety of histologic findings that mirror those we expect to see in our routine gastrointestinal pathology service. The most common finding was normal mucosa (4 stomach, 8 small bowel, and 1 colon specimen). Other gastric biopsies revealed *H pylori* gastritis (4 specimens), inactive chronic gastritis suggesting past *H pylori* infection (6 specimens), focally enhanced gastritis consisting of 1 or more circumscribed foci of inflammation with epithelial damage (3 specimens, 2 of these in patients known to have Crohn disease), and assorted miscellaneous abnormalities. Other than the specimens that were normal (8 specimens), small bowel biopsy specimens included 1 with Crohn disease, 2 with surface epithelial lymphocytosis, 1 with autoimmune enteropathy, and 2 with nonspecific reparative changes. Colon biopsy specimens included 1 normal, 2 with Crohn disease, 2 with hyperplastic polyps and/or adenoma, and 1 with inflammation that was part of autoimmune enteropathy. For 7 patients, 8 esophageal cytology samples were obtained at the time of the diagnostic biopsy; 7 specimens were esophageal brushings, and 1 was a washing. All esophageal cytologic specimens were negative for neoplasm and pathogenic organisms, including fungus.

Previous and Subsequent Esophageal Sampling

Previous esophageal biopsies had been performed on 10 patients. Of these 10 patients, 4 had previous LE (3 of whom had the severe form); 2 had eosinophilic esophagitis; 1 had changes most consistent with gastroesophageal reflux; and 1 had acute esophagitis with spongiosis and microabscesses, resembling dermatitis herpetiformis. The remaining biopsies showed normal findings. In 4 patients, esophageal brushing samples had been obtained previously. In 1 patient, esophageal

cytologic findings were normal, 1 patient had an ulcer, and 2 patients had brushings with yeast forms but no hyphae or pseudohyphae suggestive of true esophageal fungal infection.

Subsequent esophageal biopsies were performed in 9 patients. Of these 9 patients, 5 had LE again (4 of whom had the severe form), 2 had ulcers, 1 had esophageal inflammation judged to be part of autoimmune gastroenteropathy, and 1 had an esophageal resection with Barrett esophagus and an ulcer. One patient had esophageal brushings after the LE biopsy, with normal cytologic findings.

Overall, 8 patients had LE revealed by previous and/or subsequent esophageal biopsies. Of these, 6 had the severe form of LE.

Discussion

Our 42 LE cases did not differ significantly from control cases in any of the parameters identified by others¹⁻³ or in parameters that we suspected might differ. Specifically, there were no differences in the prevalence of allergic disorders, asthma, Crohn disease, celiac disease, or any other clinical diagnosis. The LE group was not significantly younger. The 2 groups were also not significantly different in terms of symptoms of dysphagia or endoscopic findings. In fact, the only difference we detected was that GERD symptoms were almost twice as common in control (17/34 [50%]) as in LE (11/42 [26%]) cases, a finding that differs from that of Wang et al,¹ who found that patients with GERD tended to have intraepithelial lymphocytosis.

It is important to note that we were unable to confirm the findings of Rubio et al³ in their study of patients with LE. Rubio et al³ found that patients with LE were younger than control subjects, with a mean age of 17 years, whereas our patients had a broad age range with a mean age of 44 years and median age of 45 years, similar to the age of control subjects. Rubio et al³ postulated an association with Crohn disease because 40% of their patients with LE, mostly younger patients, had Crohn disease. Only 12% of our patients with LE had Crohn disease, compared with 4% of control subjects, an insignificant difference. Although 3 of our 5 patients with Crohn disease were pediatric, we found no significant

differences between all LE and control cases, between pediatric LE and pediatric control cases, or between pediatric and adult LE cases with respect to Crohn disease. Perhaps there is an association between LE and Crohn disease that would be conclusive in a larger study; however, the number of patients in our LE group is more than twice that in the study by Rubio et al,³ and we found fewer patients with LE with Crohn disease. In our study, patients with LE were far more likely *not* to have Crohn disease, even pediatric patients.

In the study by Rubio et al,³ 10% of patients with LE had celiac disease, raising the possibility of an association. In our study, no patient with LE had proven gluten sensitivity, although 2 patients had duodenal lymphocytosis (one without other clinical features of celiac disease and no serologic evaluations, the other with negative celiac serology). Thus, our study group does not add any further weight to such a potential association.

We are not able to fully explain the differences in results between our study and that by Rubio et al.³ Differences in case selection might be responsible for inadvertent selection bias. Our cases were prospectively recognized by one of us in the course of signing out gastrointestinal biopsies from adult and pediatric endoscopy clinics at one institution. While this would seem to be a random process, it may have been biased in a way that we cannot determine. The selection process used by Rubio et al³ may have introduced inadvertent bias toward younger patients or patients with Crohn disease or sprue. Alternatively, the prevalence of diseases in the 2 institutions may differ. The 2 studies compared patients with LE with different control groups. Our control population was selected to reflect the background population, whereas Rubio et al³ used a set of patients with other patterns of esophagitis. Thus, the control population of Rubio et al³ was not selected in a way to control for background disease prevalence.

In patients with LE, concurrent gastrointestinal biopsy specimens show a wide variety of findings that form no discernible pattern and seem similar to the kinds of biopsy specimens that constitute our day-to-day gastrointestinal pathology service. It is interesting that of patients with LE who underwent previous or subsequent esophageal biopsies, about half had another biopsy that showed LE (previous, 4/10; 5/9 subsequent). There were only a few patients with LE who underwent previous and/or subsequent gastrointestinal biopsies other than esophageal biopsies, and these patients tended to be the patients with established chronic disease, such as Crohn, autoimmune enteropathy, lymphocytic gastritis and enterocolitis, and microvillous inclusion disease (after small bowel, pancreas, and liver transplants). Their previous and subsequent gastric, small intestinal, and colonic biopsy findings were consistent with their known disease processes.

Based on this retrospective analysis, the etiology of LE and an understanding of who is likely to get it remain

elusive. Perhaps this is because there are multiple etiologies. Are IELs and spongiosis in the squamous epithelium of the esophagus, for example, simply nonspecific findings seen as a response to a variety of pathogenic stimuli, similar to the intraepidermal lymphocytes and spongiosis seen in spongiotic dermatitis of the skin? Although many of our patients with LE had some type of allergy and a few had a history of eosinophilic esophagitis, we found no association between LE and seasonal allergies or asthma and no association with celiac disease. Only 1 of our patients with LE had a food allergy, but the possibility exists that some patients had unrecognized food allergies. LE could also be due to a nonallergic reaction to an ingested substance, such as a drug, causing topical injury to the esophageal mucosa. Although we did not find a medication common among all LE patients, our results are based on retrospective chart review. Thus, there may be important clinical information that would only be captured with a prospective study. At our institution, in the diagnostic line we say: "Lymphocytic esophagitis resembling contact allergy of the skin" with a comment stating "We have studied this and there has been no association with any specific disease." If an expanded number of cases are studied in the future that lead to a different conclusion, we will modify this comment.

Conclusion

At our institution, patients with LE are no more likely than other patients undergoing esophageal biopsies, including patients with normal biopsy findings, to have Crohn disease, nor is this population younger, which are findings different from the only other published study. In fact, the only significant difference between the patients with LE and control subjects was that GERD symptoms were almost twice as common in control subjects (17/34 [50%]) as they were in patients with LE (11/42 [26%]). Patients with LE were no more likely to have allergies than were control subjects, nor were they more likely to have *H pylori* gastritis, dysphagia, or celiac disease. There were no medications in common among patients with LE. Thus, we found no association between LE and any specific clinical condition.

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