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Lymphocytic Esophagitis: An emerging clinicopathologic disease associated with dysphagia

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Abstract

Background—Lymphocytic Esophagitis (LyE) is a recently described clinicopathological condition, but little is known about its features and clinical associations.

Aim—To characterize patients with LyE, compare them to non-LyE controls, and identify risk factors.

Methods—We conducted a retrospective study of all patients 18 years old who underwent upper endoscopy with esophageal biopsy between January 1, 2000 and June 1, 2012. Archived pathology slides were re-reviewed and LyE was diagnosed if there was lymphocyte-predominant esophageal inflammation with no eosinophils or granulocytes. Three non-LyE controls groups were also defined: reflux, eosinophilic esophagitis (EoE), and normal. Clinical data were extracted from electronic medical records, and LyE cases were compared to non-LyE controls.

Results—27 adults were diagnosed with LyE, and the majority were female (63%). The most common symptom was dysphagia (70%). 52% had a prior or current diagnosis of reflux. Endoscopic findings included strictures (37%), erosive esophagitis (33%), rings (26%), and hiatal hernia (26%); 33% of patients required dilation. After histology re-review, 78% of LyE patients were found to have more than 20 lymphs/hpf. In comparison to the normal, reflux and EoE controls, patients with LyE tended to be non-white ($p < 0.01$), were more commonly tobacco users ($p = 0.02$), and less likely to have seasonal allergies ($p = 0.02$).

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Conclusion—LyE commonly presents with dysphagia due to esophageal strictures which require dilation. Smoking was associated with LyE whereas atopy was not. LyE should be considered as a diagnostic possibility in patients with these characteristics undergoing upper endoscopy.

Keywords

Lymphocyte; dysphagia; heartburn; chest pain; endoscopy

Introduction

Lymphocytic Esophagitis (LyE) is a recently described histopathological condition first defined by Rubio et al. in 2006 as a histologic subset of chronic esophagitis characterized by >20 intraepithelial lymphocytes (IELs) per high-power field (HPF) with no more than rare granulocytes [1]. Subsequently, as recognition of this histopathologic condition has become more widespread, there has also been some controversy related to LyE as studies have both questioned prior findings and attempted to better characterize this new entity [2–8].

No definite clinical associations have been detected in adults, though both gastroesophageal reflux disease (GERD) and Crohn's disease have been linked to LyE [9,10]. Because of the relative rarity of LyE, consensus regarding the defining features and clinical associations still does not exist and great variation has been present in sample sizes and control groups. We have clinically encountered patients with LyE and found diagnosis and management to be a challenge due to lack of data.

Therefore, the aim of our study was to characterize adult patients with LyE. We sought to compare patients with LyE to non-LyE controls (GERD, eosinophilic esophagitis (EoE), and normal on esophageal biopsy) and to identify risk factors for the condition and endoscopic findings.

Methods

We performed a retrospective study of all patients 18 years old who had undergone upper endoscopy (EGD) with esophageal biopsy at the University of North Carolina at Chapel Hill between January 1, 2000, and June 1, 2012. In order to identify a cohort of patients who could have LyE, all pathology reports from this time frame were searched for terms referencing increased lymphocytes or a lymphocyte-predominant infiltrate as these were broad terms that could capture LyE diagnoses, even if the LyE itself was not recognized at the time of the prior endoscopy. The archived pathology slides were acquired for these cases and were independently re-reviewed by a study pathologist who was blinded to the original diagnoses. As there are no published diagnostic guidelines and we wanted to be broad in identifying potential cases, LyE was diagnosed if there were 10 lymphocytes/hpf (hpf=0.24mm²) in the esophageal epithelium and no eosinophils or granulocytes.

Three non-LyE control groups were also defined by reviewing the above pathology database and selecting the first 20 patients with biopsy findings consistent with the following diagnoses: 1) patients with GERD (defined by clinical symptoms and a mixed inflammatory pattern on biopsy); 2) patients with eosinophilic esophagitis (EoE) (defined by consensus

guidelines); [11] and 3) patients with a normal esophageal biopsy. Patients with “normal” esophageal biopsy are believed to be reflective of our general population at UNC undergoing endoscopic evaluation. Patients with vasculitis, lichen planus, leukemia, infectious esophagitis (cytomegalovirus, herpes, candida), graft vs host disease, or multiple myeloma were excluded [11,12].

Data including patient demographics, co-morbidities, tobacco or alcohol use, medications, endoscopic findings, treatment, and outcomes were independently extracted for all four study groups from electronic medical records, pathology reports, and endoscopic databases at UNC, by two separate reviewers. The reviewers then compared findings and re-reviewed data jointly to reach consensus on any points of discrepancy. If there was still disagreement, the data were adjudicated by the senior author.

Descriptive statistics was performed to summarize characteristics of patients with LyE. One way analysis of variance and chi squared testing were done to compare patients with LyE to controls, GERD patients, and EoE patients using Stata 13. IRB approval was obtained at the University of North Carolina prior to initiation of the study.

Results

A total of 27 patients with LyE were identified, with the first diagnosis made in 2004. The average age was 56 years, most patients were female (63%) and white (59%) (Table 1). The most common symptoms at presentation were dysphagia (70%), heartburn (26%), chest pain (19%), nausea/vomiting (19%), and abdominal pain (15%). About half of patients had a prior or current history of alcohol and tobacco use, and the most commonly used medications were proton-pump inhibitors (59%) and non-steroidal anti-inflammatory drugs (64%).

For concomitant conditions, one patient (4%) had been previously diagnosed with inflammatory bowel disease and 14 (52%) had a current or prior diagnosis of GERD (Table 1). Atopic conditions were not common in this group with 1 patient (4%) with a history of food allergy, 1 (4%) with seasonal allergies, 5 (19%) with asthma, and 1 (4%) with eczema.

The vast majority of patients had an abnormal upper endoscopy (82%) at diagnosis (Table 2). Endoscopic findings included a narrow caliber esophagus (44%), esophageal stricture (37%), erosive esophagitis as defined endoscopically (33%), esophageal rings (26%), erythema (26%), and hiatal hernia (26%) (Figure 1). Esophageal dilation was performed in 9 patients (33%). Of the patients who had strictures, 30% were pan-esophageal (representing diffuse esophageal narrowing), 30% were proximal, and 40% were distal.

On histologic re-examination of the original biopsy slides, 52% of patients had between 21–40 lymphocytes/hpf, 4% had between 41–80 lymphocytes/hpf and 22% had greater than 80 lymphocytes/hpf (Figure 2) (Table 2).

Based on the clinical and histologic findings, 9 patients had a medication change. These included: initiation or increase in proton-pump inhibitor dose in 6 patients, addition of a GI cocktail in 1, initiation of swallowed fluticasone in 1, and initiation of oral prednisone taper

in 1 (Table 2). Of the patients who had a medication change, only 1 patient had follow up EGD, 2 patients who were started on a PPI and 1 patient who was treated with swallowed fluticasone had symptomatic improvement.

When patients with LyE were compared to patients with a normal esophageal biopsy, patients with GERD, and patients with eosinophilic esophagitis (Table 3), patients with LyE were more likely to be non-white (41% vs. 15% normal vs. 0% GERD vs. 5% EoE; $p < 0.01$) and use tobacco (64% vs. 30% normal vs. 55% GERD vs. 55% EoE; $p = 0.02$). LyE patients had comparable rates of drug and food allergies, but were less likely to have allergic rhinitis (4% vs. 25% normal vs. 25% GERD vs. 40% EoE; $p = 0.02$). Other clinical features were similar.

Discussion

LyE is a recently described rare condition of the esophagus. It has not yet been well characterized, and correlation between the histologic findings and clinical features are not always clear [3,8,9,10,13,14]. Because of this, we aimed to characterize patients with LyE at our center, compare them to non-LyE controls, and identify risk factors in order to provide more data to guide care. In sum, we found 27 adults diagnosed with LyE starting as early as 2004, and the vast majority of patients had more than 20 lymphs/hpf on histology. Diagnosis tended to be in the 6th decade, and in comparison to our GERD, EoE and “normal” controls, patients with LyE tended to be non-white, were more commonly tobacco users, and less likely to have atopy. In contrast to EoE, there was also a female preponderance in LyE. However, in comparison to patients with “normal” findings, there were fewer females diagnosed with LyE, though this group still had a majority of females. In addition, we did not see a clear relation between LyE and Crohn’s disease, though previously diagnosed GERD was common. Of note, 85% of the patients in our “normal” cohort were Caucasian which is consistent with prior racial demographic data from the University of North Carolina [15].

From a symptom standpoint, our data is consistent with several other studies that have also noted dysphagia to be the most common symptom at presentation of LyE [2,16]. Relatively few of our patients complained of other upper GI symptoms such as heartburn, abdominal pain, chest pain, nausea/vomiting, or odynophagia, which is similar to other studies [2,3,5,16,17]. However, the possible association between smoking and LyE has not been previously observed. The pathogenesis of LyE is yet unknown, but it has been hypothesized that possible causes of LyE may include a hypersensitivity reaction to an ingestant or an autoimmune phenomenon [1,3,4,14]. Additionally, it has been proposed that LyE may be an early sign of GERD in patients with no other endoscopic findings [10,18]. Given our finding of a significant association with smoking, it is intriguing to speculate whether an element of cigarette smoke may act as a topical trigger of the condition. However, further studies investigating the association with smoking are needed to confirm our findings and determine any etiologic mechanisms.

Several studies have reported an association between LyE and inflammatory bowel disease, but this has not been consistent. For example, Rubio et. al compared 20 patients with LyE to

61 patients with other types of esophagitis and found an association of LyE with Crohn's disease (CD), particularly amongst pediatric patients [1]. Similarly, in a pediatric population with known Crohn's disease, 28% of those patients were found to have increased lymphocytes [9]. A large pediatric cohort study by Sutton et. al found a significant association of CD in children with LyE (19% of children with LyE had CD and 12% of children with CD had LyE) [3,19]. This was not replicated in the study conducted by Purdy et. al [3]. A less frequent association was found in a study among adults by Basseri et. al [6]. Additionally, in a study of a very large esophageal biopsy database, Haque and Genta found that in adults, LyE affects predominantly older women and is not associated with CD [5]. In our study, we identified only one patient with concomitant inflammatory bowel disease (Crohn's disease).

It is important to differentiate between esophageal lichen planus and LyE. The most characteristic histologic finding in esophageal lichen planus is a bandlike or lichenoid lymphocytic infiltrate obscuring the interface between lamina propria and basal layer epithelium, with or without Civatte bodies. The histologic lesions illustrated in our report lack a lichenoid infiltrate. Lymphocytes are numerous, but they are generally distributed uniformly within a spongiotic epithelium. Lymphocyte-mediated epithelial cell injury is present in most lesions, but the injury is higher in the epithelial layer. Therefore, we believe that LyE is a different histologic entity than lichen planus, and the two do not overlap in our series.

Limitations of our study include the fact that this was a retrospective case series at a single center. Therefore, we did not have standardized follow up data and there were few patients who had repeat endoscopic assessments. Because of the relatively small number of cases, we were unable to control for potential confounders or perform detailed sub-analyses. However, there were also several strengths. We conducted an exhaustive review of pathologic records to capture all patients with possible LyE, even if the diagnosis had not been made clinically, and then confirmed the diagnosis of our cases after re-review of pathology slides by an expert pathologist. This strategy yielded a cohort size that is comparable to other studies. Additionally, we compared our findings in patients with LyE to patients with normal esophagus, GERD, and EoE controls to help contextualize the findings and identify risk factors.

In conclusion, though it is rare, LyE should be considered as a diagnostic possibility in patients with clinical symptoms of dysphagia undergoing upper endoscopy. Our data would suggest it is more likely to be seen in older female patients who smoke and who do not have atopy. With wider recognition of LyE it is also important to ensure training of pathologists to recognize this condition and ensure semi-quantitative reporting of lymphocyte numbers noted when clinically appropriate. Larger studies are needed to better characterize LyE and gain information on the natural history of this condition.

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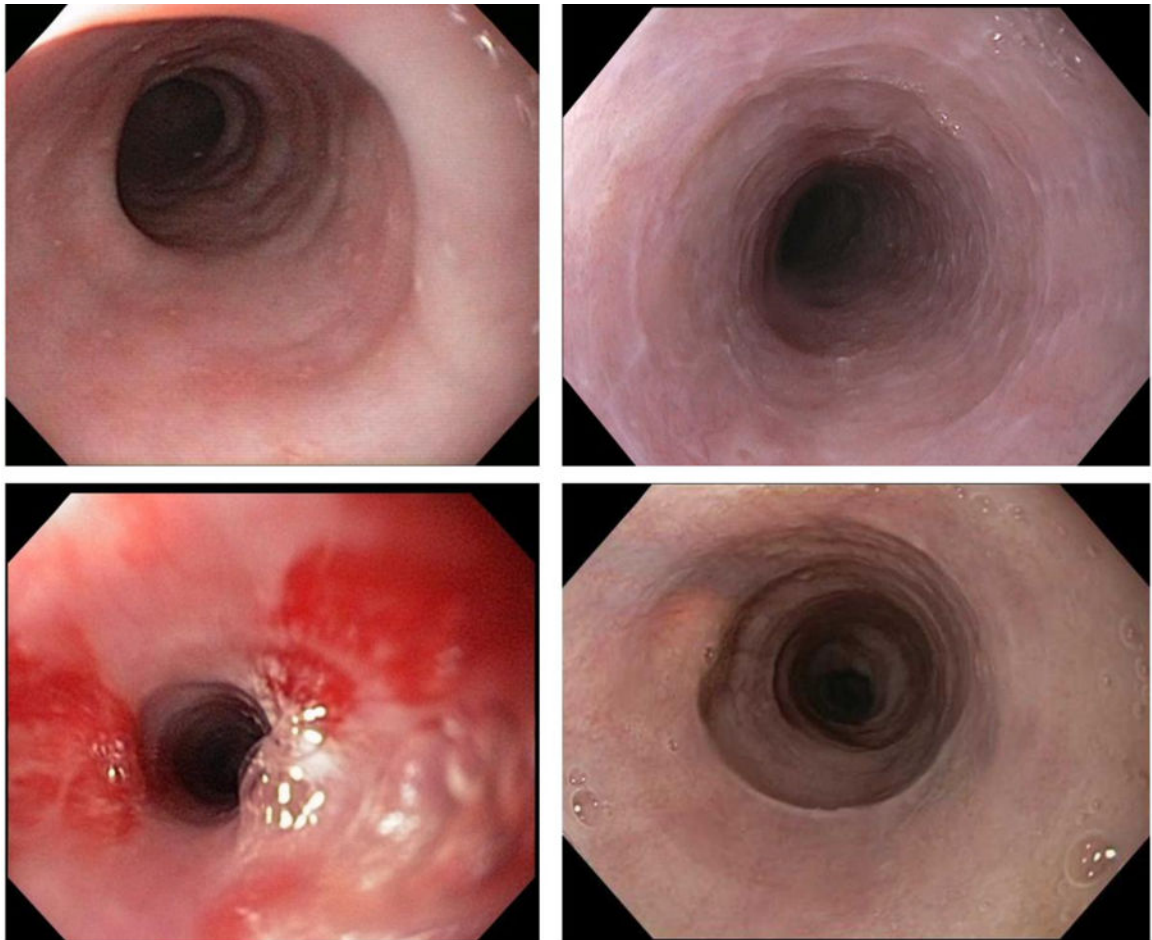


Figure 1. Endoscopic findings of patients with lymphocytic esophagitis illustrating narrow caliber esophagus, esophageal strictures, fine esophageal rings/webs, and erythema.

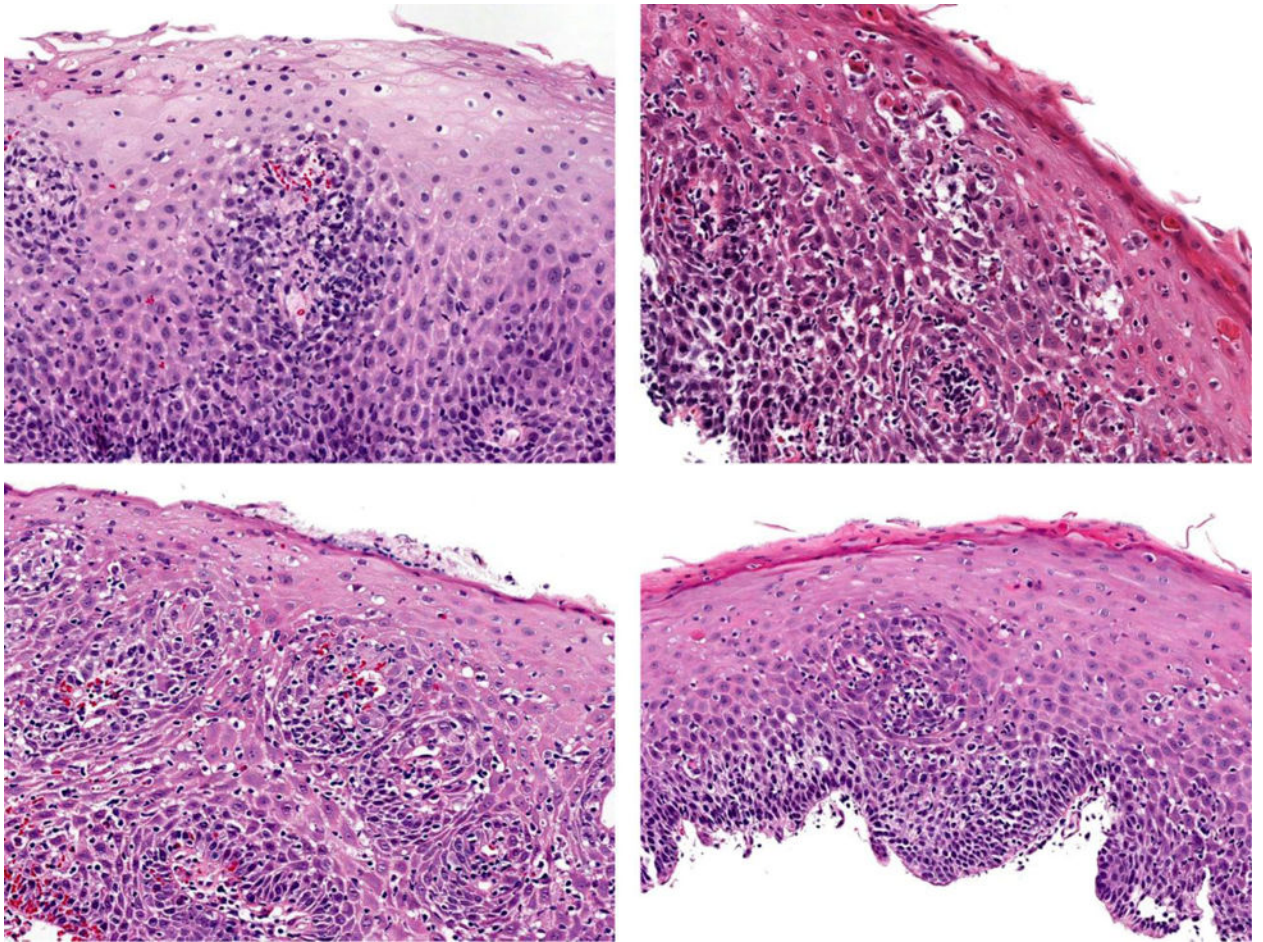


Figure 2. Histologic findings of patients with lymphocytic esophagitis showing esophageal squamous mucosa with variable spongiosis and increased numbers of intraepithelial lymphocytes in a diffuse distribution, ranging in numbers from mild to striking, occasionally forming small lymphocytic clusters, particularly in the peripapillary areas.

Table 1**Baseline Characteristics of LyE Patients (n = 27)**

Age, yrs (mean \pm SD)	56 \pm 16
Male, n (%)	10 (37)
Caucasian, n (%)	16 (59)
BMI, kg/m ² (mean \pm SD)	27 \pm 9
Year of initial diagnosis, n (%)	
2004	1 (4)
2005	2 (7)
2007	1 (4)
2008	3 (11)
2009	5 (18)
2010	5 (18)
2011	8 (30)
2012	2 (7)
Symptoms, n (%)	
Dysphagia	19 (70)
Asymptomatic	3 (11)
Heartburn	7 (26)
Abdominal Pain	4 (15)
Chest Pain	5 (19)
Nausea/vomiting	5 (19)
Odynophagia	1 (4)
Pertinent Medical History, n (%)	
Hx of Crohn's disease	1 (4)
Hx of Ulcerative colitis	0
Hx of or active GERD	14 (52)
Hx of BE	0
Hx of EoE	1 (4)
Hx of Achalasia	1 (4)
Hx of Drug medication allergies	10 (37)
Hx of Food allergies	1 (4)
Hx of Seasonal allergies	1 (4)
Hx of Asthma	5 (19)
Hx of Eczema	1 (4)
Hx of IBS	3 (11)
Hx of cancer	4 (14)
Habits, n (%)	
Alcohol Use (prior or current)	10 (37)
Tobacco Use (prior or current)	13 (48)
Pertinent Medication History, n (%)	
PPI use, n (%)	15 (59)

NSAID use (n=11), n (%) 7 (64)

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Table 2

Endoscopic findings, Lymphocytic count and Treatment

	n (%)
<u>Endoscopic Findings</u>	
Abnormal	23 (82)
Narrow Caliber	12 (44)
Esophageal Stricture	10 (37)
Esophageal Rings	7 (26)
Erythema	7 (26)
Hiatal Hernia	7 (26)
Erosive Esophagitis	9 (33)
Mucosal Pallor	3 (11)
Abnormal Vascular Pattern	2 (7)
Desquamation	2 (7)
Ulcer	1 (4)
Candidiasis	4 (15)
<u>Lymphocyte Count (n =25)</u>	
10–20 lymph/hpf	4 (15)
21–40 lymph/hpf	14 (52)
41–80 lymph/hpf	1 (4)
>80 lymph/hpf	6 (22)
<u>Medication Added or Changed After Endoscopy</u>	
PPI daily	6 (22)
GI cocktail (Maalox, viscous lidocaine, and donnatal)	1 (4)
Fluticasone	1(4)
Prednisone Taper	1(4)

Table 3

LyE patient characteristics compared to controls

	LyE (n= 27)	Normal (n= 20)	GERD (n=20)	EoE (n= 20)	P value
Age in years (Mean ± SD)	56 ± 16	57 ± 12	61 ± 15	36 ± 12	< 0.001
Female (%)	63	80	60	50	0.26
Race (%)					
Caucasian	59	85	100	95	
Black	37	15	0	5	<0.01
Hispanic	4	0	0	0	
Atopic Conditions (%)					
Drug	37	60	50	32	0.49
Food allergies	4	10	5	15	0.65
Allergic Rhinitis	4	25	25	40	0.02
Asthma	19	10	10	40	0.14
Eczema	4	0	0	0	0.67
IBD (%)	4	0	10	0	0.45
Alcohol use (%)	42	45	55	61	0.34
Tobacco use prior and current (%)	64	30	55	55	0.02
Endoscopic Findings (%)					
Hiatal Hernia	26	40	50	10	0.11
Erosive Esophagitis	33	25	40	0	0.01
Stricture	37	15	25	35	0.35
Rings	26	20	10	55	0.01
Dilation during endoscopy (%)	33	20	10	35	0.20