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Lymphocytic Esophagitis

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Abstract

Lymphocytic esophagitis is a new and rare entity, first described in 2006. Histologically, the esophageal mucosa is characterized by a dense peripapillary lymphocytic infiltrate and an intercellular edema without granulocytosis. To this day, it is not yet considered as a disease. Its etiology and clinical significance are still unclear. The predominant symptom is dysphagia and the main endoscopic feature is a normal esophagus. The absence of relationship between lymphocytic esophagitis and specific clinical conditions justifies further studies. Currently, it remains a histologic entity.

Keywords: lymphocyte, esophagitis, dysphagia, Crohn, CD4, CD8, motility

1. Introduction

Lymphocytic esophagitis is a histopathological entity described for the first time in 2006 by Rubio et al. [1]. Subsequently, several publications have confirmed the existence of this new condition. Research has allowed us to better characterize the histology of Lymphocytic esophagitis. Unfortunately, clinical presentation and treatment remain poorly understood.

2. Prevalence

Lymphocytic esophagitis is a very rare condition. In 2012, Haque et al. estimated its prevalence to 0.1% in the United States [2]. In their cohort that included 129,252 esophageal biopsies, a diagnosis of lymphocytic esophagitis was made in only 119 patients. Since Rubio’s first publication, there is a marked increase of its incidence, probably because of pathologists’ and gastroenterologists’ awareness [3].
Moreover, since it is a novel entity and most of the studies are from North America, worldwide prevalence has not been evaluated.

3. Histology

A small amount of intraepithelial lymphocytes is normally present in the esophagus [4, 5]. A majority of these lymphocytes are CD8 T cells, whereas CD4 are a minority and usually present in the lamina propria. An increase in CD8 T cells is seen in peptic and eosinophilic esophagitis. In addition, this lymphocytosis is generally accompanied by eosinophils and/or neutrophils [5–8].

Compared to other esophageal pathologies, lymphocytic esophagitis is characterized by an isolated lymphocytosis. The main histologic findings are a dense peripapillary intraepithelial lymphocytic infiltrate, an intercellular edema known as spongiosis, as well as the absence or rarity of granulocytes (Figure 1) [1]. The intraepithelial lymphocytes express CD3, CD4, and CD8, as shown by immunohistochemistry [1, 9, 11].

Unfortunately, because the histologic criteria are not yet standardized, it can sometimes lead to misdiagnosis. For instance, the presence of rare intraepithelial granulocytes is accepted in lymphocytic esophagitis [1, 2, 10, 11]. However, granulocytes can be found in various esophageal diseases, making diagnosis more difficult [11]. The acceptable number of granulocytes still needs to be better defined.

Figure 1. Lymphocytic esophagitis (H&E stain, original magnification ×40). Dense peripapillary lymphocytic infiltrate with spongiosis (arrow). Absence of neutrophils and eosinophils.
Because the lymphocytosis is patchy and uneven, we suggest not to establish a minimum number of intraepithelial lymphocytes [2]. In fact, the various studies about this entity have all used different cutoff, ranging between 10 and 50 lymphocytes per high-power field (HPF) [2, 3, 12, 13].

Furthermore, lymphocytic esophagitis affects the whole esophagus, but predominantly the distal esophagus. Thus, multiple biopsies are necessary to avoid a false negative because the lymphocyte infiltrates are not distributed evenly throughout the entire esophagus [12].

The mucosal involvement is considered mild if the intraepithelial lymphocytosis is only peripapillary and is severe if there is also an interperipapillary lymphocyte infiltration [12].

4. Clinical manifestations

Lymphocytic esophagitis seems to affect mostly women around 60 years old and smokers [2, 3, 10, 11]. The most common symptom is dysphagia [2, 8, 11, 13]. Nausea, vomiting, chest pain, heartburn, and episodes of impactions have also been reported; however, dysphagia remains the principal and most frequent complaint in 53% of cases [2, 3, 12]. Patients with lymphocytic esophagitis do not appear to show weight loss or fever.

The most serious complication is esophageal perforation. In 10 years, two cases of perforation have been reported. One of the two perforations occurred after the removal of a piece of impacted meat, while the second case was a spontaneous microperforation [14, 15].

5. Endoscopic features

Endoscopically, the most frequent findings are a normal esophagus or esophagitis [2, 3, 11]. Up to 33% of cases from the cohort by Haque et al. had findings suspicious of eosinophilic esophagitis such as stricture, rings, or felinization without eosinophilic esophagitis on the biopsies [2]. As described later, no other gastrointestinal involvement or association with gastritis or duodenitis has been described, thus stomach and duodenum endoscopic appearance is normal [12].

The endoscopic features are variable and not specific, which makes it impossible to identify and diagnose lymphocytic esophagitis by only relying on symptoms and gastroscopy. It is still a histologic condition, which is why biopsy is essential for the diagnosis.

6. Clinical associations

Some retrospective studies and case reports have tried to identify an association between lymphocytic esophagitis and other clinical conditions. Whether it was inflammatory
bowel disease, gastroesophageal reflux disease, celiac disease, asthma, allergies, irritants, or connective tissue diseases (lupus, Behçet’s disease), no relationship could be identified [2, 11–13, 16].

Lymphocytic esophagitis is isolated to the esophagus. It does not coexist with other digestive lymphocytosis such as lymphocytic colitis or lymphocytic gastritis. There is no correlation between these distinct entities. In a case series from Purdy et al., some patients had concomitant biopsies from the rest of the digestive tract (stomach, small intestine, or colon). The histologic findings in these biopsies were various and secondary to preexisting conditions. No lymphocytic entity was observed in the rest of the gastrointestinal tract [8].

6.1. Gastroesophageal reflux disease

One of the main research efforts was to identify a relationship between lymphocytic esophagitis and reflux. Unfortunately, no association has been established between these two conditions [2, 12]. Indeed, only 22 out of 119 patients in the cohort from Haque et al. had gastroesophageal reflux disease [2].

6.2. Crohn’s disease

In the cohort from Rubio et al., 8 of 20 patients had Crohn’s disease [1]. However, subsequent studies failed to replicate this association with inflammatory bowel disease [2, 11, 17]. Nevertheless, while it appears that it is not associated with inflammatory bowel disease in adults, lymphocytic esophagitis may be a manifestation of upper gastrointestinal Crohn’s disease in the pediatric population [1, 12, 10]. Indeed, seven out of eight Crohn’s disease patients from Rubio et al. were pediatric cases. Purdy et al. confirmed this association with the pediatric Crohn’s disease [1].

6.3. Eosinophilic esophagitis

Eosinophilic esophagitis has also been a subject of study and comparison with lymphocytic esophagitis. The clinical and endoscopic manifestations of lymphocytic esophagitis can be confused with those of eosinophilic esophagitis. It is only histology that allows us to differentiate these two entities. Felinization is not pathognomonic of eosinophilic esophagitis, hence the importance of biopsy [2].

In a recent cohort from Rubio et al., out of 311 biopsies with an increased number of intraepithelial lymphocytes, 33 cases were a compound of lymphocytic esophagitis and eosinophilic esophagitis [9]. We can thus ask whether these are two distinct conditions or whether one is the continuum of the other. However, this assumption remains a hypothesis and requires to be studied.

6.4. Motility disorders

Since 2014, an interest for esophageal motility disorders in lymphocytic esophagitis has arisen. Recent studies have demonstrated an association with achalasia and primary esophageal motility disorder (nutcracker esophagus, ineffective esophageal motility, and diffuse spasm) [18].
In 2015, Xue et al. noticed that esophageal biopsies in patients with primary esophageal motility abnormalities had CD4+ intraepithelial lymphocytosis. Moreover, Xue evoked the possibility of a new clinical entity that they called “dysmotility-associated LE.” We still need further studies to better understand and characterize this association [11].

7. Treatment

Treatment of lymphocytic esophagitis remains controversial. Very few studies addressed this subject. Because it is still a recent and rare entity, a majority of therapeutic trials have been reported in the form of case reports or retrospective studies.

Proton pump inhibitor, topical or oral steroids as well as esophageal dilation or injections of Botox have been tried. All these treatments have been partially effective [3, 13–16, 19–21]. Nevertheless, it is too early to establish which treatment is better and should be recommended.

The use of proton pump inhibitor is based on the belief that lymphocytic esophagitis may be associated with esophageal reflux. However, as mentioned earlier, this association remains unclear and unlikely. Nevertheless, given the low toxicity of proton pump inhibitors, we suggest using them as first line of treatment.

Concerning the efficacy of corticosteroids, it may suggest that lymphocytic and eosinophilic esophagitis belong to the same family.

8. Natural history

Unfortunately, we have very little data on the clinical course of this condition. Cohen et al. was the only one who studied this sphere through a survey he sent to 29 patients with lymphocytic esophagitis. In his cohort, patients report an improvement in their symptoms with medical treatment (proton pump inhibitor or anti-TNF for Crohn’s cases). Control endoscopies were performed in 22 out of 29 patients and 9 esophageal biopsies showed persistence of lymphocytic esophagitis despite treatment [3].

Current available literature points out that lymphocytic esophagitis is a chronic condition [12]. The risk of esophageal neoplasia is still unknown.

9. Conclusion

Lymphocytic esophagitis is a newly described clinical and histologic condition that will probably be increasingly recognized upon the next years. Recent publications have allowed us to establish clear criteria, thus facilitating the diagnosis. Clinicians need to be aware of this entity because lymphocytic esophagitis may eventually be in the diagnostic algorithm of dysphagia.

Pathologists are increasingly recognizing this condition, which is an asset for research. With larger cohorts, we will be able to further characterize its worldwide epidemiology, clinical
associations, as well as treatment and natural history. Single-cell analysis of the intraepithelial lymphocyte subtypes may help in understanding the pathophysiology of the condition and compare subgroups with compound eosinophilic esophagitis and those without. As Haque once said, “it is a condition in search of a disease.”

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