

# Lymphocytic Esophagitis

## A Histologic Subset of Chronic Esophagitis

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### Abstract

A novel histologic phenotype of chronic esophagitis, ie, lymphocytic esophagitis, is reported in 20 patients. Lymphocytic esophagitis is characterized by high numbers of intraepithelial lymphocytes (IELs) gathered mainly around peripapillary fields and by none ( $n = 12$ ) to occasional ( $n = 8$ ) CD15+ intraepithelial granulocytes. IELs expressed CD3, CD4 (42%), CD8 (36%), and granzyme B (0.2%), whereas T-cell intracytoplasmic antigen (TIA) 1 was not expressed. Of the 20 patients, 11 (55%) were 17 years or younger. Of 20 patients, 5 had no symptoms in the upper gastrointestinal tract. Only 4 (20%) of 20 patients had symptoms of gastroesophageal reflux disease and 6 (30%) of gastroduodenitis; 2 (10%) had celiac disease; 4 (20%) had carcinoma of the esophagus (1) or elsewhere (3); 1 (5%) each had hiatus hernia, gastric ulcer/asthma/blood hypertension, Hashimoto thyroiditis, and cirrhosis/diabetes; and 8 (40%) had Crohn disease. Hence, a novel histologic phenotype of chronic esophagitis called lymphocytic esophagitis is reported. Because phenotype is defined as the visible features resulting from the interaction between the genetic makeup and the environment, it is suggested that those factors might have a decisive role in the development of lymphocytic esophagitis.

The mucosa of the esophagus is built of a multilayer of squamous cells that protects the underlying tissues from possible aggressors contained in passing solids and fluids. The microenvironment on its surface is protected zealously by the alkaline pH from the saliva and the secretions of the esophageal glands.<sup>1</sup> It is, therefore, not surprising that the main offender is when the low pH of the gastric juices is refluxed into the lumen of the esophagus. This primary gastroesophageal reflux (GER),<sup>1,2</sup> if persistent, may severely alter the homeostasis of the esophageal microenvironment, leading to mucosal inflammation followed, in severe cases, by ulceration and the replacement of deeper layers by fibrotic tissue. The sequence of those events is known as gastroesophageal reflux disease (GERD).<sup>3</sup>

Inflammatory changes in the esophagus also might be induced by disparate external factors, such as fungus infections (*Candida albicans*), viruses, radiation, caustic substances, cows' milk allergy, corticoid or antibiotic therapy, or internal diseases such as diabetes, and general debilitation. Acid reflux from the stomach, however, is by far the most common cause for this condition. GERD is histologically characterized by an inward proliferation of the basal layers of the squamous epithelium.<sup>4,5</sup> Because the vascular network of the lamina propria does not follow suit, the papillae appear taller than normal. According to Ismail-Beigi and Pope,<sup>5</sup> basal cell hyperplasia and abnormally tall (ie, deep) papillae characterize grade 1 esophagitis. If the insulting factor persists or is strong enough, the epithelium becomes infiltrated by granulocytes, namely neutrophils, and/or eosinophils (grade 2 esophagitis). As a result of the inflammatory process, the mucosa may become gradually eroded or ulcerated (grade 3 esophagitis).

Several workers have studied the occurrence of intraepithelial lymphocytes (IELs) in lymphocytic granulocytic-associated GER esophagitis.<sup>4-10</sup> Wang et al<sup>11</sup> found a correlation between the number of T lymphocytes and intraepithelial eosinophils but not with the number of neutrophils. These authors concluded that intraepithelial T lymphocytes were not independent markers of reflux esophagitis.<sup>11</sup>

More recently, Butt et al<sup>7</sup> studied T-cell infiltration in cows' milk allergic esophagitis, an emerging clinical entity in children that is indistinguishable from primary GER except for its response to dietary antigen exclusion. The authors found in biopsy specimens from all subjects with cows' milk allergic esophagitis a strong up-regulation of eosinophil eotaxin expression limited to basal and papillary epithelium.<sup>7</sup> By contrast, weak expression of eosinophil eotaxin was found in a minority of control subjects and in 50% of patients with primary GER. The infiltration of CD3, CD4, and CD8 lymphocytes in cows' milk allergic esophagitis was significantly more than in control subjects. Butt et al<sup>7</sup> concluded that basal and papillary epithelial eosinophil eotaxin expression, with focal lymphocyte activation, often is present in infants with cows' milk allergic esophagitis-associated GER. The specific recruitment of T cells and eosinophils was thought to contribute to esophageal dysmotility.

Years ago, Mangano et al<sup>12</sup> reported the presence of IELs with irregular nuclear contours in the squamous epithelium of the esophagus from patients with clinical symptoms and/or endoscopic findings suggesting reflux esophagitis. More recently, in children with inadequate esophageal biopsy specimens, ie, not all parameters of esophagitis could be assessed, Esposito et al<sup>9</sup> found an elevated number of IELs with irregular nuclear contours and suggested that the number of these cells should be added to the traditional histologic features of esophagitis (such as architectural changes and granulocytic infiltration).

While reviewing the histologic features of the stomach in baboons, Rubio and Hubbard<sup>13</sup> noticed in one of them that the esophageal epithelium was infiltrated by a large number of lymphocytes with round and irregular nuclear contours but not by granulocytes. Since then, we have searched for cases with a similar histologic characteristic in human esophageal biopsy specimens.

We report our findings in 20 patients with an apparently novel subset of chronic esophagitis characterized by a high number of IELs, particularly in peripapillary fields.

## Materials and Methods

We studied esophageal biopsy specimens from 81 patients: 20 showing an increased number of IELs and lacking granulocytic intraepithelial infiltration and 61 control specimens having granulocytes and IELs (from 50 patients with

reflux esophagitis, 6 with postradiation esophagitis, and 5 with *C albicans* esophagitis).

Following the recommendations of Wang et al,<sup>11</sup> counting of IELs was done in the most densely populated field using high-power examination. According to Wang et al,<sup>11</sup> results are better when selecting those fields than when results are based on the average count of 3<sup>4</sup> or 5<sup>7</sup> fields for 2 reasons. First, the number of IELs varies considerably from one field to another, and the average count might not sufficiently reflect the severity of changes in the entire biopsy specimen. The second reason<sup>11</sup> is that the average numbers of IELs derive from varying number of fields because some of the biopsy specimens might contain fewer than 3 fields at high-power examination.

In the present work, we used high-power examination (×400). For this purpose, a 40× objective with a 0.95 aperture was used. With that setting (Labophot-2, Nikon microscope, Tokyo, Japan), the field (diameter, 490 μm) measured 188,574.5 μm<sup>2</sup>. It soon was realized that this area was too large to count IELs in peripapillary and interpapillary mucosal areas separately (one of the aims of this work). To differentiate these 2 areas, a square ocular frame limiting a 5 × 5-mm window was used. That square window (270 μm on each side) reduced the observing field to 72,900 μm<sup>2</sup>, which was 2.59 times smaller than the entire high-power area (ie, without using the 5 × 5-mm ocular frame). The reduction of the observed field permitted encompassing the peripapillary and interpapillary mucosal fields separately for counting IELs at high-power examination.

Counting was done without knowledge of the patient symptoms or possible clinical diagnosis of GER. One of us (K.S.) retrieved the clinical data from the medical charts. He was unaware of the results of the histologic review.

Besides H&E staining, several immunostains were done to subtype IELs: CD3 (recognizes T cells and a subset of natural killer [NK] cells, DakoCytomation, Glostrup, Denmark), CD4 (labels helper/inducer T cells, DakoCytomation), CD8 (detects cytotoxic-suppressor T cells, DakoCytomation), T-cell intracytoplasmic antigen (TIA) 1 (recognizes CD8+ T cells with cytotoxic potential involved in the cascade signaling Fas [CD95]-mediated apoptosis, Monosan, Uden, the Netherlands). and granzyme B (distinguishes activated cytotoxic T lymphocytes and NK-cells, Immunotech, Marseilles, France).<sup>14</sup>

The presence of neutrophilic and eosinophilic granulocytes was assessed in H&E- and Giemsa-stained sections. A recently described highly sensitive method to detect eosinophilic granulocytes using Giemsa-stained sections excited with indirect light fluorescence (Zeiss Axioskop fluorescent microscope) was applied.<sup>15</sup> CD15 immunostaining (Dako-Cytomation) was done; it recognizes neutrophils, eosinophils, and some monocytes but not basophils and lymphocytes.

Before counting, all sections in the 81 cases were coded to avoid bias. After counting, all sections were decoded. Sections from 10 consecutive cases with lymphocytic esophagitis and 10 consecutive cases with reflux esophagitis were selected for counting IELs with irregular nuclear contours in peripapillary and in interpapillary fields.

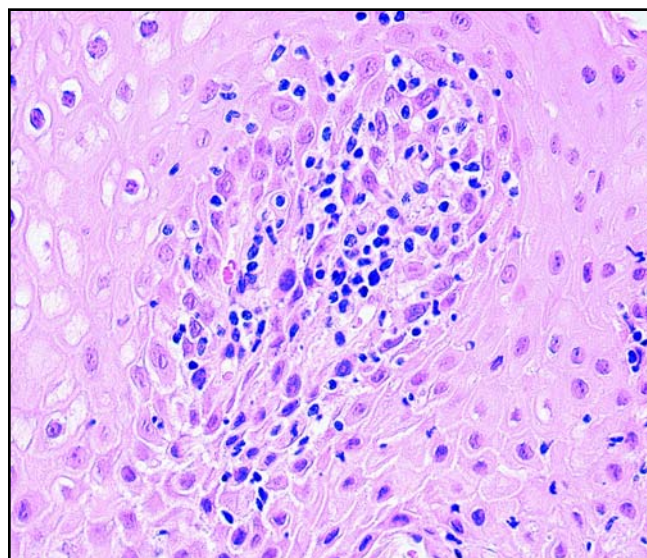
Data were analyzed by using a parametric *t* test and the nonparametric Wilcoxon test. A *P* value of less than .05 was considered significant.

## Results

The review of the study material indicated that there were 2 groups of patients: those with a high number of IELs in the squamous epithelium of the esophagus (henceforth named *lymphocytic esophagitis*) ■Image 1■ and ■Image 2■ and those with a low number of IELs (named *conventional esophagitis*).

### Lymphocytic Esophagitis

Clinical data for the 20 patients with lymphocytic esophagitis are shown in ■Table 1■. Of the 20 patients, 10 were males and 10 were females. The mean age was 31.3 years (range, 2-82 years). Of the patients, 11 (55%) were 17 years or younger. Table 1 shows that only 4 (20%) of 20 patients had symptoms compatible with GERD; 6 (30%) had gastroduodenitis; 2 (10%) had celiac disease; 4 (20%) had carcinoma of the esophagus (1) or elsewhere (3); 1 (5%) each had hiatus hernia, gastric ulcer/asthma/blood hypertension, Hashimoto thyroiditis, and cirrhosis/diabetes; and 8 (40%) had Crohn disease.



■Image 1■ Squamous epithelium of the esophagus infiltrated by high numbers of intraepithelial lymphocytes around peripapillary fields (H&E, original magnification ×40).

Notably, 5 of 20 patients had no symptoms in the upper gastrointestinal (GI) tract. Endoscopic examinations revealed esophagitis in only 8 (40%) of 20 patients; the remaining 12 patients had no signs of esophagitis at endoscopy.

Counting showed a mean of 55.1 IELs (range, 21-129) in peripapillary fields and 20.3 IELs (range, 2-55) in interpapillary fields. The difference between peripapillary fields and interpapillary fields was significant (*P* < .05).

### GI Biopsy Specimens From the Same Endoscopic Session

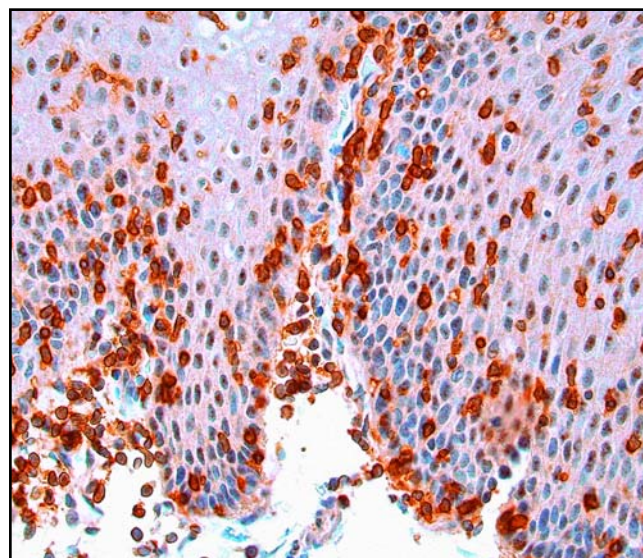
During the same endoscopic session leading to the diagnosis of lymphocytic esophagitis, biopsy specimens also were obtained from other levels of the GI tract: corpus, 14; antrum, 17; duodenum, 16; ileum (in connection with colonoscopies), 9; colon (at 9 levels), 81; and rectum, 9. Of the patients with lymphocytic esophagitis with biopsy specimens from GI sites other than the esophagus, 6 had chronic active gastritis, 2 focal active duodenitis, 2 villous atrophy of the duodenum, and 8 Crohn disease.

### Counting IELs With Irregular Nuclear Contours

A mean of 1.4% (range, 0%-5%) of the IELs in peripapillary fields were IELs with irregular nuclear contours, but as many as 57% (mean; range, 27%-69%) of the IELs in interpapillary fields were IELs with irregular nuclear contours. The difference was significant (*P* < .05).

### Immunohistochemical Findings

CD3 labeled all IELs, and CD4 was expressed in 42% (range, 22%-66%). CD8 was expressed in 36% (range, 12%-52%) and granzyme B in 0.2% (range, 0.1%-0.8%), whereas



■Image 2■ Squamous epithelium of the esophagus infiltrated by high numbers of CD3+ intraepithelial lymphocytes (CD3 immunostain, original magnification ×40).

**Table 1**  
**Clinical Data and Number of IELs in Peripapillary and Interpapillary Fields in Esophageal Biopsy Specimens From 20 Patients With a Final Histologic Diagnosis of Lymphocytic Esophagitis**

| Case No/<br>Sex/Age (y) | Upper GI Symptoms and<br>Endoscopic Findings | Endoscopically<br>Noted Esophagitis | Other Diseases             | No. of IELs   |                | Malignancy                              |
|-------------------------|--|-------------------------------------|----------------------------|---------------|----------------|---|
|                         |  |                                     |                            | Peripapillary | Interpapillary |   |
| 1/F/44                  | Hiatus hernia; GERD                          | No                                  | None                       | 43            | 6              | No                                      |
| 2/M/41                  | Gastroduodenitis                             | Yes, grade 2                        | CD; asthma                 | 41            | 15             | No                                      |
| 3/M/67                  | Gastroduodenitis                             | Yes                                 | Hepatitis B with cirrhosis | 92            | 32             | Hepatocellular cancer                   |
| 4/M/12                  | Epigastric pain; weight loss                 | No                                  | None                       | 45            | 49             | No                                      |
| 5/M/82                  | Hematemesis; melena                          | No                                  | Gastric cancer             | 91            | 13             | Poorly differentiated gastric carcinoma |
| 6/M/2                   | GERD   | Yes                                 | Food allergy               | 129           | 2              | No                                      |
| 7/F/56                  | Erosive gastritis; ulcer                     | No                                  | Asthma, blood hypertension | 66            | 16             | No                                      |
| 8/F/10                  | None   | No                                  | Villous atrophy, CD, SC    | 37            | 22             | No                                      |
| 9/M/3                   | GERD   | GERD                                | Asthma; atelectasis        | 31            | 3              | No                                      |
| 10/F/17                 | None   | No                                  | Villous atrophy, CD        | 21            | 4              | No                                      |
| 11/M/13                 | Gastroduodenitis                             | No                                  | CD                         | 96            | 22             | No                                      |
| 12/F/16                 | None   | No                                  | CD                         | 29            | 3              | No                                      |
| 13/F/11                 | None   | Yes                                 | CD                         | 56            | 21             | No                                      |
| 14/F/11                 | Achalasia                                    | No (dilated distal esophagus)       | Hashimoto thyroiditis      | 46            | 11             | No                                      |
| 15/F/11                 | None   | No                                  | CD                         | 58            | 19             | No                                      |
| 16/M/23                 | Vomiting; epigastric pain; gastroduodenitis  | Yes                                 | None                       | 23            | 14             | No                                      |
| 17/M/60                 | Dysphagia                                    | No                                  | Liver cirrhosis, diabetes  | 35            | 31             | Esophageal squamous carcinoma           |
| 18/M/72                 | None   | No                                  | None                       | 56            | 22             | Hypopharynx cancer                      |
| 19/F/61                 | GERD   | Esophagitis grade 2                 | None                       | 44            | 46             | No                                      |
| 20/F/13                 | None   | Aphthoid ulcerations                | CD; anorectal fistula      | 63            | 55             | No                                      |

CD, Crohn disease; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IELs, intraepithelial lymphocytes; SC, sclerosing cholangitis.

TIA-1 was not expressed. Occasional CD15+ cells were encountered in 8 of 20 cases of lymphocytic esophagitis. No CD15+ cells were found in the remaining 12 cases.

### Conventional Esophagitis

#### Reflux Esophagitis

Of the 50 control subjects with reflux esophagitis, 10 had grade 1 disease, 33 had grade 2, and 7 had grade 3. The mean age was 36.6 years (range, 4-76 years).

A mean of 7.2 IELs (range, 2-18) was found in peripapillary fields and a mean of 12.7 IELs (range, 6-56) in interpapillary fields. The difference between interpapillary fields and peripapillary fields was significant ( $P < .05$ ). All biopsy specimens from cases with esophagitis of grades 2 and 3 showed intraepithelial eosinophilic and/or neutrophilic granulocytes.

#### Postradiation Esophagitis

Six control subjects had clinical and histologic diagnoses of postradiation esophagitis. The mean age was 65.6 years (range, 60-72 years).

A mean of 3.4 IELs (range, 2-10) was found in peripapillary fields and a mean of 12.9 IELs (range, 3-56) in interpapillary fields. Biopsy specimens in 3 of the 6 cases had intraepithelial eosinophilic and/or neutrophilic granulocytes.

#### *C albicans* Esophagitis

Five control subjects had a histologic diagnosis of *C albicans* esophagitis. The mean age was 50.2 years (range, 32-60 years).

A mean of 1.7 IELs (range, 1-7) was recorded in peripapillary fields and a mean of 3.3 IELs (range, 3-13) in interpapillary fields. High numbers of intraepithelial granulocytes (including the most luminal epithelial layers) were present in cases with *C albicans* esophagitis.

Thus, in reflux esophagitis, postradiation esophagitis, and *C albicans* esophagitis, the mean number of interpapillary IELs surpassed that of peripapillary IELs.

### Discussion

The results of the present study showed that esophageal biopsy specimens from patients with lymphocytic esophagitis had high numbers of IELs in peripapillary fields. Much lower numbers of IELs were found in interpapillary fields. Apparently after crossing through the papillary vessels, lymphocytes congregated around peripapillary epithelial fields, suggesting that they have reached the epithelium through the basement membrane of papillary areas. This contrasted with the distribution of IELs in reflux, radiation, and *C albicans* esophagitis; in such cases, the number of

interpapillary IELs surpassed that recorded in peripapillary areas, suggesting that lamina propria lymphocytes might have reached the epithelium through the basement membrane of interpapillary areas.

The mean age of patients with lymphocytic esophagitis was less than that for control subjects. Interestingly, 55% of patients with lymphocytic esophagitis were 17 years or younger. These findings indicate that this subset of chronic esophagitis also should be sought among pediatric patients.

The main criteria for diagnosing lymphocytic esophagitis were the occurrence of high numbers of IELs in peripapillary fields and the absence of granulocytes (in 60% of the cases). Occasional granulocytes, however, were found in the remaining 40% of the cases. The presence of granulocytes was triple-checked (see the "Materials and Methods" section). In contrast, in GER-induced grade 2 and 3 reflux or *C albicans* esophagitis, many granulocytes (neutrophils and/or eosinophils) were present.

In lymphocytic esophagitis, a mean of 1.4% of the IELs in peripapillary fields showed irregular nuclear contours, but as many as 57% of the IELs in interpapillary fields had irregular nuclear contours. Although the cause for this significant difference remains unclear, it is conceivable that these irregular lymphocytes mirror cell deformation brought about by emperipolesis,<sup>16</sup> one of the mechanisms of lymphocytic transmigration within the squamous epithelium. The emperipoletic transmigration of peripapillary IELs might reflect a mechanism that is necessary to circumvent the barrier of strong desmosomes present in the intercellular spaces of the squamous epithelium.<sup>17</sup> Thus, transmigration in many IELs seems to take place sideways from peripapillary fields (rich in round IELs) to interpapillary fields (rich in IELs with irregular nuclear contours). From these results, it may be inferred that the pace of intraepithelial transmigration for deformed lymphocytes might not be the same as the pace of cell renewal of the squamous epithelium of the esophagus.<sup>18</sup>

Few of the cases with chronic lymphocytic esophagitis described herein had symptoms and/or endoscopic attributes of GER, suggesting that the high numbers of IELs and the scarcity of granulocytes might not be triggered primarily by GER but by other elusive causes.

High numbers of IELs were seen in the duodenal mucosa of 2 patients with total villous atrophy. It should be understood that high numbers of IELs is one of the important histologic parameters in duodenal biopsy specimens with villous atrophy in celiac disease. It is important to note that none of the biopsy specimens from sites other than the esophagus showed IELs. Thus, lymphocytic esophagitis seems to be a disease localized to the esophageal mucosa and not a phenomenon related to the infiltration of IELs in other mucosae of the GI tract, such as lymphocytic gastritis,<sup>19,20</sup> lymphocytic ileitis, and lymphocytic proctocolitis.<sup>21,22</sup>

Of particular interest was the finding that lymphocytic esophagitis was associated with Crohn disease. The question that arises is: Is lymphocytic esophagitis a manifestation of Crohn disease or just a haphazard association?

Part of the IELs in lymphocytic esophagitis were helper/inducer (CD4), cytotoxic-suppressor (CD8) T cells. Occasional cytotoxic T lymphocytes and NK cells (granzyme B) were found in the IEL population.<sup>23</sup> The significance of this aggressive phenotype of IELs in lymphocytic esophagitis remains unclear.

A novel histologic phenotype of chronic esophagitis, ie, lymphocytic esophagitis, is reported. The true causes for this apparently site-related chronic mucosal inflammation remain elusive. However, because *phenotype* is defined as the visible features resulting from the interaction between the genetic makeup and the environment, it is suggested that those factors might have a decisive role in the development of lymphocytic esophagitis.

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