Lymphocytic oesophagitis: clinicopathological aspects of an emerging condition

Salima Haque,1,2 Robert M Genta1,2,3

ABSTRACT
Objective Lymphocytic oesophagitis (LyE) has been reported in small series, but no consistent clinical correlations have emerged. The authors sought to determine the prevalence of LyE in a large population and define demographic, endoscopic and clinical findings associated with this condition.

Design In a pilot study, the authors established and disseminated criteria for the histopathological diagnosis of LyE to a group of gastrointestinal pathologists. Eighteen months later the authors reviewed cases with this diagnosis, collected demographic, clinical and endoscopic data, and compared them with patients with either eosinophilic oesophagitis (EoE) or normal oesophageal biopsies. The authors also determined the density of oesophageal lymphocytes in normal controls and in adults with established Crohn’s disease.

Results There were 129,252 unique patients: 40,665 had normal mucosa (median age 55 years; 32% men); 3745 had EoE (median age 43 years; 66% men). A diagnosis of LyE was made in 119 patients (median age 63 years, 40% men). Dysphagia was as common in these patients as in those with EoE (53% vs 63%; ns); gastro-oesophageal reflux disease — the most common complaint in patients with normal biopsies (37%) — was low in both the LyE and the EoE groups (18% vs 19%, ns). EoE was suspected in one-third of the patients.

Conclusion LyE was detected in ~0.1% of patients with oesophageal biopsies. The clinical and endoscopic characteristics of LyE and EoE overlap considerably; however, LyE affects predominantly older women. Although the precise clinical significance of oesophageal lymphocytic infiltrates remains to be defined, their association with dysphagia and possibly motility disorders warrants further investigations.

INTRODUCTION
Although lymphocytic infiltrates in the squamous oesophageal mucosa have been reported in association with reflux and infections,1–3 lymphocytic oesophagitis was described for the first time as an independent entity by Rubio et al in 2006.4 In their original description of 20 patients, these authors emphasised the predominantly peripapillary distribution of the infiltrating lymphocytes, which expressed CD3, CD4 and CD8 markers. Eleven of the patients were children, seven of whom had Crohn’s disease. No other clinical correlations could be established in this series, leading the authors to suggest that lymphocytic oesophagitis could be a manifestation of Crohn’s disease. In a later study Rubio et al expanded their observations to the oesophagus of baboons,5 in which a surprisingly high prevalence of lymphocytic oesophagitis (45%) was detected. However, this potentially useful animal model was not exploited further.

In an attempt to better characterise this histopathological finding, Purdy et al6 reviewed the clinical records of 42 patients in whom a histopathological diagnosis of increased intraepithelial lymphocytes had been made. No significant association with any symptoms or condition was detected and the authors dismissed it as a non-specific response of uncertain relevance. A recent report has emphasised the relationship between Crohn’s disease and lymphocytic oesophagitis in

Significance of this study

What is already known on this subject?
▶ Dense lymphocytic infiltrates are rarely found in the oesophageal mucosa.
▶ No definite clinical associations have been detected in adults.
▶ Oesophageal lymphocytic infiltrates have been found in a significant percentage of children with Crohn’s disease.

What are the new findings?
▶ One of 1000 patients who have oesophageal biopsies show dense peripapillary lymphocytic infiltrates and marked spongiosis in the oesophageal squamous mucosa.
▶ These patients present with dysphagia, odynophagia and motility disorders as commonly as patients with eosinophilic oesophagitis. Only one-fifth of these patients present with gastro-oesophageal reflux disease, as opposed to almost half of those with normal oesophagus or other types of oesophagitis.
▶ An endoscopic impression of eosinophilic oesophagitis is reported in one-third of these patients.
▶ In adults, lymphocytic oesophagitis affects predominantly older women and is not associated with Crohn’s disease.

How might it impact on clinical practice in the foreseeable future?
▶ If recognised and reported by histopathologists, more gastroenterologists will become aware of this entity and may ultimately discover aetiological associations and therapies.

SH and RMG are employees of Caris Diagnostics, Irving, Texas. This manuscript was written entirely by the authors, with no external assistance.

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children, but no correlations with oesophageal signs or symptoms were discovered.

In the past few years we observed several cases of patients who presented with dysphagia or odynophagia, had whitish punctuated elevations (‘papules’) in the oesophagus at oesophago-gastroduodenoscopy (EGD) and received a tentative clinical diagnosis of eosinophilic oesophagitis, but the oesophageal mucosa showed the characteristic dense peripapillary lymphocytic infiltration described by Rubio, rare or no eosinophils and neutrophils, and striking degrees of oedema of the intercellular spaces of the squamous epithelium (‘spongiosis’).

In another observation we noted in an experimental murine model that a lymphocytic infiltrate of CD3-positive cells, quite similar to the human ‘lymphocytic oesohagitis’, was an early response of the oesophageal squamous mucosa after an oesophagoduodenostomy.

These observations prompted us to design a study to explore the clinical, endoscopic and histopathological characteristics of patients with elevated intraepithelial lymphocytes in the oesophageal squamous mucosa.

**METHODS**

**Study setting**

This study was conducted at Caris Diagnostics, a specialised gastrointestinal laboratory receiving specimens from gastroenterologists operating in private outpatient endoscopy centres in 43 US states, the District of Columbia and Puerto Rico. Biopsies are interpreted by a group of gastrointestinal pathologists (39 at the time the study was concluded) located in three interconnected central laboratories. These pathologists share a common approach to biopsy evaluation and use a pre-determined approach to specimen handling, diagnostic criteria and terminology. To maximise consistency within the group, we rely on the following processes: (1) a daily consensus conference attended either in person or by videoconference by all pathologists in the three locations; (2) an extensive array of internally circulated diagnostic criteria, based on the published histopathological and gastroenterological literature, to which pathologists are strongly encouraged to adhere; and (3) a uniform set of diagnostic terms that include a code for electronic retrieval. Although interobserver variability cannot be eliminated in any setting, our internal data show a high level of agreement for many of the most notorious entities, including high-grade versus low-grade dysplasia in Barrett’s mucosa.

**Design**

This study was conducted in two phases. In the first phase we identified oesophageal biopsies with increased numbers of intraepithelial lymphocytes from the archives of our institution, reviewed the slides, obtained pertinent clinical data and endoscopic reports and attempted to establish criteria for the diagnosis of lymphocytic oesophagitis. In the second phase we disseminated the information to our group and established a code for diagnosis and retrieval. Eighteen months later we retrieved all cases that had a diagnosis of lymphocytic oesophagitis according to our suggested criteria.

**Sources of data**

During the first phase we analysed electronic data from the Caris Diagnostics database, which includes demographic and clinical information for each patient, a summary of the endoscopic findings or the entire endoscopic report, the site of origin of each specimen and the histopathological report for each biopsy. To identify the records for eligible oesophageal biopsies we extracted data for all patients who had undergone an EGD with a biopsy from January 2007 to June 2009, and whose biopsies were diagnosed at the Caris Diagnostics laboratory. Information regarding the histopathological features of the oesophageal biopsies was obtained by analysing individual diagnostic lines using additional search terms and Boolean logic in Visual Basic for Applications (VBA). Slides from all cases that included the terms ‘increased oesophageal lymphocytes, oesophageal lymphocytosis, lymphocytic oesophagitis or chronic oesophagitis’ were retrieved. Control cases were selected as detailed below.

For the second phase of the study we extracted appropriate clinical and histopathological information from all patients who had a diagnosis coded as lymphocytic oesophagitis from July 2009 through December 2010. We then reviewed the slides from each case and determined whether the diagnosis met the criteria. For comparison, we also searched the database for patients who had a histopathological diagnosis of ‘normal squamous mucosa’ in all their oesophageal biopsy specimens. In addition, we extracted patients with a histopathological diagnosis of ‘eosinophilic oesophagitis (EoE) pattern of injury’. In our laboratory this diagnosis is made when 15 or more eosinophils per high-power field, a superficial distribution of infiltrating eosinophils and eosinophilic microabscesses are detected in oesophageal biopsies from any site of the oesophagus excluding the gastro-oesophageal junction alone. Although most patients with these histopathological findings are likely to have the clinical condition known as eosinophilic oesophagitis, in the absence of a clinical confirmation, for the purposes of this analysis this group is referred to as ‘patients with oesophageal eosinophilia’.

**Histopathology**

For all histopathological observations we used an Olympus BX41 microscope equipped with a WHN10X-H/22 eyepiece. At a magnification of 40x the visual field corresponds to an area of 0.237 mm² (high-power field, or HPF). Results are reported in lymphocytes per mm²; however, because pathologists are more familiar with counts per HPF, these figures are also provided. The lymphocytes within the oesophageal squamous epithelium were counted in an average of 5 HPFs in each biopsy specimen.

Additional 4 μm sections were prepared from selected cases and immunohistochemical staining for the detection of CD3-, CD8- and CD20-positive lymphocytes were performed using commercially available immunoperoxidase-conjugated antibodies (Ventana Medical Systems, Tucson, Arizona, USA).

**Clinical and endoscopic information**

Information on the clinical indications that led to the performance of EGD was obtained from a specific field in the pathology requisition form, which in most patients is filled directly with data transferred from electronic report writers. In addition, the gastroenterologist who performed the endoscopy was then contacted by one of the authors and the full endoscopy report, a summary of the pertinent clinical, therapeutic and follow-up information (when available) were requested.

**Control subjects**

To determine the spectrum of normal content in our population, we counted lymphocytes in oesophageal biopsy specimens from either the lower or the middle third of the oesophagus from 100 patients who had a diagnosis of ‘unremarkable squamous mucosa’, no reported history of gastro-oesophageal reflux disease (GERD) and no known history of Crohn’s disease.
To determine whether the association with Crohn’s disease suggested by earlier work could be corroborated in our population, we also counted intraepithelial oesophageal lymphocytes in 20 adult patients who had a simultaneous ileocolonoscopy with a clinical and histopathological diagnosis of Crohn’s disease.

**Statistical analysis**

Statistical calculations were performed using SigmaStat V3.5 (Systat Software, Inc, Point Richmond, California, USA). Distributions of categorical variables were compared by an uncorrected \( \chi^2 \) test. Medians, means and standard deviations were calculated for continuous variables (age in years) and comparisons between groups were made by the Student’s \( t \) test. When normality check failed, the Mann-Whitney rank sum test for non-parametric data was used. Simple ORs were calculated using an online OR calculator.

**RESULTS**

**Control subjects**

**Normal subjects**

There were no detectable lymphocytes in 26 of the 100 normal control subjects; in the remaining 74 subjects the mean count (±SD) was 22±17 lymphocytes/mm\(^2\) (5±4 per HPF). The highest count found in a single subject was 50 lymphocytes/mm\(^2\) (12/HPF).

**Patients with Crohn’s disease**

The mean lymphocyte count per mm\(^2\) in 20 adults with clinically and histopathologically documented intestinal Crohn’s disease was 16±15 (3.9±5.5 per HPF), with a maximum of 63 lymphocytes/mm\(^2\) (15/HPF) in one patient.

**Patients**

**Phase I**

A total of 42 patients whose oesophageal biopsies were initially interpreted as having increased intraepithelial lymphocytes or features suggestive of lymphocytic oesophagitis had patchy peripapillary lymphocytic infiltrates with a density of at least 125 lymphocytes/mm\(^2\) (30/HPF) and were included in this phase of the study. This group included 26 women and 16 men and their median age was 52 years (range 20–84). The reasons for undergoing an EGD were: dysphagia or odynophagia (30 patients, 71.4%); GERD (11 patients, 26.2%); and non-cardiac chest pain (one patient, 2.4%). Possibly relevant clinical history included Crohn’s disease in two patients and sarcoidosis in one. None had a known history of either coeliac disease or gastrointestinal lymphocytic disorders. Medications prior to the endoscopy included proton-pump inhibitors in 41 patients (97.6%) and \( \mathrm{H}_2 \)-receptor blockers in one.

Endoscopically, nine patients (21.4%) had a normal oesophagus; 15 (31.0%) had distal oesophagitis; 13 (31.0%) had findings suspicious for eosinophilic oesophagitis, including rings or

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**Figure 1** Patchy peripapillary infiltrates in lymphocytic oesophagitis. 
(A) The left portion of the mucosa has only minimal infiltrates, which would have been insufficient to make a diagnosis of lymphocytic oesophagitis. In contrast, dense infiltrates are visible around most, but not all, papillae in panels B and C. Panel D is similar to panel A, with only minimal infiltrates. All four biopsy specimens were from the middle and lower oesophagus of the same patient.
features described as ‘felinisation;’ and 4 (9.5%) had a stricture. An impression of decreased motility was reported in three patients (8.8%).

Histologically, the oesophageal mucosa was characterised by patchy, predominantly peripapillary lymphocytic infiltrates (figure 1A). Virtually all intraepithelial lymphocytes were CD3+ T cells (figure 2B), with a majority also being CD8+. B cells were not seen within the squamous epithelium. Extremely rare neutrophils or eosinophils were seen in a patient. In addition, all patients had a striking amount of intercellular oedema ('spongiosis'), particularly pronounced in the areas affected by the lymphocytic infiltrates. The considerable patchiness of the peripapillary infiltrates can be appreciated in figure 1.

As a consequence of this study we suggested the following criteria for a diagnosis of lymphocytic oesophagitis: (1) dense peripapillary lymphocytic infiltrates; (2) peripapillary spongiosis involving the lower two thirds of the epithelium; and (3) absence of significant neutrophil or eosinophilic infiltrates.

**Figure 2** Lymphocytic oesophagitis. (A) Moderately dense peripapillary lymphocytic infiltrate in the squamous mucosa of the oesophagus, showing also intercellular oedema (spongiosis). Neither neutrophils nor eosinophils are present. (B) An immunohistochemical staining shows that virtually all infiltrating lymphocytes are CD3(+).

**Figure 3** Proposed criteria for the diagnosis of lymphocytic oesophagitis. Panel A depicts a section from a normal oesophageal mucosa: there are no infiltrating lymphocytes, the basal layer (B) is thin and uniform, and the cells are closely adherent to one another; the papillae, whether well oriented in the section (P1) of tangential cuts (P2) contain extravasated red blood cells, but no inflammatory cells. Panel B shows a heavy lymphocytic infiltration of the papillae and the peripapillary areas (P) in the absence of either neutrophils or eosinophils; the cells in the basal layer (B) have large nuclei and form several layers (‘basal hyperplasia’), and, particularly in the areas between arrows, are separated by intercellular oedema (‘spongiosis’). Although the two latter features may be found in reflux oesophagitis, dense lymphocytic infiltrates are not characteristic of this entity. Panel C shows an extraordinarily heavy lymphocytic infiltrate affecting three adjacent papillae (P); there is also severe spongiosis and basal layer hyperplasia. The specimen in panel D was not optimally oriented; therefore, the papillae (P) have a round appearance and the lymphocytic infiltration appears more diffuse. An additional feature in this specimen is the presence of numerous necrotic keratinocytes (arrows), a common finding in cases with heavy infiltrates such as this one.
Because of the intense, characteristically peripapillary and patchy nature of the infiltrates, we concluded that including a ‘required’ minimum lymphocyte count could be potentially misleading and would not increase the specificity of the diagnosis. These initial criteria are illustrated in figure 3.

**Phase II**

**Categorisation of oesophageal conditions**

Between July 2009 and December 2010, a total of 129,252 unique patients had oesophageal biopsies; of these 142 had a diagnosis of lymphocytic oesophagitis and 3,745 had a diagnosis of EoE pattern of injury. In 40,665 patients all biopsies from the oesophagus and the gastro-oesophageal junction were diagnostically normal. The remaining 84,700 patients with other diagnoses (including reflux and other types of oesophagitis and Barrett’s mucosa) are not included in this analysis.

**Case selection**

After reviewing both report and slides from each of the 142 cases diagnosed as lymphocytic oesophagitis, we reached a consensus to exclude 23 patients (8 had concurrent fungal infection; 7 had lymphocytic infiltrates only in the immediate vicinity of the squamocolumnar junction; 6 patients had rare lymphocytes unaccompanied by distinctive peripapillary spongiosis; one patient met the histological criteria for eosinophilic oesophagitis; and one patient had active oesophagitis with the characteristic histopathological features of reflux-induced damage). Therefore, a total of 119 patients with the histopathological features of lymphocytic oesophagitis were included in the final analysis. Demographic data from these patients are summarised in table 1.

**Clinical presentation**

Compared with those with normal oesophageal biopsies, patients with lymphocytic oesophagitis were older (median age 63 vs 55 years; p<0.001), and slightly, but not significantly, more likely to be female. Clinically, they presented more often with dysphagia (52.9% vs 33.0%; p<0.0001) and were more likely to be suspected of having EoE (31.1% vs 26.3%; p<0.001). In contrast, a significantly lower proportion of patients with lymphocytic oesophagitis (18.2%) presented with GERD than patients with a normal oesophagus (37.4%; p<0.01). Patients with lymphocytic oesophagitis were almost as likely as patients with oesophageal eosinophilia to present with dysphagia (52.9% vs 63.3%; not significant) or GERD; a clinical suspicion of EoE was reported less commonly in patients with lymphocytic oesophagitis than in those who had oesophageal eosinophilia (31.4% vs 57.9%; p<0.0001) (table 1). The endoscopic features, summarised in table 2, were considered suggestive of EoE in more than one-third of the patients. These included ‘felinisation’ with furrows (figure 4), whitish plaques and strictures. A concurrent Zenker’s diverticulum was found in one patient; one patient had food in the oesophagus and was suspected to have achalasia.

Possibly relevant medical history included radiation or chemotherapy for treatment of tonsillar, vocal cord, jejunal and colon carcinoma in four patients; and rheumatological conditions (systemic lupus erythematosus, scleroderma, unspecified arthritis, Raynaud’s phenomenon and fibromyalgia) in five patients. There was a reported history of alcohol abuse in three patients. Virtually all patients had received proton-pump inhibitors; use of aspirin and other non-steroidal anti-inflammatory drugs was highly prevalent, but none emerged as being more commonly used in this group of patients.

Follow-up information was available for a very limited number of patients: the most common treatments consisted of

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**Table 1** Simultaneous gastric biopsies were available in 70 patients with LyE, 2,113 patients with EoE and 31,758 with normal oesophagus; duodenal biopsies were available in 39 patients with LyE, 1,052 patients with EoE and 15,007 with normal oesophagus; and ileal or colonic biopsies were available in 13 patients with LyE, 389 patients with EoE and 6,095 with normal oesophagus.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Lymphocytic oesophagitis</th>
<th>Oesophageal eosinophilia (&gt;15 eos/HPF)</th>
<th>OR (95% CI) (LyE vs EoE), probability</th>
<th>Normal oesophageal mucosa</th>
<th>OR (95% CI) (LyE vs normal), probability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number</strong></td>
<td>119</td>
<td>3,745</td>
<td>—</td>
<td>40,654</td>
<td>—</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>63</td>
<td>43</td>
<td>p&lt;0.001</td>
<td>55</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>47 (39.5%)</td>
<td>2,461 (65.7%)</td>
<td>0.34 (0.23 to 0.49), p&lt;0.0001</td>
<td>14,119 (31.6%)</td>
<td>1.24 (0.86 to 1.78), ns</td>
</tr>
<tr>
<td><strong>Clinical manifestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>63 (52.9%)</td>
<td>2,371 (63.3%)</td>
<td>1.00 (0.66 to 1.51), ns</td>
<td>10,490 (33.0%)</td>
<td>4.97 (3.32 to 7.46), p&lt;0.0001</td>
</tr>
<tr>
<td>GERD</td>
<td>22 (18.5%)</td>
<td>707 (18.9%)</td>
<td>0.95 (0.60 to 1.52), ns</td>
<td>11,894 (37.4%)</td>
<td>0.54 (0.34 to 0.85), p&lt;0.01</td>
</tr>
<tr>
<td>Suspected EoE</td>
<td>37 (31.1%)</td>
<td>2,170 (57.9%)</td>
<td>0.33 (0.22 to 0.49), p&lt;0.0001</td>
<td>8,379 (26.3%)</td>
<td>1.76 (1.20 to 2.59), p&lt;0.01</td>
</tr>
<tr>
<td><strong>Concurrent pathology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori gastritis (n=79)</td>
<td>7 (8.9%)</td>
<td>100 (4.7%)</td>
<td>2.16 (1.02 to 4.92), p&lt;0.05</td>
<td>2,330 (7.3%)</td>
<td>1.01 (0.47 to 2.17), ns</td>
</tr>
<tr>
<td>Coeliac disease (n=39)</td>
<td>3 (7.7%)</td>
<td>10 (1.0%)</td>
<td>9.50 (2.57 to 34.9), p&lt;0.01</td>
<td>179 (1.1%)</td>
<td>5.75 (1.81 to 18.2), p&lt;0.0001</td>
</tr>
<tr>
<td>Duodenal lymphocytosis</td>
<td>2 (5.1%)</td>
<td>24 (2.3%)</td>
<td>2.60 (0.61 to 11.5), ns</td>
<td>451 (3.0%)</td>
<td>1.49 (0.36 to 6.04), ns</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>0</td>
<td>5 (0.2%)</td>
<td>—</td>
<td>31 (0.5%)</td>
<td>—</td>
</tr>
</tbody>
</table>

EoE, eosinophilic oesophagitis; eos, eosinophils; GERD, gastro-oesophageal reflux disease; HPF, high-power field; LyE, lymphocytic oesophagitis.

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**Table 2** Endoscopic impressions reported in 119 patients with lymphocytic oesophagitis.

<table>
<thead>
<tr>
<th>Endoscopic impression</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal oesophagus</td>
<td>27</td>
<td>22.6</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>22</td>
<td>18.5</td>
</tr>
<tr>
<td>With suspicion of Barrett’s</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Eosinophilic oesophagitis</td>
<td>40</td>
<td>33.6</td>
</tr>
<tr>
<td>With rings or furrows</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>With whitish plaques</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>With stricture</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Stricture</td>
<td>12</td>
<td>10.1</td>
</tr>
<tr>
<td>Motility disorder</td>
<td>6</td>
<td>5.0</td>
</tr>
<tr>
<td>Schatzki ring</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Candida</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Achalasia</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Not reported</td>
<td>6</td>
<td>5.0</td>
</tr>
</tbody>
</table>
had simultaneous ileal or colonic biopsies and none had Crohn’s disease, ulcerative colitis or microscopic colitis.

**DISCUSSION**

Lymphocytic oesophagitis, defined histopathologically as the presence of dense lymphocytic infiltrates in the peripapillary oesophageal squamous mucosa and marked spongiosis in the absence of significant numbers of neutrophils or eosinophils, is a rare condition. When the above criteria were applied, it was diagnosed in approximately one in a thousand patients who had oesophageal biopsies. This low prevalence explains why it is so infrequently detected in pathological practices; it also explains why in the Kalixanda study, a population-based study of EoE in which also intraepithelial lymphocytes were counted in oesophageal biopsy specimens from 1000 Swedish volunteers, no cases of lymphocytic oesophagitis were detected.11

Initially, while attempting to formulate a set of practical criteria for the histopathological diagnosis of this condition we considered requiring a minimum of 30 lymphocytes per high-power field. However, as we gained more experience, it seemed clear that lymphocytic infiltrates were patchy; while non-affected areas had often only scattered lymphocytes, the counts could easily exceed 50 and even 100 in the affected peripapillary zones. Therefore, also to avoid the controversies that have plagued the definitions of eosinophilic oesophagitis,12–15 we refrain from requiring a minimum density of lymphocytes. We feel that their distribution, peripapillary location and association with spongiosis are more important and reliable criteria.

Oedema of the intercellular spaces of the squamous epithelium (‘spongiosis’) is a non-specific inflammatory response that may also occur in patients with gastro-oesophageal reflux and eosinophilic oesophagitis; however, in neither of these two conditions does the intensity of the inflammatory response approach that found in association with peripapillary lymphocytic infiltrates.

In our series, more than two-thirds of the patients presented with symptoms attributable to oesophageal disease, most commonly dysphagia or odynophagia, which elicited a clinical suspicion of EoE in about one-third of the patients. GERD was less common than in patients with other diagnoses, confirming the observations of Purdy et al.6 Endoscopically, findings suggestive of eosinophilic oesophagitis, including rings and, more rarely, furrows, white plaques, and strictures were reported in one-third of the patients. Notably, none of these patients had eosinophilic infiltrates. An impression of oesophageal motility disorder was noted in 6 patients and strictures in a total of 13 patients; since sufficient sampling of the submucosa is rarely available in oesophageal biopsy specimens, it was impossible to determine whether a process similar to the tissue remodelling that occurs in patients with EoE was taking place in these patients, possibly induced by long-standing chronic inflammation.16 A similar number of patients had oesophagitis (in most cases designated as LA grade A) and an endoscopically normal oesophagus (19% vs 17%).

In a study such as this one it is impossible to speculate about a possible aetiology for these lymphocytic infiltrates. Proton-pump inhibitors have been implicated in the aetiology of lymphocytic and collagenous colitis.17,18 Although almost all patients (both in phase I and II of the study) were regular users of proton-pump inhibitors, the widespread usage of this class of drugs and the rarity of lymphocytic oesophagitis make it virtually impossible to establish an association. Similarly, non-steroidal anti-inflammatory drugs were widely used by these

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**Histopathological associations**

The prevalence of possibly relevant concurrent pathological changes in other parts of the gastrointestinal tract are summarised in table 1. Helicobacter pylori infection had similar prevalence in the 79 patients with lymphocytic oesophagitis who had simultaneous gastric biopsies and in patients with a normal oesophageal mucosa (8.9% vs 7.3%, non-significant). In contrast, the prevalence of H pylori was significantly lower in patients with oesophageal eosinophilia (4.7%, p<0.05). None of the patients had also lymphocytic gastritis.

Coeliac sprue was diagnosed in 2 of the 39 patients with lymphocytic oesophagitis who also had duodenal biopsies (7.7%), in contrast to 1.1% in patients with normal oesophagus and 1% in those with oesophageal eosinophilia (p<0.001 and <0.01, respectively). Only 13 patients with lymphocytic oesophagitis had simultaneous ileal or colonic biopsies and none had Crohn’s disease, ulcerative colitis or microscopic colitis.
patients, but no single drug emerged as being more commonly used than others.

In our patients EoE was more prevalent in younger men (median age 43 years, 66% men); in contrast, lymphocytic oesophagitis affected predominantly older women (median age 63 years, 60% women). Even if more patients with lymphocytic oesophagitis had coeliac sprue than other patients with oesophageal biopsies, the numbers were small. Overall, the simultaneous presence of other lymphocytic conditions of the gastrointestinal tract was rare, so that in none of the patients it was possible to speculate on the existence of a lymphocytic diathesis.

Notwithstanding some of the associations mentioned above, the clinical significance of this constellation of histopathological findings that we are calling lymphocytic oesophagitis remains elusive. In part, this may be due to the limitations imposed by the nature of our study. Although clinicians provided written clinical and endoscopic information for 94 of our 119 patients, the long interval frequently elapsed between the diagnosis and the request for information was not conducive to a distinct recollection of the clinical aspects of each patient. Furthermore, it became apparent that most clinicians interpreted the diagnosis of lymphocytic oesophagitis as somewhat equivalent to reflux oesophagitis and in the majority of patients responded by increasing the dose of proton-pump inhibitors. When follow-up information was provided it was relatively generic (symptoms persisted or waned) and no follow-up biopsy specimens were obtained.

In spite of these uncertainties, or perhaps because of them, we surmise that it would be short-sighted for pathologists not to report lymphocytic oesophagitis in oesophageal biopsies. A distinct histopathological entity exists. For the time being, to paraphrase Luigi Pirandello, it is a condition in search of a disease. As for all rare conditions, only the careful reporting of all cases will allow collecting numbers sufficient to unveil the clinical and aetiological relationships. Also, considering the indolent clinical response to a diagnosis of lymphocytic oesophagitis, pathologists might want to consider contacting the clinicians directly to discuss the findings and the possible significance in each case.

Acknowledgements Ms Brandy Smiddy, Client Services, Caris Diagnostics, cooperatively assisted with the requests of additional clinical and endoscopic information from the physicians involved in the care of the patients reported here.

Competing interests None.

Ethics approval This study was approved by the Institutional Review Board of Caris Diagnostics, Irving, Texas, USA.

Contributors SH and RMG contributed equally to the study. Specifically, they conceived and designed the study; collected data; reviewed the slides, the clinical histories and the endoscopic reports. RMG wrote the manuscript and SH participated in and approved the completion of each draft, including the final draft hereby submitted.

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Lymphocytic oesophagitis: clinicopathological aspects of an emerging condition

Salima Haque and Robert M Genta

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