Review paper

# Lymphocytic gastritis

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Organic basis of gastrointestinal symptoms is in the scope of many specialists. In this article lymphocytic gastritis, relatively newly described and not widely-known entity is presented. The lesion is characterized by presence of numerous mature lymphocytes in the surface and foveolar epithelium, as well as lymphocytic infiltration of the lamina propria. According to the definition at least 25 lymphocytes per 100 gastric epithelial cells is now required for the diagnosis. Literature found in wide range of databases was searched for morphological features of lymphocytic gastritis and its relationship with others coexisting or predisposing conditions or lesions. A strong positive correlation between celiac disease and *Helicobacter pylori* infection, and occurrence and severity of lymphocytic gastritis was revealed. A relationship was also found between lymphocytic gastritis and gastric lymphomas and other conditions.

**Key words:** lymphocytic gastritis, chronic gastritis, intraepithelial lymphocytes, *Helicobacter pylori*, celiac disease.

## Introduction

About thirty years ago, Haot *et al.* [1] described endoscopic and microscopic features of the condition, they called lymphocytic gastritis (LG), characterized by accumulation of lymphocytes in the gastric epithelium. In fact, the lesion probably corresponds to previously reported one (in 1945) called varioliform gastritis with very unusual gross appearance, i.e. thick gastric folds with central umbilications surrounded by redness [2].

Lymphocytic gastritis is regarded rare entity, comprises 1-5% of all chronic gastritis cases underwent upper gastrointestinal endoscopy [1]. However, based on broad series of microscopically examined gastric biopsies, Odze [3] estimated its prevalence as less than 0,3%. It usually concerns adults in 5-6$^{th}$ decade, men and women equally [3], but in patients with celiac disease the condition is more frequent in women [3]. Patients with LG do not present specific symptoms. The most common ones are dyspepsia, upper abdominal pain, heartburn, vomiting or weight loss [3, 4]. The symptoms may also be caused by primary diseases that are believed to be linked with LG, like gastric lymphomas, HIV infection, Crohn's disease, Menetier's disease, inflammatory polyp, or esophageal carcinoma. However, there are the convincing evidences of association of LG with two other conditions which are: *Helicobacter pylori* (HP) infection and celiac disease (CD) [3]. The frequency and character of the linkage between these conditions vary between different studies.

## Morphology of lymphocytic gastritis

In many endoscopic examinations, the stomach in patients with LG seems unchanged, however variable macroscopic lesions might be visible. The most frequent are erosions with or without mucosal elevations, as they are found in 55% of cases [5]. The others might include nodularity or mucosal elevations, polyps, aphthous erosions, ulcers or ulcer scars. Thickened or giant gastric folds like that in hypertrophic gastritis, or above mentioned – nodular targetoid

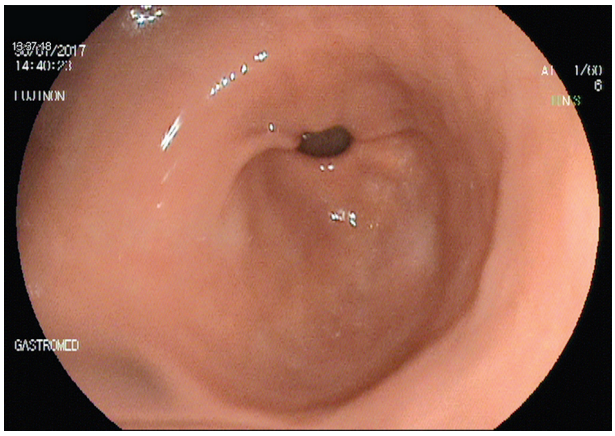


**Fig. 1.** Endoscopic image of gastric mucosa of patient with incidentally diagnosed lymphocytic gastritis. Local spots in antral part of the stomach

erosions (varioliform) are rarely observed [5, 6, 4]. Moreover, local spots (Fig. 1) or mosaic structure of the mucosa might be found. The most common location of the lesions are the body and the antrum as together they are included almost 90% of cases [7].

The diagnosis of LG is based on microscopic examination of gastric mucosa and according to current definition the main feature is a presence of at least 25 intraepithelial lymphocytes (IEL) per 100 gastric surface and foveolar epithelial cells [1, 2, 3]. Those lymphocytes are usually round and small [2]. Inside the cells, there is a clear halo, nuclei are small, hyperchromatic and round. The cells stay usually single, spread evenly in the surface and foveolar epithelium [2] (Fig. 2A, B). Most of these lymphocytes present CD3+ and CD8+ phenotype [6] (Fig. 3A-C). Microscopic examination can also reveal other lesions like foveolar epithelial hyperplasia, epithelial proliferation and glandular atrophy as well as intestinal metaplasia [2, 3, 7]. Apart from lymphocytes, neutrophils might be occasionally found in the gastric mucosa [2, 3].

## Pathogenesis of lymphocytic gastritis

### Association of lymphocytic gastritis with *Helicobacter pylori* infection

*Helicobacter pylori* infection is known to cause a condition called chronic active gastritis, which can be defined as presence of inflammatory infiltrate composed of lymphocytes, plasmocytes, and neutrophils within the gastric mucosa [8].

*Helicobacter pylori* infection is also known to be associated with LG. The presence of infection in patients with LG varies between studies, reaching from 0 up to 27% [2, 6]. It rarely concerns children and young adults below 2nd decade of life [8, 9, 5]. On one hand, only less than 5% of patients with HP infection develop LG, while chronic active gastritis is developed in up to 80% of cases [8]. It has been noticed that eradication of HP decreases number of IELs, even if the symptoms remain [10]. Nielsen *et al.* [6] suggested that due to that fact, the condition should be rather named "active chronic gastritis", not "lymphocytic gastritis", but nowadays the former term is used to describe an above-mentioned, different pathology. However, some studies show lack of important correlation between HP infection and LG [6].

There is some evidence that lower number of bacteria is present in LG, than in non-lymphocytic HP-associated gastritis [6]. On the other hand, LG is sometimes present only in a serologically positive *H. pylori* infection and in such cases levels of antibodies are higher than in patients with non-LG. It may

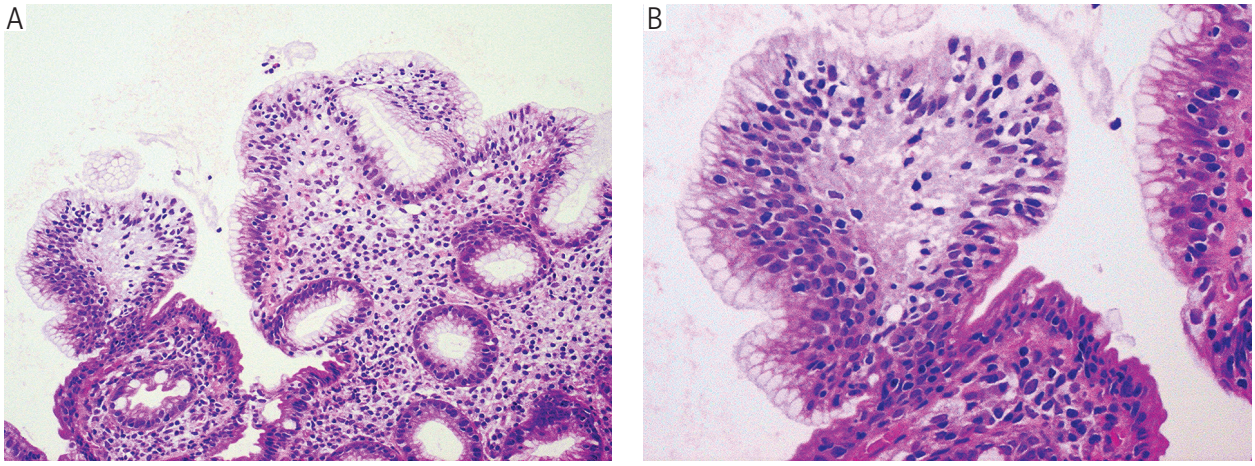


**Fig. 2.** Dense lymphocytic infiltration of both surface and foveolar epithelium and proper gastric in lymphocytic gastritis (A and B: HE, objective magnification A – 10×; B – 20×)

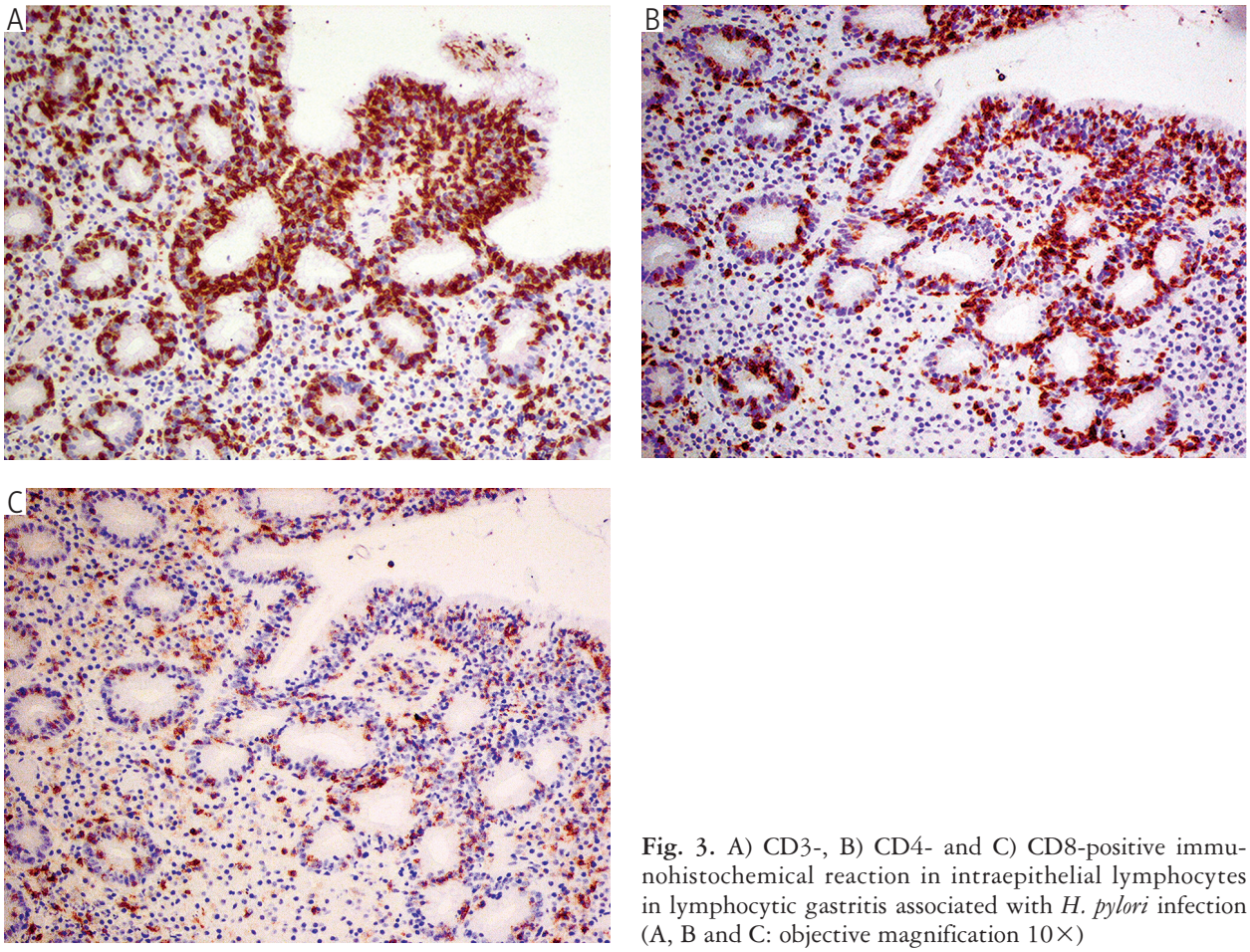


**Fig. 3.** A) CD3-, B) CD4- and C) CD8-positive immunohistochemical reaction in intraepithelial lymphocytes in lymphocytic gastritis associated with *H. pylori* infection (A, B and C: objective magnification 10×)

lead to the conclusion that the presence of antigen, not infection itself contributes to development of LG [6].

Additionally, spontaneous remission of LG after treatment only with H2 blockers or proton pump inhibitors without antibiotics, has been described in the literature [11]. It has also been noted that therapy of HP infection even without microscopically confirmed presence of the bacteria can lead to improvement of patients' clinical state [11]. Even without presence of HP in the gastric biopsy, it is possible that a result of a serological test towards HP in patients diagnosed with LG is positive. This might be caused by either unnoticeable level of the infection or by the fact that LG might only be an immunological reaction to the presence of bacterial antigen without an infection itself. The second thesis can be additionally supported by the finding that a considerable number of patients develops LG in only serologically positive HP infection [12]. Nielsen *et al.* [6] observed that in nine of their microscopically-negative patients, two had positive serology towards HP. Treatment of HP infection can lead to a significant reduction not only the number of bacteria but also in the number of IELs [11] or only lower of IEL count, but it also leads to improvement in microscopic appearance of mucosa in terms of increased proliferation, foveolar hyperplasia, inflammatory activity and glandular atrophy that are present in HP-associated LG [7].

The kind of IEL that appear in HP infection associated with LG seems to be slightly different in comparison to other clinical situations. There is less activated cytotoxic T-cells in the epithelium in HP infection, which means that their cytotoxic activity is lower. Activated T-cells show activity of granzyme B (GrB). In HP associated LG, the number of such cells is 10.8%, while in celiac disease (CD), for example, it is 12-18.9% [13]. On the other hand, there are more GrB+ cells in HP-associated LG that in other types of HP-associated gastritis [13]. Moreover, in such cases, the amount of GrB+ cells positively correlate with apoptotic activity [13]. A more detailed study shows that there is a slight increase of CD4+ cells in HP than in CD, and no statistical difference of B- and NK cell compare to a healthy control group [12].

Moreover, apoptotic and cytotoxic activity of the lymphocytes is more strongly marked in HP-associated LG than in chronic HP gastritis. In cases

of the latter lager number of T-helper cells are observed among IEL than in LG [12]. In HP-infection-associated LG a presence of many granulocytes in gastric mucosa is noted [2], which is not observed in celiac-disease-associated LG [13].

However, some studies show lack of correlations between occurrence of HP infection and development of LG. Nielsen *et al.* [6] revealed that the percentage of the patients with HP infection is equal in both: those who present LG and those who do not. In this study, 54 patients with a diagnosis of LG were examined, and none of them suffered from a HP infection, confirmed by microscopic examination of a gastric biopsy, while e.g. CD was found in 12 of them. As mentioned before, nine of the patients had been serologically tested for HP but only 2 were positive. That finding led to the conclusion that LG is not caused by HP, and that it is not a specific disease, but only a symptom presents in a wide range of various pathologies [6].

Summing up, the connection between HP infection and development of LG seems not to be very strongly established. Many studies show that HP infection is not more common in patients with LG than in general population or that LG is more common in patients with the infection, other studies confirm that eradication of HP lowers the number of IELs or that, in some cases, HP infection can lead to a development of LG. What also needs to be mentioned, is that a well-known correlation between chronic active gastritis and HP infection does not appear in up to 21% of cases of confirmed infection [8]. These findings may suggest that LG, like chronic active gastritis, is just a histological symptom of HP infection.

Moreover, it has been noted that there is a stronger correlation between LG and only serologically positive HP infection and that there are actually lower number of HP bacteria in patients who present LG than in those who do not, which leads to a statement that LG might be to some extent caused by HP antigens rather than the infection itself. Some authors recommended for patients with LG and negative HP histology to undergo serological tests, in order to exclude the infection [1]. The precise connection between those two conditions is yet to be established.

### Association of lymphocytic gastritis with celiac disease

The connection between LG and CD is stronger than between LG and HP infection, as it varies from 10 to 38% [14,15] and appears to be higher in HP-negative CD than in HP-positive CD [15]. In pediatric patients, most cases of LG (42%) are associated with CD [15]. It is confirmed that the amount of IELs lowers as the patient introduces gluten-free diet [16]. Many patients with LG possess HLA DQ2: DQB1*0201 alleles as 95% of CD do [15]. It is also suggested that LG may be one form of presentation of CD, along with Duhring's disease, epilepsy or depression. Due to that, it is strongly suggested to exclude gluten-dependent diseases in patients diagnosed with intraepithelial lymphocytosis [17].

In one big study almost 300 000 patients with different pathologies were evaluated [18]. Out of almost 4000 examined CD patients only 16% had shown a correct gastric histology. Only 0.3% of patients with HP infection presented LG, while only 0.15% patients without CD had LG. In CD patients, villous atrophy correlated with occurrence of LG. This observation was confirmed by a recent Italian study, in which almost 90% of CD patients with LG had villous atrophy, crypt hyperplasia and increased small bowel IELs count [16]. The rest of the patients present, either increased IELs alone, or increased IELs and crypt hyperplasia. Brown *et al.* [19] also noted a correlation between the severity of CD and occurrence of LG. They observed higher neutrophil count, and stronger eosinophilic infiltration in CD patients with LG. The gastritis generally tended to occur in patients with more advanced stages of CD. There is also evidence that in CD patients, the mean count of IELs is higher than in healthy controls, even if LG cannot be diagnosed [28]. It might lead to a conclusion that the diagnosis of LG is only arbitrarily taken from a wider spectrum. Moreover, patients with LG and villous atrophy tend to have a higher antibody count and lower serum albumin level [18].

In another study, 10% out of 70 patients with diagnosed CD presented LG [14]. Their age was slightly higher that the average of the group, three patients were new ones and four did not follow the rules of gluten-free diet. The sex had no influence on occurrence of LG [14]. The authors noted only slightly higher IELs count in small intestine biopsy in group with LG in comparison to group that did not have LG. The lymphocytes in the duodenal epithelium were also CD3+ T-cells.

However, a more detailed study showed that in CD the prevalence of CD8+/CD4– T cells in gastric epithelium in LG is significantly higher than in HP-associated LG [6]. There is slightly lower number of CD4+ cells in comparison to HP-associated LG and there is no difference in count of B and NK cells in comparison to the norm [6].

Additionally, there is a study that compares CD and LG in terms of immunological regulation of the expression of the inflammation in the epithelium [20]. It is known that the NKG2D-NKG2DL (Natural Killer Group 2D-Natural Killer Group 2D Ligand) system and the IL-15 are important CD8+ infiltration-inducing factor in CD. The study shows that the same can be said about LG, but not in HP infection itself, which indicates that both CD and LG have the same immunological regulation path [20].

Another important observation is that not only LG is more frequent in patients with CD, but also the general number of lymphocytes in the gastric epithelium is higher in this group. In one study, in 11.4% of patients with CD the number of IELs was between 15 and 25/100 and in as much as 65.7% the IEL count was in a range of 5-15, while in non-coeliac control group the average count of IEL was 5.15 [14]. The count of the IELs used to persist in patients who did not stick to gluten-free diet. The last observation was confirmed by Gabrieli *et al.* [16], that revealed that in CD patients, LG withdrew after an introduction of a gluten-free diet is more than 90%. This could be said about only 20% of CD-associated chronic active gastritis. It is suggested that LG in case of CD is a gastric immunological response to gluten, only less intense than in the small bowel [16]. On the other hand, however, there is a case of a collagenous gastritis that was successfully cured by an introduction of gluten-free diet, which may indicate a similarity between LG and chronic gastritis [17].

Vogelsang *et al.* [21] reported 43 patients diagnosed with CD, without or with already introduced gluten-free diet. They conducted endoscopic biopsy of both gastric and duodenal mucosa, and within a week they performed oral permeability test in order to establish a correlation between microscopic lesions and increased gastric and small bowel permeability. A positive correlation between LG, CD and increased gastric permeability was found. The authors also observed that CD-associated LG leads to symptoms connected rather with abnormal function of the stomach than upper intestine. It is also suggested that microscopic lesions in stomach mucosa can lead to increased gastric permeability even if the patient does not present any symptoms. No correlation between increased permeability and LG itself was observed [21].

Summing up, the correlation of LG and CD is well-established. Introduction of a gluten-free diet causes a reduction in the number of IELs. Moreover, there is a strong representation of certain HLA alleles in both CD and LG, which would be a further support for its immunological etiology. It is also known that histological changes in gastric mucosa to some extent correlate with severity of CD.

### Association of lymphocytic gastritis with other diseases

Connection of LG with other pathologies is not well evaluated, but there are some studies that bring very important information. One condition that seems to correlate with LG is lymphoma. In one report [22], LG occurs in 32% of patients with primary gastric lymphomas, which is a higher percentage than in case of dyspepsia or chronic active gastritis, however histological types of lymphoma specific were not specified. There is evidence of coincidence of LG and gastric low-grade B-cell MALT-lymphoma [23]. In terms of typical histopathological features, the lymphocytes in lymphoma have different morphology than in LG. In lymphoma-associated lymphoepithelial lesions they form groups and have bigger nuclei in comparison to LG [22]. Lymphoma lymphocytes are mainly B-cells, while in gastritis they are mostly T cells. On the other hand, there are reports of T-cell lymphoma which microscopic view highly resembles LG [24]. There is no correlation between stage or type of lymphoma and the number of IELs [22]. The presence of LG itself does not indicate an increased risk of lymphoma [1]. However, some case studies show that LG can arise on the basis of a treated lymphoma and atrophy of gastric mucosa. There is also an observation that HP infection seems to be much less common in lymphoma with LG than in lymphoma without LG [22]. It may be caused by extinction of previously present bacteria due to loss of acid secretory function of the gastric mucosa. The authors also observed the same number of eosinophils in patients with or without LG, more neutrophils in LG and more advanced body atrophy in LG in comparison to lymphoma-associated intraepithelial lesions [22].

A recent study finds a connection between development of LG and colonization of gastric mucosa by bacteria different than HP [20]. It was discovered that *Propionibacterium acnes* may contribute to developed of LG, as it was almost 50% of taxa in gastric microbiota in LG in comparison to only about 22% in healthy control group. It was also noted that *P. acnes* activates an above-mentioned NKG2D-NKG2DL system [20]. What is very important, it is underlined that the use of antibiotics, depending on their spectra can indirectly lead, either to induction, or suppression of this system. This fact may explain why application of antibiotic therapy may lead to improvement of patient's state and decrease of IELs count even without a presence of *H. pylori*, which, on the other hand, fails to induce this inflammation regulation path [20].

Another study describes an association of LG and increased gut permeability [25].

There is also evidence of a connection between LG and protein loss with *Campylobacter* infection [25]. A conclusion is drawn, that the presence of IELs can be the cause of impairment of function of gastric mucosa that leads to protein loss, similarly to the patients with CD.

Moreover, there is evidence that LG can occur without any coexistent pathologies. Recent case studies show possibility of a genetic factor in pathogenesis of LG [15].

One more recent study revealed, that IELs, in comparison to lymphocytes in healthy individuals, show higher expression of TIA-1 and lower expression of perforin and GrB [26].

Early studies suggested that LG and Menetier's disease might be two diseases that are a part of the same spectrum. It was due to frequent coexistence of the conditions and common situation in which LG appeared in absence of Menetier's disease. It was additionally supported by the finding that, in LG, most of the lymphocytes are α/β T-cells, not γ/δ ones [27].

Last but not least, it should be mentioned that there is evidence that LG might be drug-induced. Ticlopidine is known to a be possible factor that contributes to development of LG [20]. Another drug that is linked to development of LG is pembrolizumab. There is a recent report of a patient suffering from recurrent melanoma lung metastases, who developed LG after being treated by the drug for a month [28].

There are reports that LG can associate collagenous gastritis [29, 30]. The latter, although, can present a lymphocytic gastritis-like histological pattern [31].

## Summary

The analysis of the above-described scientific studies leads to a few conclusions. There is no one exact cause of LG. It might be easy to find HP-infection in LG, due to its relatively frequent abundance. The fact that antibiotic therapy lowers number of IEL might, as well, be caused by eradication of different bacteria, what influences inflammation regulatory paths [20]. There is a strong immunological resemblance with CD, as the same cytokines trigger the reaction [20] and LG reacts to gluten-free diet in cases where the two conditions coexist [16] On the other hand, those conditions also differ, since in CD the lymphocytes that infiltrate the epithelium are T γ/δ cells and in LG those cells are the α/β type.

Even though the morphological resemblance of LG and lymphoma might cause diagnostic problems [24], LG does not behave like a neoplasm [22], however they might coexist, or, more often, might develop on a basis of post-lymphoma lesions [23].

There is also evidence that LG might occur in many more medical conditions like protein losing enteropathy [25], that it is connected to Menetier's disease [27] or that it can even exist without any other coexisting pathology [15].

Due to all these facts, the only conclusion that can be drawn is that, rather than being a separate disease, LG is more likely an immunological reaction to certain factors, a symptom of certain diseases. That is why a finding of LG should be an information for a clinician to look for a coexistent pathology.

*The authors declare no conflict of interest.*

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