Abstract. Background: In 1985, two independent reports highlighted a novel subtype of chronic inflammation in the gastric mucosa, characterized by the intraepithelial lymphocytic infiltration (ILI) both in the surface and the foveolar epithelium. The disease, subsequently called lymphocytic gastritis (LG) is a rare form of gastritis (0.8%-1.6% of cases), with unclear pathogenesis. More recently, LG was recorded in pigs and in non-human primates. Materials and Methods: The frequency of LG (>25 lymphocytes/100 epithelial cells) was assessed in gastric specimens from 92 consecutive baboons, initially filed under the diagnosis of “gastritis”. Results: LG was found in 13 (14%) out of the 92 animals. Helicobacter pylori was not found. Discussion: LG mirrors an immunological phenomenon at the surface-foveolar cell level elicited by an uncertain etiological factor. In similarity to humans with LG, no Helicobacter pylori were found in baboons with LG. The search for the lymphocyte-attracting protein contained in affected cells might bring forward an alternative therapy capable of abrogating the specific surface-foveolar cell-lymphotaxis present in LG. The baboon emerges as a possible animal model to study the agent(s) leading to LG.

In 1985, two independent reports highlighted a novel subtype of chronic inflammation in the gastric mucosa, characterized by the infiltration of lymphocytes both in the surface and the foveolar epithelium (1, 2). This subtype of gastric chronic inflammation received trivial names, such as the lympho-epithelial phenomenon of the gastric mucosa (1) and la gastrite à lymphocytes, respectively (2). In our initial communication (1), we wrote: “Lymphocyte-like cells surrounded by a clear halo were found within the surface-foveolar epithelium both in the fundus and the antrum in a gastrectomy specimen containing concomitantly a benign gastric ulcer“. In a subsequent publication (3) we reported in electron microscopic studies that these “in halo” cells had the ultrastructural characteristics of lymphocytes. “In halo” lymphocytes were found in the subnuclear aspect of the foveolar cell cytoplasm, even in areas without inflammation in the lamina propria.

In 1988, Haot et al. (4) proposed the term lymphocytic gastritis, a term that has prevailed ever since in the English literature. Lymphocytic gastritis (LG) is a rare form of gastritis (0.8%-1.6% of cases) with unclear pathogenesis (5) characterized by the intra-epithelial lymphocytic infiltration of the surface and the foveolar epithelium (>25 lymphocytes/100 epithelial cells).

In a study of 48 entire gastrectomies carrying a carcinoma (6) we found LG in two specimens. All 156 sections in the two specimens showed LG, even in areas lacking chronic mucosal inflammation in the lamina propria mucosa (lpm). Whereas specimens with “conventional” chronic gastritis demonstrated that the inflammation in the lpm had a focal distribution, specimens with LG showed a continuous lymphocytic infiltration of the surface and foveolar epithelium in all 156 sections.

It should be pointed out that LG might also be found in areas with hypertrophic mucosal folds. Studies of 13 gastrectomy specimens (7) demonstrated in 5 specimens with diffuse hypertrophic fundic mucosal inflammation in the lamina propria mucosa (lpm). Whereas specimens with “conventional” chronic gastritis demonstrated that the inflammation in the lpm had a focal distribution, specimens with LG showed a continuous lymphocytic infiltration of the surface and foveolar epithelium in all 156 sections.

LG is not a disease exclusive to humans. In earlier investigations we found that LG occurred spontaneously in the gastric mucosa of pigs (8). More recently we detected LG in the gastric mucosa of 3 baboons (9). This latter finding prompted us to investigate the frequency of LG in the stomachs in a consecutive cohort of baboons with gastritis.
Materials and Methods

The baboons were members of colonies at the Southwest National Primate Research Center, Southwest Foundation for Biomedical Research, San Antonio, TX, USA. The Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing, and Education were applied (10).

The conditions of animal housing have been reported elsewhere (10). Briefly the baboons were housed in metal and concrete indoor-outdoor cages and were fed commercial monkey diets occasionally supplemented with a variety of fruit and vegetables. Water was available *ad libitum*.

Baboons were euthanized with a commercial barbiturate agent because of non-GI diseases or natural causes such as old age. All procedures were performed in accordance with the Institutional Animal Care and Use Committee guidelines (11).

At necropsy, longitudinal tissue samples from the esophagus were fixed in 10% neutral-buffered formalin, processed conventionally, embedded in paraffin, cut at 5 µm, stained with hematoxylin and eosin (H&E), and evaluated by light microscopy.

A total of 92 well-preserved gastric specimens from baboons dying of natural causes between 1996 and 2006, filed initially under the diagnosis of “gastritis” at histological examination, were reviewed. LG in baboons was defined as the intraepithelial infiltration of the surface and the foveolar epithelium of the gastric mucosa by >25 lymphocytes.

Results

The results in Table I show that LG occurred in 13 (14%) out of the 92 animals. The Table also shows that various subtypes of acute and chronic gastric inflammation also occurred in the gastric mucosa in baboons. Some of these subtypes are illustrated in Figures 1-3. For comparison, the normal mucosa of the antrum and the corpus in other baboons are shown in Figures 4 and 5.

Discussion

In the present survey, 14% of gastric specimens from consecutive baboons having an initial diagnosis of “gastritis” at histological examination had LG. This percent is up to 10 times higher than the percentage of LG reported in humans, namely 0.8%-1.6% (12).

Several authors claim that *Helicobacter pylori* is the etiological agent of LG in humans (5, 13). However, *H. pylori* infection was found in only 4 out of 21, in none out of 5, and in 4 out of 7 cases with LG (14-16, respectively). In one of our studies (17), no *Helicobacter pylori* was found in any of the 156 Giemsa-stained sections taken from the two gastrectomy-specimens showing LG.

In the present work, no *Helicobacter pylori* were found in the gastric mucosa of baboons having LG. In fact, the scrutiny of H&E sections of the 13 cases of LG revealed structures compatible with *H. pylori* in only one. The staining of parallel sections with Giemsa stain, however, was negative for *H. pylori*.

The prevalence of the *H. pylori* infection in gastric biopsies with patients with dyspepsia varies from country to country, from 82% in Yemen (18) to 30% in Germany (5).
In the light of this knowledge, several questions arise: i) If \textit{H. pylori} causes LG (5, 13, 19), why are there no reports indicating that the prevalence of this condition is higher in countries with a high prevalence of \textit{H. pylori}? ii) If \textit{H. pylori} causes LG, why is intraepithelial lymphocytosis of the surface-foveolar epithelium of the stomach so rare among patients with the more common form of \textit{H. pylori}-induced gastritis (17, 20) characterized by a high number of lymphocytes in the \textit{Lamina propria mucosa (lpm)}? iii) If \textit{H. pylori} causes LG in baboons, why are the bacteria not detected in Giemsa stains (a common marker for \textit{H. pylori} in routine gastric biopsies in humans)?

LG may concur with other conditions showing intraepithelial lymphocytosis, such as celiac disease and lymphocytic colitis (16, 19, 21, 22), implying that in these patients, the intraepithelial lymphocytosis is elicited, simultaneously, in the absence of \textit{H. pylori} in the small and large intestines.

The absence of \textit{H. pylori} bacteria in baboons with LG suggests that cause(s) other than \textit{H. pylori} might be responsible for the development of the intraepithelial inflammatory process in the gastric mucosa.

In our initial work (1) we suggested that LG might mirror an immunological phenomenon at the surface-foveolar cell level elicited by an elusive etiological factor.

The search for the lymphocyte-attracting protein contained in affected cells might bring forward an alternative therapy capable of abrogating the specific surface-foveolar cell-lymphotaxis.

Since the etiological factor responsible for this disease remains uncertain, the baboon emerges as a possible animal model to study the cause(s) leading to LG, a disease also affecting humans.

References


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