

Plasma cells and lymphoid aggregates in sleeve gastrectomy specimens

Normal or gastritis?

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Abstract

Lymphoid follicles/aggregates in gastric biopsies have been traditionally linked to *Helicobacter pylori* gastritis, and less commonly to other inflammatory and neoplastic conditions. The frequency of such aggregates in normal stomachs has yet to be adequately evaluated. This is especially relevant when it comes to diagnosing non-specific chronic gastritis in biopsy specimens with chronic inflammation but no evidence of *H pylori* infection. Sleeve gastrectomies represent an opportunity to study adequately preserved gastric mucosa in patients who are otherwise asymptomatic and lack a history of gastric disease.

To study sleeve gastrectomy specimens to quantify the amount of lymphoid follicles/aggregates and lymphocytic infiltration in normal stomachs.

Sixty-eight bariatric sleeve gastrectomies and 13 control specimens from Whipple resections were examined for multiple histologic features including type, quantity, and distribution of chronic inflammation and lymphoid follicles/aggregates. Presence of *H pylori* was documented by both Hematoxylin and eosin-stained (H&E) and immunohistochemistry (IHC). Clinical information including age, sex, medication intake, prior endoscopy, and/or *H pylori* infection was recorded. The patient population was divided in 2 groups, *H pylori* negative versus *H pylori* positive, and statistical analysis was performed by a biostatistician.

Two hundred sixty three fundic sections from 68 bariatric patients were examined. Fifty three patients were found to be *H pylori*-negative, compared with 15 who were positive for *H pylori*. Among the *H pylori*-negative group, the average number of lymphoid aggregates was 3.33, compared with an average of 6.26 in the *H pylori* positive group (the difference was statistically significant with a *P*-value of .008). The average number of plasma cells per high power field was 2.15 in the *H pylori* negative group, compared and average of 5.07 in the *H pylori* positive group (the difference was also statistically significant with a *P*-value <.001). Clinically, 10 of the 53 *H pylori*-negative patients had esophagogastroduodenoscopy (EGD) that showed endoscopic mild non-erosive gastric erythema. The remaining had no documentation of symptoms or medication intake, including Non-steroidal anti-inflammatory drugs (NSAIDs) and Proton Pump Inhibitors (PPI).

Our results suggest that the presence of lymphoid aggregates and plasma cells infiltration can be a normal finding in otherwise normal gastric mucosa, though more pronounced in *H pylori* infected patients.

Abbreviations: EGD = Esophagogastroduodenoscopy, GC = germinal centers, H&E = Hematoxylin and eosin-stained, *H pylori* = *Helicobacter pylori*, IHC = immunohistochemistry.

Keywords: chronic inflammation, gastric biopsies, lymphoid aggregates, lymphoid follicles, normal stomach, sleeve gastrectomy

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1. Introduction

Gastric biopsy is one of the most frequent specimens received in a regular pathology practice. Inflammation (acute and chronic) and *Helicobacter pylori* (*H pylori*) organisms are among the most frequent pathologic findings in these biopsies. The presence of lymphoid follicles in gastric mucosa has been traditionally associated with the presence of *H pylori* infection.^[1] Some reports have even argued that the presence of germinal centers (GC) in gastric mucosa is a specific feature of *H pylori*-associated gastritis.^[2] This claim, however, was disputed by other studies showing the presence of lymphoid follicles in association with gastric stromal tumors/sarcomas, pernicious anemia, and even in the stomachs of 32-week-old fetuses.^[3–5] Overall, findings seem to support the idea that lymphoid follicles are related, but not exclusively, to *H pylori* gastritis and that they may be found in patients with other medical conditions, as well as in putatively normal gastric mucosa.

The Sydney System for the classification of gastritis was developed >25 years ago in order to standardize the diagnosis of gastritis. According to this system, the presence of few scattered chronic inflammatory cells is accepted as part of the normal histology of the stomach. There is, however, no universally accepted standard for the number, frequency, and distribution of chronic inflammatory cells in normal gastric mucosa.^[2] The absence of specific diagnostic criteria likely resulted in “mild chronic gastritis” or “non-specific chronic gastritis” becoming a relatively common diagnosis with questionable clinical relevance, and the pathologist often struggling where to draw the line between normal stomach and mild chronic gastritis in the absence of demonstrable *H pylori* microorganisms. It therefore follows that pathologists may have been overdiagnosing chronic gastritis in many patients whose histological findings may indeed fall within the spectrum of normal.

To our knowledge, few studies have included “putatively” normal stomachs in their appraisal of lymphoid aggregates in gastric mucosa.^[5–7] Sleeve gastrectomy is a relatively common operation to decrease morbid obesity and is a good source of generous gastric specimen. Our aim is to examine sleeve gastrectomies, representing putatively normal stomachs resected in an elective procedure, to quantify the amount of chronic lymphoplasmacytic inflammation present in these samples, and to provide a baseline for the acceptable amount of chronic inflammation in normal stomach mucosa. This will hopefully clarify the definition and spectrum of normal stomach histology, and determine whether a diagnosis of chronic non-specific gastritis is meaningful or justified.

2. Materials and methods

The Institutional Review Board approved the study with waiver of patient consent. Formalin-fixed, paraffin-embedded bariatric sleeve gastrectomy specimens performed at the American University of Beirut Medical Center were identified and retrieved from the archives of the department of Pathology and laboratory medicine, spanning the years 1996 to 2011. Inclusion criteria were any patient who underwent sleeve gastrectomy for obesity. There were no exclusion criteria. Hematoxylin and eosin-stained (H&E) sections for each patient were reviewed and examined by 2 pathologists (FB and MS).

The following parameters were evaluated and recorded: number and location of sections taken (antral vs fundic), number of lymphoid aggregates, the size of the largest aggregate and the

presence of GC, the average number of superficial and deep interglandular plasma cells per high power field, the presence of acute inflammation, and the presence of *H pylori* microorganisms, both on H&E stained sections and by immunohistochemistry (IHC). The official diagnostic pathology report was recorded for each case and compared with the aforementioned histologic findings and *H pylori* immunohistochemical results. Finally, clinical information including patients’ age, sex, smoking, alcohol consumption, medication intake, history of prior endoscopy, and/or *H pylori* infection were also recorded. The patients were divided into 2 groups, *H pylori* positive and *H pylori* negative. As a negative control, we added gastric mucosal samples from 13 *H pylori* negative, non-morbidly obese patients who had undergone Whipple procedure.

2.1. Statistical analysis

Descriptive statistics was carried out using number and percent for categorical variables, whereas mean and standard deviation were presented for continuous ones, along with their median and range. Associations between groups were assessed using student *t* test. *P*-value < .05 was used to indicate statistical significance. The Statistical Package for Social Sciences (SPSS, Version 25.0. Armonk, NY: IBM Corp.) program was used for data management and analyses.

3. Results

Two hundred sixty-three full-thickness fundic mucosal sections from 68 patients (32 men, 36 women) were collected and examined. The number of sections available for study ranged from 2 to 7 per patient with an average of 4. The sections ranged from 2 to 2.5 cm in size. Lymphoid aggregates were absent in only 3 of the 68 patients.

Sections revealed a total of 980 lymphoid aggregates, of which 11.5% (113) had germinal centers (Fig. 1A), with an average of 14.4 lymphoid aggregates per patient or 3.7 per section. Germinal centers (GCs) were present in 30 patients. Lymphoid aggregates lacking GC were present in 35 patients (51% of all patients). Most lymphoid aggregates were unevenly distributed and lacked germinal centers. Morphologically, the aggregates were located deep in the mucosa or muscularis mucosae with occasional extension to the surface (Fig. 1B).

In order to adequately assess the significance of a chronic inflammatory infiltrate (plasma cells and lymphoid aggregates) in gastric specimens, we divided the patients into 2 subgroups based on the presence of *H pylori*, whether by history, H&E, or immunohistochemistry. Our cohort was comprised of 53 *H pylori* negative patients and 15 *H pylori* positive patients. The number of lymphoid aggregates in the *H pylori* positive group ranged from 1 to 40 per patient with an average of 6.26 per section. As for the *H pylori* negative group, the number of lymphoid aggregates per patient ranged from 0 to 35 with an average of 3.33 per section (*P* = .008). Of the patients with lymphoid aggregates, 17 out of 50 *H pylori* negative patients had GCs within the lymphoid aggregates, with a range of 0 to 7 GCs, while 13 out of 15 lymphoid aggregates had GCs in the patients with *H pylori*, with a range of 0 to 10 GCs.

The lymphoid aggregates ranged from 0.2 to 1.5 mm in greatest dimension (mean: 0.58). The location of the aggregates (deep vs superficial) was equally distributed among both categories. Similarly, the average number of plasma cells per

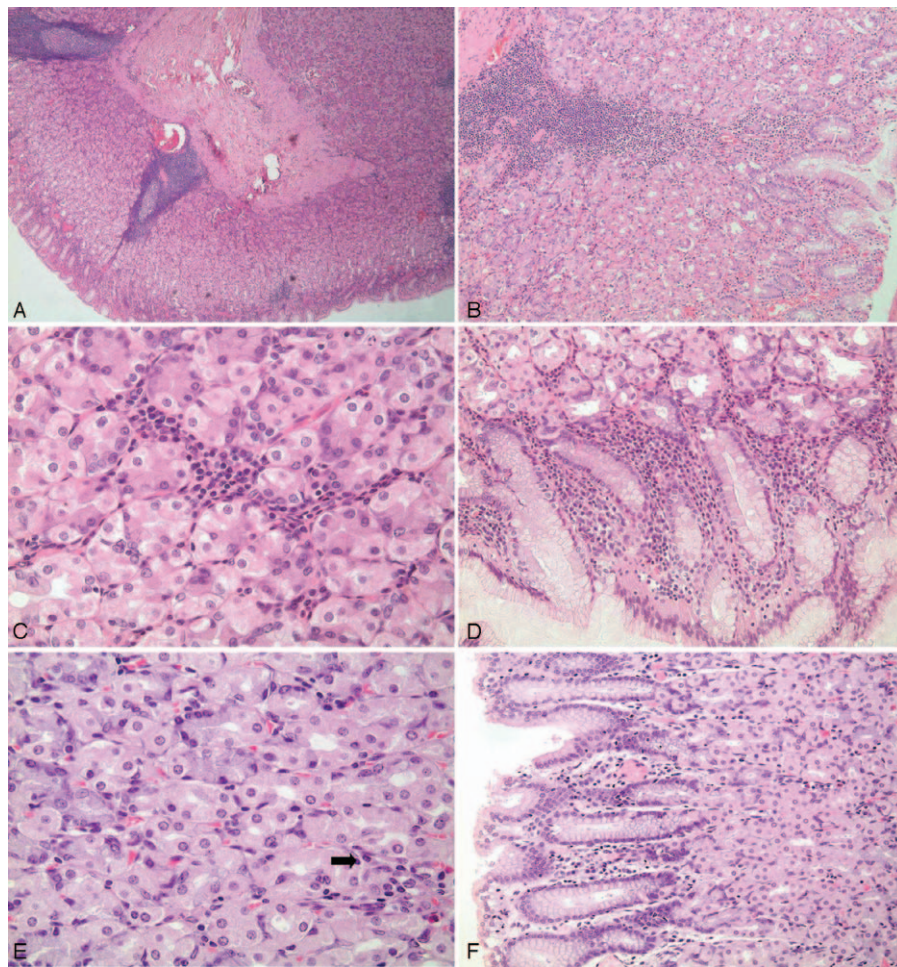


Figure 1. A. Case with large lymphoid follicles and germinal centers as well as increased plasma cells in the superficial foveolar mucosa. No association with *H pylori* could be demonstrated. B. Most lymphoid aggregates were similar to this one, without germinal centers. The aggregates tend to have a large base near the muscularis mucosae and tend to extend to the surface. C. An example of increased plasma cells in the deeper fundic mucosa, though admixed with lymphocytes. By the quantitative method used, this corresponds to 2 to 3 interglandular plasma cells as a maximal count. D. An example of increased plasma cells in the superficial foveolar mucosa. By the quantitative method used, this corresponds to 5 to 6 interglandular plasma cells. E. Normal appearing deep fundic mucosa with a maximum of one interglandular plasma cell (arrow). F. Normal appearing superficial foveolar mucosa with a maximum of 2 to 3 interglandular plasma cells.

high power field in patients with *H pylori* was 5.07 (range 2–8) as compared with 2.15 (range 0–7) in patients without *H pylori* ($P < .0001$).

As for the control group, 55 full-thickness gastric mucosal sections (22 fundic, 23 antral) were collected from 13 patients who had underwent Whipple procedure. Similarly, the sections ranged from 2 to 2.5 cm in size. Lymphoid aggregates were absent in only 1 out of the 13 patients. The sections revealed a total of 66 lymphoid aggregates without germinal centers. The lymphoid aggregates per patient ranged from 0 to 22, with an average of 5 per patient or 1.8 per section. The lymphoid aggregates ranged in size from 0.1 to 1.5 mm. As for plasma cells, the average number of interglandular plasma cells per high power field was 2.4 with a range of 1 to 8. The average number of deep plasma cells per high power field was 2.2 with a range of 0 to 6.

Esophagogastroduodenoscopy (EGD) information was available for 52 patients (76.5%). Unremarkable EGD with no abnormalities was reported in 42 patients. Ten patients were found to have erythematous changes suggestive of gastritis, all of

whom were heavy smokers (1–2 packs per day), while 2 had a history of treated *H pylori*, 4 reported the use of NSAIDs, and 2 reported at least moderate alcohol consumption.

4. Discussion

Chronic gastritis is a contentious diagnosis with questionable clinical relevance and poor correlation with clinical and endoscopic findings. The Sydney system was specifically designed to increase uniformity and improve inter-observer agreement in the diagnosis and reporting of chronic gastritis. In a study of 69 dyspeptic patients, Andrew et al^[8] demonstrated that this grading system can be applied consistently by pathologists, especially in the setting of *H pylori*-positive gastritis. Wider disagreements and inconsistencies arose however in the recognition and distinction of *H pylori*-negative gastritis, reactive gastritis, and gastric biopsies with no pathologic abnormality.

The main objective of our study was to specifically address the potential differences between *H pylori*-positive and negative patients

by examining the range of inflammatory histologic findings in stomachs partially resected for the treatment of obesity without known concomitant or prior gastric pathology or infection.

One of the most obvious histologic findings pathologists encounter in gastric biopsies are lymphoid follicles, which many experts suggest should be absent in a normal mucosal environment. One of the most common causes of gastritis, *H pylori* gastritis, is widely accepted to cause the formation of lymphoid follicles, as illustrated in Genta's et al^[11] findings, where they note that lymphoid follicles were exclusively found in biopsy specimens from *H pylori* infected subjects. On the other hand, other studies, including 1 that evaluated 84 gastric sarcomas, have proposed that gastric mucosal lymphoid follicles frequently accompany intramural and mucosal tumors and are also seen in putatively normal mucosa.^[4,5] Some authors still maintain that mucosal lymphoid aggregates do not or rarely occur in normal stomachs.^[1,6,9–11]

Our data however attests to the contrary. While lymphoid follicles were significantly more pronounced and frequent in *H pylori*-infected patients (more numerous plasma cells and germinal centers), there appeared to be significant overlap and no pathognomonic features in the histology of stomachs with or without documented gastric symptoms or *H pylori*. This is supported by the fact that several otherwise asymptomatic and *H pylori*-negative patients with normal EGD had large lymphoid aggregates, some with germinal centers, and/or an increase in plasma cells in their superficial foveolar mucosa (Fig. 1A). Furthermore, these patients also had a range of superficial and deep interglandular plasma cells (Fig. 1C–F) with high and low amounts inconsistently found in *H pylori*-negative and positive patients alike. Similarly, our negative control group showed an overlapping range of both lymphoid aggregates and plasma cells (deep and superficial) that overlapped with what was seen in our cohort group, further strengthening the argument that many of these findings can be appreciated in otherwise normal gastric mucosa.

Some previous studies do support our findings and opinion that lymphoid follicles and aggregates occur in a wide variety of gastric pathologies, as well as in normal stomachs. Jaskiewicz et al^[12] state that lymphoid follicles were not exclusively related to *H pylori* infection, as they did identify them in chronic active gastritis devoid of *H pylori*. They also propose the possible association between autoimmune inflammatory responses and the presence of lymphoid follicles in gastric mucosa. In Carpentieri's et al study of 605 antral biopsies, they note that lymphoid follicles, although intimately associated with *H pylori* infection, can be seen in normal stomachs. They also note, however, that lymphoid aggregates without follicles were not significantly associated with this infection, and may be a normal component of gastric mucosa.^[6] In his study of gastric mucosa from 86 subjects ranging from fetuses to 87 year-olds, Carney concluded that primary lymphoid follicles were a relatively normal finding in otherwise normal stomachs, or stomachs with a variety of different pathologies such as intramural tumors, mucosal tumors, and inflammatory conditions.^[5]

Similarly, although plasma cells are significantly and more frequently associated with *H pylori* infection, our data also demonstrates a significant overlap and a wide range of plasmacytic infiltration observed in what can be considered a normal gastrectomy specimen (0–7 per high power field in the *H pylori*-negative group vs 2–8 per high power field in the *H pylori* positive group, as illustrated in Table 1).

A Swedish study performed to establish the prevalence of gastritis and *H pylori* in the general population found that biopsy-proven gastritis was present in 50% of the volunteers that underwent endoscopy and biopsy. Eighty-seven percent of the subjects with gastritis had an associated *H pylori* infection, and the remaining were largely associated with NSAID consumption. However, the study did not demonstrate a significant correlation between an individual having digestive symptoms, such as nausea or bloating, and the chance of that person having histology-proven gastritis.^[13] This raises the important question as to the definition of gastritis whether it is clinical, pathologic, or a combination of both. A few retrospective studies that looked at the histopathology of sleeve gastrectomy specimens showed different prevalences of what they referred to as chronic gastritis.^[7,14,15] For example, Adali et al^[14] described the presence of chronic gastritis in 73% of their patient population, however 91.9% of the patients were infected with *H pylori*. On the other hand, Ge et al^[7] described chronic and follicular gastritis without association to *H pylori* (nonspecific) in 9.7% of their patient population, which is twice the percentage of *H pylori*-associated gastritis in their study sample (4.9%). The authors could not identify an underlying cause or symptoms associated with such findings. The question remains as to whether these represent a pathologic chronic inflammatory condition in otherwise asymptomatic patients, or a spectrum of what can be considered normal gastric mucosa, as previously discussed.

A potential limitation of our study is the exclusive evaluation of fundic mucosa, given that *H pylori* has been reported to predominate in the antrum.^[16] However, since many of the studies are largely based on small biopsy findings, whereas our study is based on gastrectomy specimens giving us a larger representative section of the stomach, we believe that this is a potential strong suit despite being limited to gastric fundus samples. Moreover, one could argue that our population could be considered outside the scope of what is considered normal, due to obesity, however there is no strong evidence that supports obesity in itself as a cause of gastritis.^[17] In addition, a large proportion of our population underwent endoscopy, and a majority had normal findings, were clinically asymptomatic, and had no history of NSAID or alcohol use or abuse, a methodology that is not available in other studies compiling pathologic findings from sleeve gastrectomies. One would therefore argue that the presence of lymphoid aggregates is part of the spectrum of normal mucosa, and using their mere presence to support the diagnosis of chronic gastritis, based on current guidelines, could be leading to an overcall in patients who would otherwise be normal.

Given the lack of standardized numbers for the presence of inflammatory cells in normal gastric mucosa,^[2] and despite

Table 1

Average number of lymphoid aggregates (LA) and plasma cells/high power field of *H pylori* positive versus *H pylori* negative patients.

<i>H pylori</i> status	<i>H pylori</i> (+) = 15	<i>H pylori</i> (-) = 53	P-value
Average number of LA	6.26 (SD = 4.509)	3.33 (SD = 3.119)	.008
Average number of plasma cells per high power field	5.07 (range 2–8, SD = 1.87)	2.15 (range 0–7, SD = 1.262)	<.0001

certain limitations in our study such as the lack of antral mucosa, our results suggest that lymphoid aggregates and interglandular plasma cells, in a wide array of sizes and distributions, can be part of the spectrum of normal gastric histology, and are not only associated with *H pylori* infection, as is often stated. It may be reasonable to widen the range of what is accepted to be normal histologic findings in the stomach, and minimize the use of vague diagnoses with uncertain clinical implications and significance.

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