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ORIGINAL CONTRIBUTIONS

Spectrum of Gastric Histopathologies in Severely Obese American Patients Undergoing Sleeve Gastrectomy

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Abstract
Background Laparoscopic sleeve gastrectomy (LSG) is a commonly performed weight loss procedure, but the pathologic findings in sleeve specimens have not been investigated in a US population.
Methods We performed a retrospective review of histopathologic findings in LSG specimens from 310 consecutive bariatric patients at the Hershey Medical Center between June 2008 and August 2014.
Results Patients were 19 to 75 years old (mean 45 years) with a female-to-male ratio of 3:1. The histopathologic findings included the following: no pathological alteration in 214 patients (69.0 %), chronic inactive gastritis in 41 (13.2 %), fundic gland polyp in 17 (5.5 %), proton pump inhibitor therapy effect in 12 (3.9 %), *Helicobacter pylori* (*H. pylori*)-associated chronic active gastritis in 10 (3.2 %), chronic active gastritis (*H. pylori* negative) in 5 (1.6 %), chronic gastritis with intestinal metaplasia in 4 (1.0 %), gastrointestinal stromal tumor (GIST) in 3 (1.0 %), and hyperplastic polyp, granulomatous inflammation, xanthogranulomatous inflammation, and mucosal ulceration in 1 patient each (0.3 %). Prior endoscopy was performed in 8 patients (2.6 %) for unrelated causes, and the results did not change the surgical management. Nine patients (2.9 %) had a concurrent liver biopsy for visual evidence of significant hepatic fibrosis.
Conclusion Although most cases showed no pathologic alteration, a minority had significant findings, with the incidence of GISTs higher than that reported in other series. Despite negative preoperative *H. pylori* testing, 3.2 % were still histologically positive, raising questions about the accuracy of preoperative methods used for *H. pylori* testing and treatment. Preoperative endoscopy may not be needed in sleeve patients.

Keywords Sleeve gastrectomy · Bariatric surgery · Obesity · Histopathology

Introduction

With the continued increased incidence of obesity and the advancing techniques of minimally invasive bariatric surgery, there has been a dramatic rise in the number of laparoscopic sleeve gastrectomies (LSG) performed as a primary weight loss option [1]. The prevalence of obesity in the USA remains high with a recent paper estimating this number to be 16.9 % in youth and 34.9 % in adults in 2011–2012 [2]. The health consequences and costs associated with obesity are well documented and add significantly to the burden of chronic health disorders. Obesity increases the incidence and prevalence of multiple co-morbidities including hypertension, type 2 diabetes mellitus, stroke, cardiovascular disease, dyslipidemia, osteoarthritis, asthma, gallbladder disease, and many cancers [3, 4]. Given that approximately one third of American adults are obese, it is not surprising that in the recent past, there has been a 450 % increase in the number of bariatric surgeries performed in the USA, along with a 146 % increase in the number of bariatric centers and 144 % increase in the number of

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bariatric surgeons [1]. Also, the increase in the number of laparoscopic bariatric surgeries substantially exceeds the number of open bariatric surgeries [1]. This trend will likely continue as LSG has been shown to have greater improvement in weight loss outcomes and associated comorbidities compared with non-surgical interventions and some other surgical modalities [5].

Although the number of LSG is on the rise, the spectrum of gastric histopathologic findings in this patient subset has not been widely investigated in the American database. The present study aims to recognize the prevalent histopathologic findings in severely obese American patients who underwent LSG at the Hershey Medical Center (HMC).

Materials and Methods

Patient Selection

A Health Insurance Portability and Accountability Act (HIPAA) compliant retrospective review of the surgical pathology database of the HMC was performed. This retrospective study was conducted exclusively at the Penn State Hershey Medical Center with approval from our Institutional Review Board. A total of 310 consecutive patients between June 2008 and August 2014 were identified who underwent a LSG for morbid obesity. Indications for LSG for obesity were based on 1991 National Institute of Health (NIH) guidelines [6].

Preoperative *Helicobacter pylori* Testing

As a standard protocol at HMC, all bariatric patients were tested preoperatively for *H. pylori* in a standardized manner. The first screening test is IgM antibodies against *H. pylori*, followed by a stool antigen test in case of positive IgM antibodies. In the event of a positive result, the patients get treated for *H. pylori*. Only once they test negative, they proceed to surgery. All patients in this study underwent surgery with an understanding that they were negative for *H. pylori*.

Preoperative Upper Gastrointestinal Endoscopy

The data was also assessed to see how many patients underwent preoperative endoscopy owing to related or unrelated causes within 1 year prior to surgery. An attempt was made to see if the preoperative endoscopy changed the course of the surgery or the postoperative course.

Intraoperative Liver Biopsy

Information was also gathered on any liver biopsy performed concurrently with a LSG.

Histopathologic Examination

As a routine, two random sections were taken and routine staining with hematoxylin and eosin stain was performed. Additional sections were submitted in cases of any lesions or masses found on gross examination or in cases of any unexpected significant pathology on histologic evaluation of the initial H&E sections. Additional special or immunohistochemical staining was performed in selected cases, if indicated by the initial H&E assessment. The histopathologic data was collected and analyzed.

Clinical Course

The medical records were assessed for patients with documented pathology during routine histologic assessment of the LSG specimens. Their clinical findings and postoperative course was noted.

Results

Clinical Characteristics

A total of 310 patients were included in this study. The mean age of the patient was 45 years with an age range of 19 to 75 years (Fig. 1).The female-to-male ratio was 3:1 (236 females, 74 males).

Pathologic Examination

The number of histologic sections ranged from 2 to 7 per case. Additional special and/or immunohistochemical stains were performed on LSG specimens in 40 cases. This consisted of immunohistochemical stains for *H. pylori* in 34 cases.

The histologic results are depicted in Fig. 2 and were as follows:

1. No pathologic alteration: The majority of the cases showed no pathologic alteration on gross as well as histologic examination ($N = 214$, 69.0 %).
2. Chronic gastritis: Chronic gastritis was seen in 29 % of the patients. This was subdivided into the following:
   (a) Chronic inactive gastritis ($N = 41$, 13.2 %). This was diagnosed by expansion of lamina propria by lymphoplasmacytic inflammation (Fig. 3a).
   (b) *H. pylori*-associated chronic active gastritis ($N = 10$, 3.2 %). This was diagnosed by chronic gastritis along with the presence of active neutrophil-mediated epithelial injury. Additionally, *H. pylori* organisms were identified either on H&E stain and/or immunohistochemical stain for *H. pylori*.

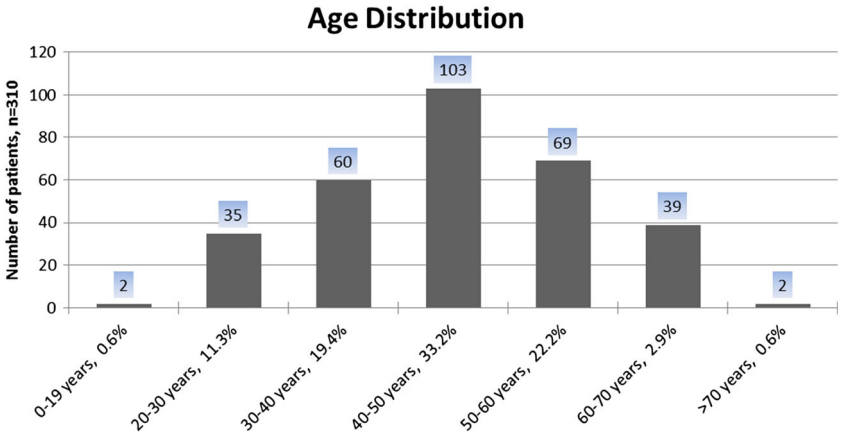

Fig. 1 Age distribution of patients undergoing laparoscopic sleeve gastrectomy

Noticeably, all these 10 patients tested negative on preoperative *H. pylori* screening, described above (Fig. 3b, c).

(c) Chronic active gastritis, *H. pylori* negative ($N = 5$, 1.6 %). This was diagnosed by chronic gastritis along with the presence of active neutrophil-mediated epithelial injury; however, no *H. pylori* organisms were found on the H&E stain and this was also confirmed by negative immunohistochemical staining for *H. pylori*.

(d) Chronic gastritis with intestinal metaplasia ($N = 4$, 1 %). This was diagnosed by chronic gastritis along with the presence of intestinal metaplasia, as diagnosed by the presence of goblet cells (Fig. 3d). No *H. pylori* organisms were found on the H&E stain, and this was also confirmed by negative immunohistochemical staining for *H. pylori*.

3. Gastrointestinal stromal tumors (GIST): A significant number of 3 patients (1 %) demonstrated incidental GIST within the LSG specimen (Fig. 4a, b).

The first patient was a 42-year-old male with a 0.4 × 0.2 × 0.2 cm tan-white firm intra-mural nodule; the second patient, a 45-year-old female, had an intramural/subserosal nodule measuring 0.8 × 0.6 × 0.3 cm; and the third was a 45-year-old female with a lesion within the muscularis propria measuring 0.4 cm in greatest dimension. Immunohistochemical stains were performed on all these GISTs, and all were found to be positive for DOG1, CD117, and CD34 and negative for S100 protein, supporting the above diagnosis (Fig. 4c, d). No mitotic figures were seen in two specimens, and the third one showed a mitotic count of 2/50 high power fields (HPF). Based on the size (<2 cm), site (stomach), and mitotic count (<5/50 HPF), all GISTs were determined to have almost no

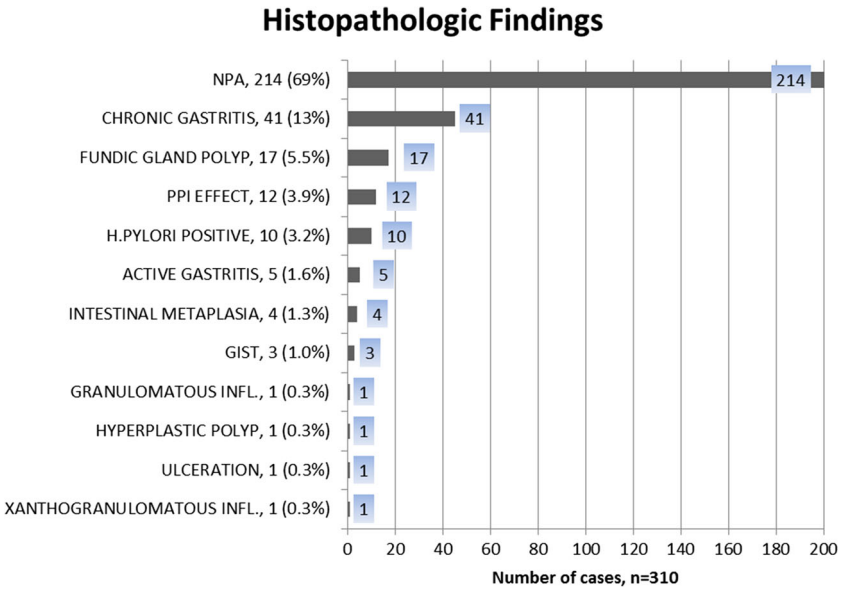

Fig. 2 Gastric histopathology findings in patients undergoing laparoscopic sleeve gastrectomy

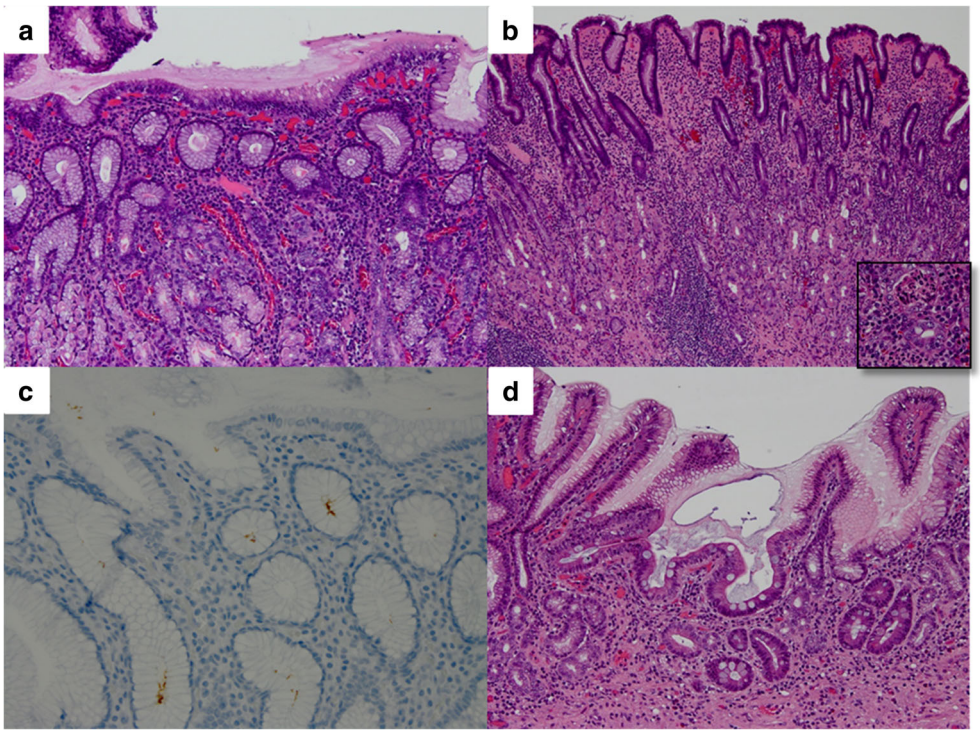

Fig. 3 Chronic gastritis. **a** Chronic inactive gastritis characterized by expansion of lamina propria by lymphoplasmacytic infiltrate is seen. **b** Chronic active gastritis is seen with additional neutrophil mediated epithelial injury (*inset* shows a high power view of neutrophils destroying the gastric glands). **c** Immunohistochemical stain for *H. pylori* highlighting numerous positive organisms in brown. **d** Chronic gastritis with intestinal metaplasia characterized by goblet cells in addition to chronic gastritis [**a**, **b** *inset*; **d** hematoxylin and eosin stain ×200,100, 400, 200; **c** *H. pylori* IHC ×400]

risk of progressive disease [7]. The postoperative courses were unremarkable and no recurrence has been seen on clinical follow-up. All three patients with GISTs identified within their LSG specimens had nutritional assessments following surgery, and their postoperative courses were unremarkable, with no recurrence seen on clinical follow-up.

4. Fundic gland polyps (FGPs) and proton pump inhibitor therapy effect: FGPs were seen in 17 patients (5.5 %), and proton pump inhibitor therapy effect, characterized histologically by an apocrine-like cytoplasmic swelling of parietal cells and parietal cell hyperplasia, was seen in 12 patients (3.9 %). Both these subsets of patients were on

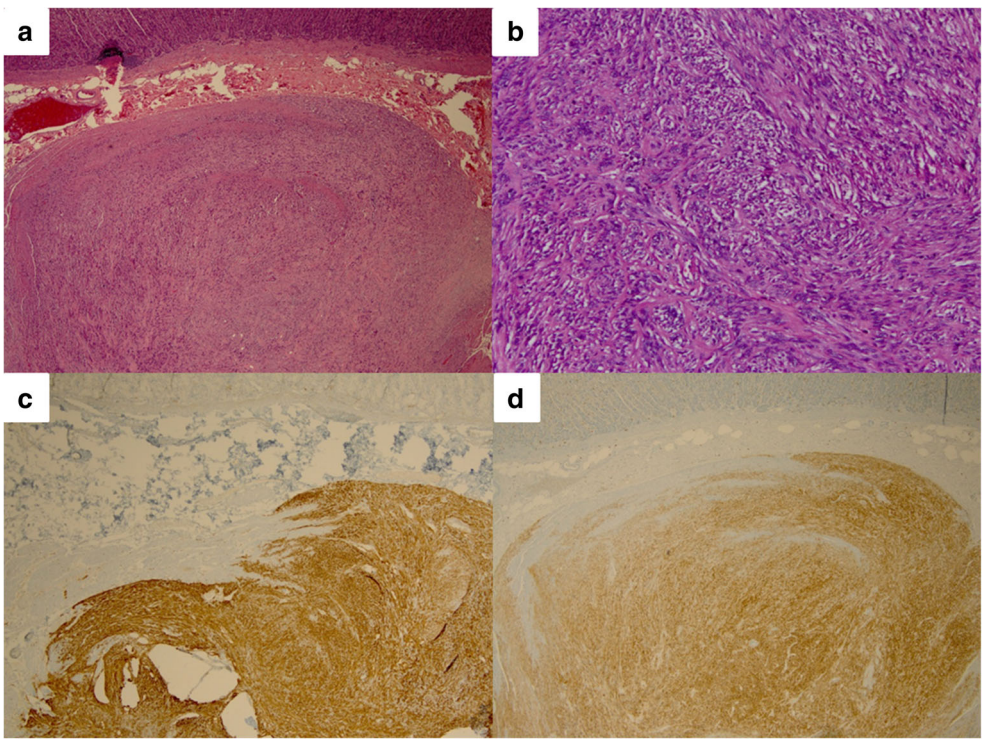

Fig. 4 Gastrointestinal stromal tumor(GIST). **a** Low-power photomicrograph showing a spindle cell proliferation centered in the muscularis propria. **b** Spindle cells have oval to spindled out nuclei and moderate amount of eosinophilic cytoplasm. **c**, **d** Immunohistochemical stain for DOG1 and CD117, respectively, showing strong, diffuse positivity in the lesional cells [**a**, **b** hematoxylin and eosin ×40, 100; **c**, **d** DOG1 and CD117 IHC ×40]

proton pump inhibitor therapy owing to clinical complaints of reflux disease (Fig. 5a).

5. Hyperplastic polyp: An isolated hyperplastic polyp was seen in 1 patient (0.3 %) (Fig. 5b).
6. Granulomatous inflammation: One patient (0.3 %) showed non-caseating granulomatous inflammation (Fig. 5c). This was a 46-year-old male with a history of asthma and no known history of sarcoidosis or significant infections. AFB and GMS stains were negative for acid fast bacilli and fungal organisms respectively (Fig. 5c inset). Postoperatively, his chest radiograph was re-reviewed and there were no significant findings and no evidence of hilar adenopathy. His postoperative course was unremarkable.
7. Xanthogranulomatous inflammation: Xanthogranulomatous inflammation with focal microabscess formation was seen in one patient (0.3 %). This was a 52-year-old male with an adjustable gastric band in place for 5 years which was removed at the same time as LSG, and most likely, the histologic findings were seen as a reaction to the gastric band (Fig. 5d). Immunohistochemical stain for CD68 highlighted the foamy histiocytic population. This patient continues to have an unremarkable postoperative course with appropriate weight loss.
8. Mucosal ulceration: This was seen in 1 patient (0.3 %), a 53-year-old female on pain medications for chronic back pain as well as on immunosuppressants for an orthotopic heart transplant. The mucosal ulceration was most likely due to drug-induced mucosal injury in this patient.

Clinical Characteristic Correlation with Histopathologic Findings

Taking into account that the sample sizes are fairly different, when comparing the subset of patients with histopathologic findings (96 patients) with the group as a whole (310 patients), there was no apparent difference in mean preoperative age (46 vs. 45 years), mean preoperative BMI (49.5 vs. 49.9), or percent female gender (78 vs. 76 %). In addition, weight-related comorbidities were similar across the two groups.

Conversional Patients

Of note, 14 of the patients included in this study were undergoing sleeve gastrectomy not as a primary weight loss procedure, but as a conversional procedure after failed adjustable gastric banding. Of these patients, 13 underwent band removal and conversion to sleeve gastrectomy in a single stage. The remaining patient underwent a two-stage procedure, with band removal followed by sleeve gastrectomy about 1 year later. Among these 14 conversional patients, there were 6 histopathologic findings, suggesting that when sleeve gastrectomy is performed as a primary weight loss procedure, the likelihood of abnormal findings will be even lower.

Preoperative Upper GI Endoscopy

Upper gastro-intestinal (GI) endoscopy was only performed in 8 of 310 patients within a year prior to surgery and, 2 of these

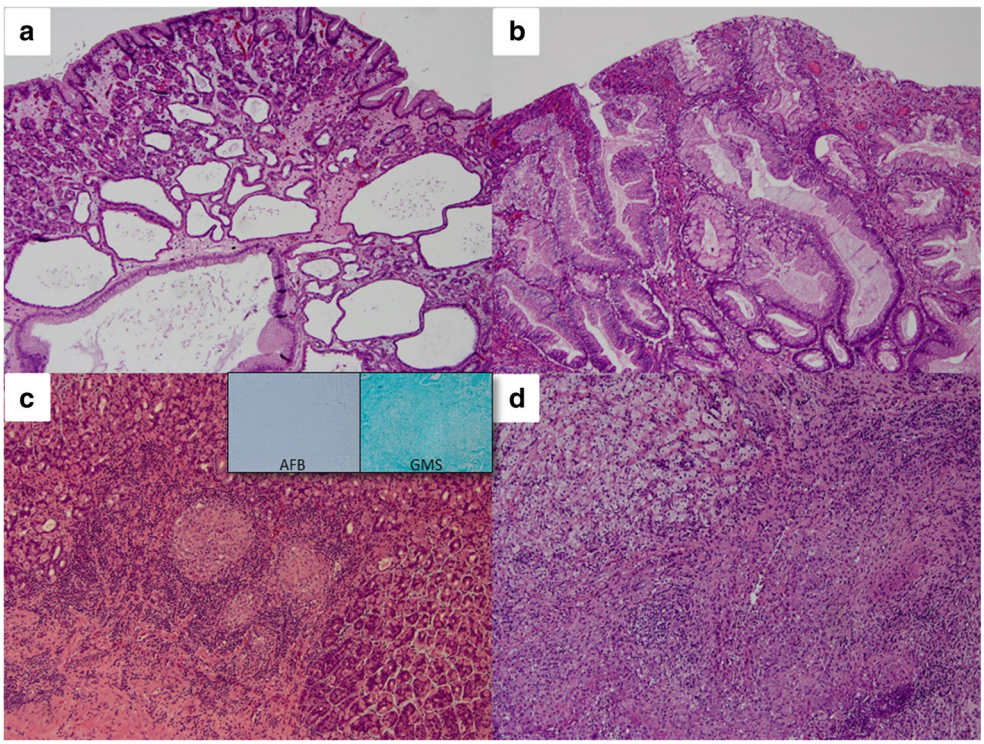

Fig. 5 **a** Fundic gland polyps characterized by cystically dilated fundic epithelium. **b** Hyperplastic polyp characterized by inflamed gastric epithelium with polypoid foveolar hyperplasia. **c** Non-caseating granulomatous inflammation characterized by multiple non-caseating granulomas (*inset* shows that special stains for GMS and AFB are negative for fungal organisms and acid fast bacilli, respectively). **d** Xanthogranulomatous inflammation and micro abscess, seen likely as a response to foreign body (gastric band) in our patient [**a**–**d** hematoxylin and eosin stain ×100, 100, 100, 200; **c** *inset* AFB and GMS ×400]

8 were within 1 month of surgery. Of these 8 patients undergoing endoscopy, only 5 underwent a gastric biopsy. The pathology results demonstrated a fundic gland polyp (1 specimen), changes consistent with proton pump inhibitor therapy effect (1 patient), no pathologic alteration (1 patient), and reactive gastropathy in 2 patients (only antral biopsy performed in these 2 patients). The endoscopy was performed because of unrelated causes in these patients and did not change the surgical management of any of the patients.

Concurrent Liver Biopsy

Concurrent liver biopsy was performed in nine (2.9 %) cases, in which there was an intraoperative unexpected suspicion of advanced fibrosis or cirrhosis. Of these nine biopsies, two biopsies documented well-developed cirrhosis and one had bridging fibrosis, secondary to steatosis/steatohepatitis. The remaining biopsies had variable foci of pericellular, perivenular fibrosis, and/or portal fibrous expansion. There were no changes in the intraoperative course or postoperative results as a result of the liver biopsy.

Significant Intraoperative Findings

None of the patients had any significant intraoperative findings to change the course of the surgical procedure or affect the surgical outcome or the postoperative course in any of our patients.

Discussion

As significant and sustained weight loss is generally difficult to achieve by diet, exercise, and drug therapy alone, bariatric surgery has become the most effective treatment for obesity and control of its medical complications, especially in severely obese patients [5, 8, 9]. The surgical options are broad and have evolved from open bariatric procedures to the more popular LSG, which in some studies is shown to have a reduced rate of surgical complications compared to other weight loss procedures [5, 8]. With LSG becoming more popular, there has been an increasing number of sleeve gastrectomy specimens encountered in clinical practice. However, the spectrum of gastric histopathologic findings encountered in this patient subset has not been widely investigated, especially with very limited studies in the American database. In this study, we investigated the clinico-pathologic characteristics of 310 consecutive patients undergoing LSG at our institution. A female preponderance was seen in our study, similar to that seen in prior studies, although not all of these studies were performed on a US population. [10–13].

We found that a significant majority of our patients had no pathologic alteration (69 %) on thorough gross and pathologic examination of LSG specimens, while the remaining minority had histologic findings ranging from the more common chronic gastritides to less common but very significant GIST. The results in this study seem to differ from some other studies, which have reported fairly high percentages of pathologies in their studies. Almadeezi et al. [11] reported a very high prevalence of positive histopathology (almost 100 %) in patients undergoing LSG in Kuwaiti population. Noticeably, all these patients underwent a routine preoperative upper gastro-intestinal (GI) endoscopy. The majority of these (74.4 % of their total patients) were found to have chronic gastritis. Additionally, in a recent abstract [12] studying histopathologic findings in LSG in an American database, the authors found that although the most prevalent diagnosis in LSG was "no significant pathologic change," this was seen in just 35.2 % of the cases. The most common pathology found in their series of 250 LSG were lymphoid aggregates (31.2 %), chronic inflammation (12 %), and gastritis (12 %). We also found that the most common pathology seen in our study was chronic gastritis (including both inactive and active gastritis as well as *H. pylori* positive cases); however, this was seen in a relatively small percentage of cases (29 %), as compared to prior studies. A part of the reason for this could be inter-observer variability in diagnosing chronic gastritis. Some pathologists would call the presence of occasional plasma cells as chronic gastritis, while others require a significant expansion of lamina propria to diagnose chronic gastritis. The other reason may be different databases of populations' studies in these papers. Our study focuses predominantly on an American database, while some other studies have a predominantly non-American (like Kuwaiti and Romanian) population [10, 11]. We found 10 cases in our study to be *H. pylori* positive (3.2 %). The percentage of *H. pylori*-positive cases in our study is slightly less compared to other prior studies [11, 12]. Still, we found our percentage of *H. pylori*-positive cases to be unexpectedly high, considering that all preoperative bariatric patients at HMC underwent IgM antibody and/or stool antigen test for *H. pylori* and underwent surgery with the understanding they were negative for *H. pylori*. This suggests that these above tests are not entirely sensitive for detection of *H. pylori* cases and raises questions about the accuracy of preoperative methods used for *H. pylori* testing and treatment. Surprisingly, Almazeedi et al. [11] who found 7.3 % of their patients to be positive for *H. pylori* on LSG mentioned that all their patients underwent routine preoperative upper GI endoscopy, with a *Campylobacter*-like organism (CLO) test for *H. pylori* detection. In the event of CLO test positivity, the patient was treated before undergoing a LSG. Raess et al. [12] in their abstract reported 5.2 % cases to be *H. pylori* positive, which again is slightly higher than our series and mentioned that their patients undergo a rigorous preoperative evaluation including upper GI series. However, in their abstract, they do not discuss how many patients were *H. pylori* positive preoperatively and how many were treated before undergoing LSG.

Another unexpected significant pathology found in our study was the presence of GIST in three of 310 surgical LSG specimens (1.0 %). Beltran et al. [14] described the first case report of an incidental gastric GIST resected during LSG in 2009. The incidence of GIST during LSG found in our study is slightly higher than what has been previously reported in the literature in this patient population. Almazeedi et al. [11] reported an incidence of 0.2 % (1 of 656 bariatric patients), Yuval et al. [15] found an incidence of 0.6 % (5 of 827 bariatric patients), and Vrabie et al. [10] reported none in their series of 87 sleeve gastrectomies. Sanchez et al. found a 0.8 % incidence (4 patients) of gastric GISTs in their series of 517 severely obese patients undergoing laparoscopic Roux-en-Y gastric bypass [16]. GISTs are rare mesenchymal neoplasms found most commonly in the stomach with a yearly incidence of 0.32 per 100,000 persons and a 15-year prevalence of 1.62 per 100,000 persons in the USA [17]. Based on the above data, it seems a higher incidence of GISTs may be seen in obese patients compared to the general population. The reasons for this could be that many asymptomatic GISTs remain undiagnosed in the general population but are diagnosed incidentally when resections are performed for other indications, as in this series. However, a possibility that there is an association between these tumors and obesity, as also suggested by some other authors, cannot be entirely excluded [15]. Also, prior authors have reported that incidental GISTs are seen more commonly in patients older than 50 years, with the youngest patient in their study being 48 years old [15]. However, in our series, all patients with incidental GISTs were under 50 years of age, specifically 42, 45, and 45 years old.

There are conflicting opinions in the literature regarding preoperative endoscopy in bariatric surgery. While there are many opinion pieces, there are few data-driven recommendations. It has been recommended that all symptomatic bariatric patients should undergo preoperative upper endoscopy before surgery, and this procedure should be considered in all patients [18, 19]. Such studies have found that findings on preoperative endoscopy in bariatric patients are common that the procedure is safe and the cost is low. However, there is no comment regarding a change of the surgical plan in any of their bariatric patients in many such studies [20, 21]. Hence, not surprisingly, the significance of a routine preoperative screening upper GI endoscopy in asymptomatic patients remains debatable [22, 23]. Some studies suggest that given the lack of association between patient symptoms and endoscopic findings, routine preoperative endoscopy may be useful in detecting pathology [13, 20, 21, 24, 25]. However, others have contrary views, given the cost of an extra procedure, its invasiveness, and the fact that the majority of detected lesions have little or no clinical significance. In addition, endoscopic findings rarely change the surgical management of these patients. Loewen et al. [26] found that endoscopic findings led to a change in medical treatment in 18 % of patients but led to a change in the surgical plan in <1 %. Others have also found that endoscopic findings are common but do not usually change the surgical plan [26–28]. Almadeezi et al. [11] reported a very high prevalence of positive histopathology (almost 100 %) in patients undergoing LSG in a Kuwaiti population. Noticeably, all these patients underwent a routine preoperative upper gastro-intestinal (GI) endoscopy. However, the paper did not discuss how the results of the endoscopy altered the surgical management except in *H. pylori*-positive cases, who were treated before surgery.

In our study, only 8 of 310 patients underwent preoperative upper GI endoscopy with only 2 of these patients undergoing endoscopy within a month prior to surgery. The results in these patients did not alter the surgical course of the patient. Additionally, the surgical findings did not alter the intraoperative or postoperative course in any of our patients. This, along with some of the prior studies, supports that there is little to recommend preoperative endoscopy on asymptomatic bariatric patients [27, 28]. Because histopathologic findings were so unusual in this cohort, we continue to propose that preoperative endoscopy not be routinely performed only for purposes of ruling out pathology, but only for other clinical indications, such as severe reflux or dysphagia that might lead to a change in surgical plan.

Nine of our 310 (2.9 %) patients had intraoperative clinical suspicion of advanced fibrosis prompting an intraoperative liver biopsy. Despite the presence of cirrhosis in 2 patients and bridging fibrosis in 1, there was no change in the surgical course. Not surprisingly, non-alcoholic fatty liver disease (NAFLD) was seen in all 9 biopsies. NAFLD is a known comorbidity in obesity and has the potential to progress to cirrhosis and hepatocellular carcinoma. Studies have shown that bariatric surgery is associated with regression of NAFLD by decreasing the grade of steatosis [29].

Conclusion

Although the majority of cases had no pathologic alteration, a minority had significant findings warranting a thorough gross and histopathologic examination of LSG. In fact, the incidence of GIST detected in this study subset is higher than previously reported. Also, despite negative preoperative *H. pylori* testing, 3.2 % cases still were histologically positive, raising questions about the accuracy of preoperative methods used for *H. pylori* testing and treatment. Additionally, the results substantiate that there is little to recommend preoperative endoscopy for operative management on bariatric patients. Our study shows a range of histopathological findings within sleeve gastrectomy surgical specimens performed for severely obese American patients.

Conflict of Interest The authors declare that they have no competing interest.

Statement of Informed Consent The informed consent was waived (IRB approved, HIPAA compliant retrospective study).

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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