



Heterotopic gastric mucosa and possible new onset Crohn's disease causing stricture in bariatric patient

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Abstract

A 51-year old Caucasian female had presented with intractable Gastroesophageal Reflux Disease (GERD), chronic dysphagia and food intolerance over a period of 6 years following a sleeve gastrectomy. With conservative management options having failed she underwent a Revisional Roux-en-Y gastric bypass. Although the patient did well initially, she developed dysphagia once again with her BMI falling to 17.7 (initial BMI 44.6). Upper endoscopy showed a patent anastomosis but with a stricture in the roux limb and an ulcer distal to that stricture with no marginal ulceration at the anastomosis itself. Workup resulted in increased suspicion for carcinoid tumor and Inflammatory Bowel Disease (IBD) due to elevated chromogranin A, Single Photon Emission Computed Tomography (SPECT) study and elevated fecal calprotectin respectively. Final pathology of the stricture was positive for gastric mucosa which was subsequently excised. Two months later, abdominal pain and signs of dehydration led to a small bowel series X-ray with barium showing high suspicion for Crohn's disease.

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Back ground

Ectopic gastric mucosa is most commonly found incidentally post mortem on autopsy with few to no clinical manifestations during life. The commonest locations include Meckel's diverticulum and the proximal esophagus, known as the "gastric inlet patch". Although rarely, when it is clinically apparent, ectopic gastric mucosa can lead to bleeding, intussusception, and bowel obstruction [2,23]. To our knowledge, there have been no cases reported of bariatric surgery patients becoming symptomatic due to ectopic gastric mucosa. In light of the rarity of this discovery, we present a 51-year-old female post Roux-en-Y gastric bypass anastomosis who developed an accessory limb stricture due to ectopic gastric mucosa, all while having a patent anastomosis.

To add to the uniqueness of this case, the patient has recently undergone workup due to high suspicion for Crohn's disease. With no family history of Inflammatory Bowel Disease (IBD) and no symptoms prior to surgery, she may be amongst a handful of cases to date who developed new onset Crohn's disease following, and possibly in response to, bariatric surgery [9].

Case presentation

Following a sleeve gastrectomy and revisional Roux-en-Y gastric bypass for intractable Gastroesophageal Reflux Disease (GERD), a 51-year old Caucasian female experienced chronic dysphagia and food intolerance. These symptoms led to a de-



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crease in BMI from 44.6 prior to initial bariatric surgery to 17.79 over the course of almost 6 years. Her entire clinical course is described below.

In 2011 at the age of 45, the patient underwent an uncomplicated laparoscopic sleeve gastrectomy and almost immediately experienced consistent episodes of abdominal pain. A laparoscopic cholecystectomy in 2012 failed to improve abdominal pain. The patient progressively began to develop multiple episodes of intolerance to oral feeding in the form of nausea and vomiting sometimes requiring IV hydration and antiemetic medication. An upper GI study performed in July 2015 showed severe Gastroesophageal Reflux Disease (GERD), which was confirmed by esophageal manometry. A small hiatal hernia, mild gastroparesis, confirmed by a gastric emptying test, and chronic antral gastritis were also detected. Biopsies of the Gastroesophageal (GE) junction and *Helicobacter pylori* testing were both negative. Patient was started on proton pump inhibitors and Reglan with little improvement of symptoms.

Intractable GERD led to a laparoscopic revision of the sleeve gastrectomy to a Roux-en-Y gastric bypass in January 2016. Prior to the conversion, a non-contrast CT scan of the abdomen and pelvis showed no definite focal inflammatory or obstructive processes. The procedure was without complications. A few months following the procedure the patient again began to complain of abdominal pain, nausea and vomiting. After admitting to new life stresses, she was evaluated by a psychiatrist and prescribed Lexapro and Ativan for anxiety. Following the use of the medications the patient had total relief of all previously noted symptoms and described feeling well and full of energy. The patient remained symptom free for five months.

In June 2016 dysphagia and progressive food intolerance in the form of vomiting again reappeared. An abdominal and pelvic CT showed no inflammatory or obstructive process. Another upper GI study on July 2017 revealed "stricture in the vicinity of the anastomotic structure". A following endoscopy showed a patent anastomosis with a stricture in the roux limb, 2-3 cm beyond the anastomosis, with a 1 cm ulcer distal to that stricture. No marginal ulceration at the anastomosis itself was evident. An Esophagogastroduodenoscopy (EGD) with fluoroscopic guidance and Controlled Radial Expansion (CRE) balloon was unable to relieve the stricture. The stricture was noted to be tight, although contrast eventually passed into the proximal ascending colon. A biopsy of the area demonstrated benign small intestinal mucosa associated with focal superficial mucosal erosion and mild chronic inflammation at the erosion site. Submucosal focal fibrosis and histiocytic reaction was also noted.

At that time, the patient was vomiting up to 6 times per day and with a BMI of 17.79. Due to her chronic malnutrition and fatigue, a Peripherally Inserted Central Catheter (PICC) line was placed for Total Parental Nutrition (TPN). The differential included: vasculitis such as granulomatosis with polyangiitis (Wegener's Disease), celiac disease, carcinoid tumor and inflammatory bowel disease such as Crohn's.

Vasculitis was ruled out following normal results for serine protease 3 antibody, Antineutrophil Cytoplasmic Antibodies (ANCA) and Erythrocyte Sedimentation Rate (ESR) profiles. Celiac disease was also ruled out following normal tissue transglutaminase antibody IgA levels.

A carcinoid tumor workup included an OctreoScan which revealed a low uptake level in the right lower quadrant. This

area was determined to be at the site of the stricture when compared to previous upper GI study and Single Photon Emission Computed Tomography (SPECT) imaging. The possibility of a carcinoid tumor was further validated by markedly elevated chromogranin A at 1045 ng/mL (normal 0-95 ng/mL). However, a 24 hour 5-hydroxyindoleacetic acid (5-HIAA) assessment for carcinoid cancer results were 6mg/g CR, within the normal limits of 0-14 mg/g CR. An MRI revealed no apparent liver metastasis or inflammatory abdominal mass.

The possibility of inflammatory bowel disease increased the diagnostic dilemma with the finding of elevated fecal calprotectin at 181 mcg/c (normal < 50 mcg/g). Follow-up colonoscopy results were extremely limited due to restricted bowel prep passage into the colon because of the stricture. However, areas that could be visualized revealed no primary lesions.

In September 2017, a laparoscopic revisional gastrojejunostomy was performed with resection of the stricture in the roux limb. Stricture pathology results revealed borders consistent with normal jejunal mucosa and a stricture composed of "focal mature fundic type gastric mucosa with full mucosa thickness" and associated focal superficial mucosal erosion. Surgery validated a patent gastrojejunostomy anastomosis.

After resection of the gastric mucosa, calprotectin (normal <162.9 mcg/g) levels normalized from 181ng/mL to 101.8ng/mL by the end of September 2017. Chromogranin A levels (normal 95ng/mL) dropped from 1045 to 362ng/mL by September 25, 2017 and 214ng/ml by October 10, 2017. At this time, the patient experienced relief of abdominal discomfort and ability to tolerate a bariatric diet for one and a half months.

On November 16, 2017, a small bowel series X-ray with barium was performed due to recurrence of abdominal pain in the right lower quadrant and signs of dehydration. Results revealed persistent mildly irregular narrowing of the terminal ileum with the remainder of the small bowel appearing normal. This raised suspicion for early Crohn's disease.

At this time, the patient will continue to follow up with her Bariatric surgeon who will monitor chromogranin A serially to see if it continues to fall to the normal limit of <95ng/mL. The patient will also follow up with a gastroenterologist for a full Crohn's disease workup.

Discussion

The case presented is interesting for a multitude of reasons. Firstly, the patient experienced food intolerance in the form of nausea and vomiting on multiple separate occasions throughout her postoperative course. Each time the symptoms were worked up, found to have different possible causes and were treated accordingly. Second, the presence of a stricture, led to a full workup of a wide range of differential diagnoses. Our discussion will include a description of the pathophysiology of our top differentials; carcinoid tumors and Crohn's disease, and an explanation of the workup and results of each. The final pathology of the stricture revealed gastric mucosa, therefore we will discuss the pathophysiology of heterotopic gastric mucosa and how its presence affected our screening test results. Ultimately, we will dive into the final discovery of inflammatory bowel disease and reassess our test results.

Different diagnoses leading to similar symptoms of recurrent food intolerance in the form of nausea and vomiting

Adverse gastrointestinal symptoms, such as nausea, vomit-

ing, and diarrhea are often an expected consequence of bariatric surgery due to anatomic and physiologic changes created by the operation. One of the most common causes is a phenomenon known as “dumping syndrome”. Dumping syndrome presents as nausea, vomiting, cramps, diarrhea, bloating, palpitations, hypotension, and a number of other sympathetic signs in reaction of certain foods, specifically those highest in sugar. If compliant with the bariatric diet, these symptoms typically only last for a few months transition period and eventually resolve [6]. Our patient experienced a number of those symptoms on multiple different occasions with no relation to her food intake.

Almost immediately following her initial sleeve gastrectomy in 2012, the patient experienced abdominal pain that progressed to food intolerance in the form of nausea and vomiting. An upper GI study and esophageal manometry revealed severe GERD. The results of multiple studies have concluded that there is a known causal relationship between laparoscopic sleeve gastrectomy and the onset of GERD [1,18]. A small hiatal hernia, mild gastroparesis and chronic antral gastritis were also detected. A combination of these factors was believed to be the cause of her symptoms. Since the patient did not respond to conservative measures, she underwent a revisional Roux-en-Y gastric bypass.

Following the revisional surgery the patient again began to experience similar symptoms of nausea and vomiting. She was evaluated by a psychiatrist and prescribed Lexapro and Ativan which relieved the symptoms completely. The cause of the symptoms this time were believed to be physiologic reactions to life stressors.

Six months later the same symptoms again were reported. A full workup revealed a now anatomic cause- a stricture. The limited ability of food to pass through this stricture led to the symptoms of nausea and vomiting as well.

Differential diagnosis of a stricture in a bariatric patient

Post bariatric strictures are a well-known surgical complication. It is the most common complication following Roux-en-Y gastric bypass [15], with 6-20% of patients developing one at the gastrojejunostomy anastomotic site [16]. These strictures generally present with food intolerance within the first 6 months after surgery [13]. Late strictures beyond the first 6 months, as our patient experienced, are far less common. Late strictures are usually associated with excessive acid, aspirin, Nonsteroidal Anti-Inflammatory Drug (NSAID) use, or postoperative anastomotic leak [7]. First line management includes endoscopic balloon dilation [15]. If still refractory, as in our patient’s case, surgical management is often involved with revision of the gastrojejunostomy anastomosis [7].

While strictures at the gastrojejunostomy are very prevalent and highly studied, strictures *distal* to this anastomosis are wildly abnormal with very little literature on their causative nature. In the general population, strictures could be due to physical obstructions such as adhesions and hernias or less frequently pathologic causes such as carcinoid tumors, inflammatory bowel disease, vasculitis, and very rarely ectopic gastric mucosa [15]. Highest on our differential were a possible carcinoid tumor and inflammatory bowel disease. An explanation of each as well their workup results will be explained below.

Carcinoid tumor

Carcinoid tumors are well differentiated neuroendocrine tumors found throughout the gastrointestinal tract, most commonly in the jejunum and ileum. They present as intramural or submucosal masses that can lead to bowel obstruction. The overlying mucosa of the tumor may be found intact but is also commonly seen to be ulcerated. The tumor may produce several secretory products including histamine, somatostatin, gastrin, serotonin, cholecystokinin, substance P, polypeptide YY, and chromogranin A which contribute to the symptoms associated with the tumor and may play a role in tracking the location and progression of the tumor size [20].

In our patient, we screened for a carcinoid tumor using chromogranin A. Chromogranin A has a multitude of different functions including serving as a prohormone for future peptides, a role in regulation of secretory function of cells and antimicrobial properties. Clinically, chromogranin A is used as a marker for neuroendocrine cells, which tend to produce it excessively [19]. Normal levels of gastrin promote a baseline level of chromogranin A physiologically [5]. It is hypothesized that chronically elevated gastrin levels encourage the progression of hyperplasia to dysplasia and possibly metaplasia of Enterochromofin Like (ECL) cells to a carcinoid tumor [22]. There are several scenarios proven to increase gastrin levels. Most notable for our purposes is the use of Proton Pump Inhibitors (PPIs). By blocking acid secretion, PPIs inhibit the negative feedback of gastrin, resulting in an increase of gastrin levels and in turn chromogranin A [14]. This is of particular interest because it is common medical management to prescribe PPIs to patients status post Roux-en-Y gastric bypass to prevent marginal ulcers, our patient included [12]. It could then be hypothesized that the use of PPIs could lead to the development of a carcinoid tumor and revealed by the elevation of chromogranin A.

Inflammatory bowel disease – Crohn’s disease

Crohn’s disease is one form of inflammatory bowel disease that can affect any portion of the small or large intestine, but most commonly has lesions in the ileum. Pathogenesis of Crohn’s disease is not fully understood, but believed to have a strong genetic component along with combined effects of altered gut microbiome, mucosal immune responses, and host interactions with the intestinal wall. Crohn’s disease often initially presents as an ulcer that progresses to transmural intestinal wall inflammation associated with granulomas, marked lymphoid reaction and fibrosis. Crohn’s disease is associated with “skip lesions” signifying focally affected areas that are separated by seemingly normal areas of gut mucosa [20].

Crohn’s disease was of high suspicion when evaluating our patient due to symptoms experienced and the location of the stricture. Fecal calprotectin was assessed as a screening tool. Fecal calprotectin is associated with intestinal inflammation, with sensitivities and specificities of 90%, but cannot be used to differentiate the cause of inflammation as infection or inflammatory bowel disease [8]. The elevated fecal calprotectin and associated stricture in the terminal ileum all pointed towards Crohn’s disease. A follow up colonoscopy revealed poor visualization, however no ulcers or strictures were apparent in the accessible areas, which neither confirmed or rejected the diagnosis of Crohn’s disease. Crohn’s disease could be confirmed with the biopsy of the stricture revealing features such as clusters of neutrophils known as crypt abscesses, mucosal atrophy, or noncaseating granulomas [20], which was not found.

Ectopic gastric mucosa

The final pathology of the stricture revealed a source so rare that it was not even investigated as a differential diagnosis – ectopic gastric mucosa.

Most cases of ectopic gastric mucosa are diagnosed on incidental finding on autopsy. Of these, the most common locations include Meckel's diverticulum, an anatomic anomaly due to incomplete obliteration of the vitelline duct, and the proximal esophagus, known as an "inlet patch" [4]. While strictures due to heterotopic gastric mucosa are not unheard of, their presence in the small intestine outside of Meckel's diverticulum is extremely rare [2].

Heterotopic gastric mucosa has two possible origins; congenital or metaplastic. Congenital ectopic gastric mucosa is a result of pluripotent endodermal differentiation in an abnormal location. This type leads to full thickness differentiation which contains all the cells that normal gastric tissue contains. The congenital type is typically clinically silent. When it does become clinically relevant it is usually due to gastric acid secretion causing bleeding or ulcers [18].

Metaplastic differentiation of gastric mucosa is an acquired condition resulting from error in the regenerative process in response to chronic inflammation. These types are most frequently of partial thickness and contain mucus secreting cells, with few to no acid producing parietal cells [2,18].

Since our patient's pathology revealed full thickness gastric mucosa, it can be assumed that this was a congenital abnormality. The gastric tissue was entirely fundic type tissue, whose main role is secreting gastric enzymes. It contains cells such as parietal cells (also known as oxyntic cells) that are responsible for secreting acid, chief cells (also known as peptic cells) which secrete pepsinogens, mucous cells which secrete mucous, and ECL cells which will be described later [4]. Hypothetically, the acid produced by this fundic tissue could lead to an inflammatory response. If remarkable enough, this reaction could possibly have led to the stricture.

Enterochromaffin Like (ECL) cells are a form of gastric endocrine cells. ECL cells' main secretory products include histamine and chromogranin A, released in response to the hormone gastrin [11]. We used chromogranin A as a screening tool for a carcinoid tumor. Its elevation led us to falsely believe that a carcinoid tumor was present. However, the presence of fundic gastric tissue with ECL cells is what most likely led to the increase in chromogranin A, especially with the associated use of PPIs increasing gastrin levels and in turn chromogranin A secretion as stated above.

So, while the discovery of heterotopic gastric mucosa explained the presence of a stricture and the elevation of chromogranin A, what still remained was an elevated fecal calprotectin at 181 mcg/c (normal < 50 mcg/g). Fecal calprotectin is often used as a screening tool for inflammatory bowel disease, as it is associated with intestinal inflammation, with sensitivities and specificities of 90%. It cannot, however, be used to differentiate the cause of inflammation as infection or inflammatory bowel disease [8]. Since stricture biopsy results revealed gastric mucosa as opposed to features such as clusters of neutrophils known as crypt abscesses, mucosal atrophy, or noncaseating granulomas (as would be expected in Crohn's disease) [20], Crohn's disease differential was rejected and elevated calpro-

tecin was assumed to be due to the inflammatory reaction of the gastric mucosa which caused the stricture. This was confirmed as calprotectin levels dropped into normal range (<162.9 mcg/g) after resection of the gastric mucosa.

Discovery of inflammatory bowel disease

Two months after resection of the stricture and diagnosis of heterotopic gastric mucosa, the patient again began to experience a recurrence of abdominal pain and signs of dehydration. The following work-up was highly suspicious for early Crohn's disease.

Since 2005 there have been only a handful of reported bariatric patients diagnosed with Crohn's disease status post Roux-en-Y gastric bypass surgery. None of these patients experienced symptoms prior to the surgery, nor did they have a family history of inflammatory bowel disease [9], as is the same with our patient. All of the patients experienced improved symptoms with immune suppressant and salicylate treatment [10].

No definite causal mechanism has been determined, yet hypotheses have been suggested. Most notably focusing on the change in physical anatomy's effect on the alteration of bacterial microbiome. The combination of afferent limb stasis and decreased gastric acidity following Roux-en-Y gastric bypass is felt to predispose to bacterial over growth [3]. It has been suggested that this altered bacterial microbiome of the gut, activates the immune system, triggering chronic intestinal inflammation in the form of Crohn's disease [9,10]. Since this phenomenon is only apparent in a small minority of bariatric patients, it is possible that genetic predisposition may play a role in susceptibility [10].

Further workup will be necessary for a definite diagnosis of Crohn's disease. Upon the official diagnosis we are left with a few unanswered questions. Most notably, was the original stricture discovered due to the gastric mucosa or Crohn's disease? If due to Crohn's disease, why was the typical histology of non-caseating granulomas, marked lymphoid reaction and fibrosis not present? As we continue to monitor chromogranin A and fecal calprotectin, we should expect chromogranin A to decrease to normal limits with the excision of the gastric mucosa. Fecal calprotectin would be expected to again rise, due to the ongoing intestinal inflammation, this time suspected to be due to Crohn's disease.

Conclusions

Post bariatric surgery strictures are not an uncommon finding, present in 3-5% of total cases [21], and even more prevalent in Roux-en-Y gastric bypass cases [16]. These strictures are most commonly seen at the sight of anastomosis. What is unique about this case is the fact that the anastomosis was clearly open and patent, with the stricture being beyond it. Furthermore, the pathology of the stricture revealed congenital heterotopic gastric mucosa. What further complicates this case is the reappearance of symptoms following excision of the stricture associated with a high suspicion for Crohn's disease. Having no previous symptoms prior to bariatric surgery and no family history, it could be hypothesized that this patient developed the disease in reaction to the Roux-en-Y gastric bypass. Further tests will need to be completed to officially establish the diagnosis of Crohn's disease, along with continued monitoring of fecal calprotectin and chromogranin A.

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