

# A Case to Remember: Enlarged Gastric Folds — A Management Dilemma

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## Citation

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## Abstract

Enlarged gastric folds are infrequently encountered at endoscopy. A variety of conditions such as hypertrophic gastropathy, malignancies, infiltrative diseases or infections can lead to gastric fold enlargement. Their gross appearance may be similar. In this article, we will present a patient with enlarged gastric folds and a management dilemma.

## CASE

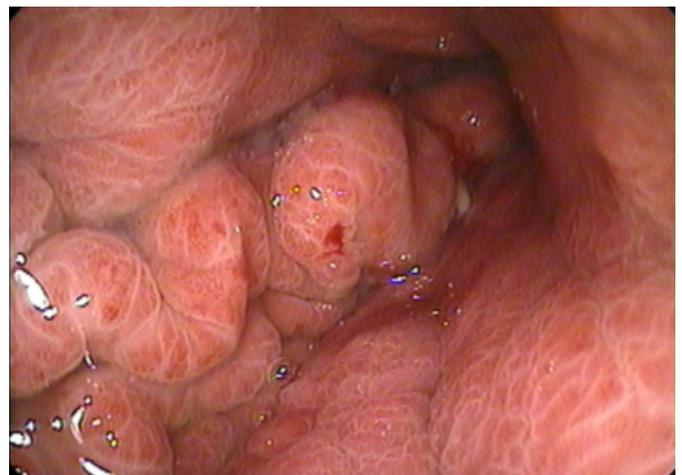
Our patient is a sixty-eight year-old female with a past medical history of hypertension and an ectopic pregnancy who presented with a one-month history of intermittent nausea and vomiting. She also described epigastric “hunger” pain that worsened with eating. She denied fever, chills, dysphagia or weight changes. She had some loss of appetite. Her surgical history included a salpingectomy secondary to a ruptured ectopic pregnancy many years back. She quit smoking twenty-five years ago and drank alcohol occasionally. She denied a family history of gastric or colon cancer. Her brother died of liver cancer.

On physical examination, the patient was afebrile, her heart rate was seventy-four beats per minute, respiration rate was sixteen per minute, and blood pressure was 144/88 mmHg. Her head and neck, skin, cardiac, respiratory, and extremity exams were unremarkable. Her abdominal exam revealed a soft abdomen without organomegaly, abdominal distention or tenderness. Her laboratory evaluation revealed a normal basic metabolic panel, complete blood count and liver function test. Serum gastrin level was also within normal limits. The patient was given omeprazole twenty milligrams twice a day for symptomatic treatment.

As her symptoms did not improve with omeprazole, she underwent an esophagogastroduodenoscopy (EGD), which showed prominent gastric folds in the body of the stomach (Figure 1). The gastric folds were noted to be irregular, friable and firm. The stomach was poorly distensible. Multiple gastric biopsies were taken.

## Figure 1

Figure 1: EGD revealed thick, friable and firm gastric folds.



The gastric biopsy revealed an edematous lamina propria with vascular congestion and minimal chronic inflammation. There was no evidence of malignancy or amyloidosis. An immunohistochemical stain for *H pylori* was negative. Because of the concern for gastric cancer, an endoscopic ultrasound (EUS) with tissue biopsy was done. EUS findings confirmed thick gastric wall of 14-16 mm, although suspicious for Linitis Plastica, this was more suggestive of Menetrier's disease (Figure 2). A snare biopsy revealed mild foveolar hyperplasia without evidence of malignancy (Figure 3).

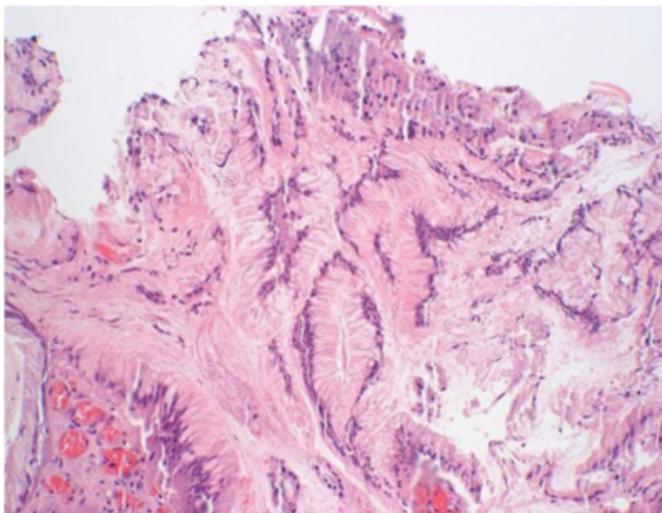
**Figure 2**

Figure 2: EUS revealed thick gastric mucosa suspicious for linitis plastica but more suggestive of Menetrier's disease.



**Figure 3**

Figure 3: Gastric body biopsy revealed mild focal edema of the lamina propria and vascular congestion with minimal inflammation. Immunochemical stain was negative for amyloid proteins.



The patient subsequently had a CT scan of the abdomen and pelvis that confirmed gastric fold thickening and it showed no lymphadenopathy. A low attenuation lesion was noted in the left lobe of the liver and a fine needle aspiration biopsy of this revealed mild focal macrosteatosis without malignancy. In addition, a PET/CT scan showed no increased uptake or evidence of malignancy.

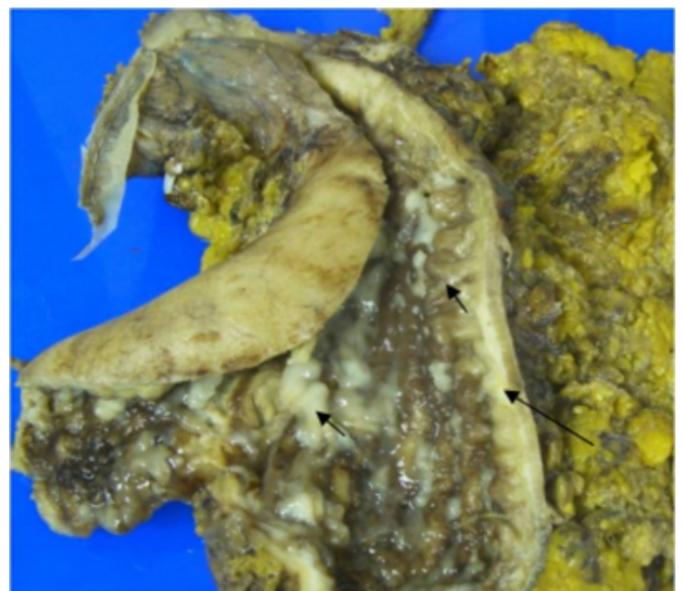
Based on the clinical history, EGD, EUS and biopsy findings, the differential diagnoses include Menetrier's disease, *Helicobacter pylori* induced hypertrophic gastropathy and Zollinger-Ellison syndrome, although

gastric adenocarcinoma could not be excluded because a full thickness gastric biopsy was not obtained. The patient continued to have poor oral intake and a percutaneous jejunal feeding tube was placed. Based on the information available to the medical team, a dilemma is faced trying to determine the most appropriate management. If the patient had Menetrier's disease, medical therapy such as Octreotide or Cetuximab, a monoclonal antibody against epidermal growth factor receptor, may be used. However, gastrectomy should be considered if malignancy cannot be excluded.

With conservative management, the patient did not gain any weight despite enteral feeding. A decision to undergo surgical exploration for definitive diagnosis was made. She underwent a robotic total gastrectomy performed two months after her initial presentation (Figure 4). The pathology revealed a hyperplastic gastric mucosa that was consistent with Menetrier's disease, as well as a poorly-differentiated adenocarcinoma (signet ring type) infiltrating the submucosa, muscularis propria and serosa (Figures 5 and 6). Three local lymph nodes were found to have metastatic carcinoma. Patient was subsequently started on adjuvant chemoradiation with 5- fluorouracil (5-FU) based therapy recommended by her oncologist.

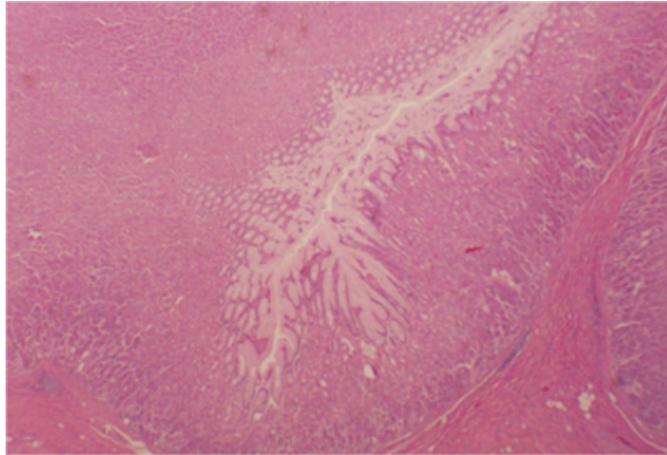
**Figure 4**

Figure 4: Gross photo of the opened gastrectomy specimen showing hypertrophic mucosal folds and thick viscid mucus overlying the mucosa (short arrow). The specimen also showed thickened, firm, and stiff (leather-like) muscular layer (long arrow) and a reduced stomach volume.



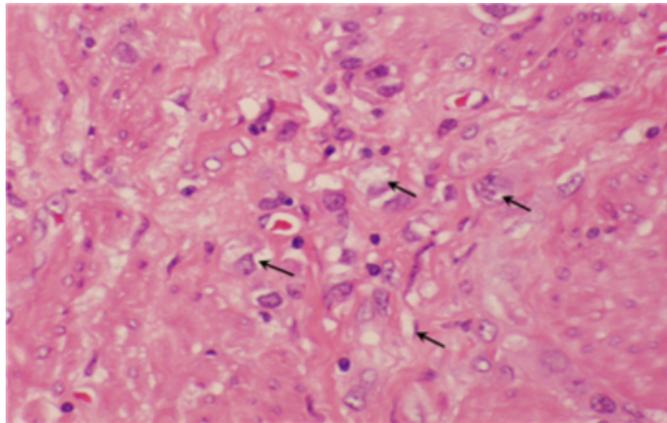
**Figure 5**

Figure 5: Low magnification view of the hyperplastic mucosal layer extending deep into the muscular layer. The benign hyperplastic changes of gastric mucosa are typical of Menetrier’s disease.



**Figure 6**

Figure 6: Higher magnification view of the muscularis propria showing the infiltrating poorly differentiated adenocarcinoma (signet ring type). The arrows demarcate the tumor cells with signet ring features and with large pleomorphic nuclei containing cytoplasmic mucin. The tumor cells also infiltrated the serosal layer.



**DISCUSSION**

Hypertrophic gastropathies are infrequently encountered on imaging or endoscopic studies. They may represent infiltrative diseases like lymphoma, sarcoidosis, adenocarcinoma, or carcinoid; infectious diseases like *H pylori*, cytomegalovirus (CMV) or histoplasmosis; proliferative diseases like Menetrier’s disease or Zollinger-Ellison syndrome (ZES) (Table 1). In 1973, Ming et al. introduced the term hypertrophic gastropathy and they classified it into three types: 1. Foveolar hyperplasia with normal or atrophic oxyntic glands which is characteristic of

Menetrier’s disease; 2. Hyperplasia of oxyntic glands with largely unaffected mucous components which can be seen in ZES; 3. Mixed type where both mucous and oxyntic glands show variable hyperplasia which can be seen in *H pylori*, CMV, eosinophilic gastroenteritis or Cronkite-Canada syndrome (1).

**Figure 7**

Table 1: Classification of different types of hypertrophic gastropathy

Type	Individual Disease
Infiltrative	lymphoma, sarcoidosis, adenocarcinoma, or carcinoid
Infectious	<i>H pylori</i> , cytomegalovirus (CMV) or histoplasmosis
Proliferative	Menetrier’s disease, Zollinger-Ellison syndrome (ZES)

Menetrier’s disease was first described by Pierre Menetrier in 1888 as cerebriform enlarged rugal folds in gastric mucosa of cadavers. It affects mostly adults, but can occur in children. While other causes of enlarged gastric folds are diffuse and generalized, hyperplastic changes seen in Menetrier’s disease usually involve the body and/or the fundus of the stomach but spare the antrum (2). Patients with Menetrier’s disease may present with one or more symptoms such as epigastric pain (65%), asthenia (60%), anorexia (45%), weight loss (45%), edema (38%) or vomiting (38%) (3). Laboratory studies may show hypoalbuminemia and increased enteric protein loss. Full thickness biopsy of the stomach may show foveolar hyperplasia with glandular atrophy.

The pathogenesis of Menetrier’s disease is not entirely understood, but it has been proposed that it may involve the transforming growth factor-alpha (TGF- $\alpha$ ). TGF- $\alpha$  increases gastric mucous production and inhibits acid secretion. In patients with Menetrier’s disease, TGF- $\alpha$  immunostaining appeared to be mostly concentrated in the parietal cells in the gastric mucosa compared to normal subjects. In transgenic mice that over-expressed TGF- $\alpha$  in the stomach, surface mucous cells expanded and serum gastrin levels were inappropriately low. This was also observed in patients with Menetrier’s disease. Therefore, it is speculated that low serum gastrin level leads to increased signaling of epidermal growth factor receptor and subsequently contributes to the histological features of Menetrier’s disease (4).

There have been reports of association between Menetrier’s disease and gastric cancer. In some reports, up to 15% of the patients with Menetrier’s disease had associated gastric

cancer including several cases of progression of dysplasia to carcinoma (5). Saadia et al. reported four cases of Menetrier's disease associated with gastric adenocarcinoma and low-grade dysplasia (6).

Spontaneous resolution of Menetrier's disease has been reported especially in children with viral disease such as CMV induced hypertrophic gastropathy. Medical therapies such as histamine 2 receptor antagonists and proton pump inhibitors have been shown to improve symptoms (3). If H pylori infection is identified, prompt treatment should be initiated and symptoms may improve. In addition, if foveolar hyperplasia is associated with CMV gastritis, ganciclovir has been shown to be beneficial. In a case report, a pediatric patient who had CMV-associated hypertrophic gastropathy was treated with IV ganciclovir for five days, albumin transfusions were no longer required after treatment and complete recovery was achieved after several weeks (7).

Octreotide 100 micrograms subcutaneous (SQ) twice a day was shown to block the effect of epidermal growth factor and decrease enteral protein loss in a patient with Menetrier's disease (8). Similar findings were noticed in Green's patient who was given SQ Octreotide 100 micrograms three times a day. In addition, when treatment was changed to Octreotide LAR 10 milligrams intramuscularly every twenty eight days, gastric folds became less prominent on EGD two months later, although histological findings were unchanged (9).

Because it has been hypothesized that TGF- $\alpha$  may be involved in Menetrier's disease, monoclonal antibody against the epidermal growth factor receptor like Cetuximab is an alternative treatment. In one study, patients with Menetrier's disease presenting with nausea and vomiting had marked improvement after Cetuximab infusion. Furthermore, serum TGF level increased by a factor of three and serum albumin level also increased due to decrease in protein loss, although EGD and biopsy findings did not change (10).

If medical management fails to improve symptoms, subtotal or total gastrectomy should be considered. It generally stops protein loss, eliminates hyperchlorhydria, and ultimately prevents malignant transformation to adenocarcinoma (11). With the advance in surgical technique, laparoscopic total gastrectomy with Roux-en-Y esophagojejunostomy allows patient to have a shorter hospital stay and be able to tolerate oral food intake as soon as seven days after the surgery (12).

Environmental factors such as high salt-preserved or high nitrate-containing foods, smoking, excessive alcohol intake and infections like Epstein-Barr virus (EBV) or H pylori have been shown to increase the risk for gastric cancer in addition to atrophic gastritis. Underlying gastric cancer is another concern for patients with Menetrier's disease. High incidence of gastric cancer can be found in countries such as Japan, Venezuela and Chile (1).

Signs and symptoms of gastric adenocarcinoma are nonspecific and may include vague epigastric pain, nausea, vomiting, weight loss, anemia or early satiety. When patients present with advanced disease, they may also experience dysphagia, severe weight loss, anorexia, ascites, hepatomegaly and not uncommonly gastrointestinal bleeding. Paraneoplastic syndromes are rare in gastric cancer, but it may have dermatologic manifestation such as acanthosis nigricans.

Diagnosis of gastric cancer is usually made by laboratory tests, imaging studies and tissue biopsy. Basic laboratory tests should include complete blood count, metabolic panel and liver function test. Tumor makers such as carcinoembryonic antigen (CEA), glycoprotein CA-125 antigen (CA-125) and CA 19-9 may be elevated in patients with gastric cancer. Initial imaging like barium study can identify gastric tumors or enlarged gastric folds. Once a lesion is identified on barium study, EGD should be performed for tissue biopsy to make a definitive diagnosis. Endoscopic ultrasound (EUS) may be useful to evaluate the depth of invasion of the cancer especially in early lesions (13). After the diagnosis is made, further imaging studies such as CAT scan of the abdomen and pelvis should be obtained to evaluate for metastatic disease. A combined positron emission tomography (PET) scan and CAT scan has a high sensitivity in detecting distant metastatic disease and it can also be used for staging the cancer (14-16). A more invasive procedure like staging laparoscopy may be required when more advanced disease such as peritoneal carcinomatosis is suspected and fluid cytology is crucial in confirming the diagnosis (17-19). Eventually, the TMN staging system developed by American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) will be used to stage the cancer.

Treatments for gastric cancer have changed over the years as more results from evidence-based meta-analyses become available. For patients with resectable local disease, two meta-analyses have shown survival benefits in patients treated with adjuvant (postoperative) systemic chemotherapy

with 5-FU and leucovorin (20-21). Adjuvant chemoradiotherapy has been adopted in the US as a standard therapy largely due to the survival benefits that were shown in the Intergroup Trial 0116 study (22). For patients with advanced gastric cancer at presentation, management is more complicated and it involves various regimens of chemotherapy that will not be reviewed in this article. Complete resection of the gastric cancer along with adjuvant chemoradiotherapy or neoadjuvant (preoperative) chemoradiotherapy in patients with local advanced disease has shown to have increased long term survival benefits (23). Neoadjuvant chemotherapy or chemoradiotherapy may be used preoperatively to decrease tumor size and makes local advanced disease resectable, although the approach has not been widely adopted due to the lack of randomized trials (24).

Our case has demonstrated the difficulty in the diagnosis of Menetrier's disease vs. gastric cancer and the multidisciplinary approach needed to establish the diagnosis and appropriate treatment.

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