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**Upper gastrointestinal bleeding as an unusual manifestation of localized Ménétrier's disease with an underlying lipoma: A case report**

**INTRODUCTION**

Ménétrier's disease is rare; only a few hundred cases have been reported worldwide. Characteristic features of the disease are gastrointestinal symptoms, enlarged gastric folds (usually in the whole body and fundus of the stomach) and protein-losing gastropathy, which manifests as hypoalbuminemia and peripheral edema<sup>[1,2]</sup>. The disease is associated with a higher risk of developing gastric adenocarcinoma<sup>[3]</sup>.

We report an infrequent case of localized Ménétrier's disease elevated by an underlying submucosal lipoma, making it look like a polypoid mass. The mass was successfully removed with tunneling endoscopic submucosal dissection (ESD).

**CASE PRESENTATION**

***Chief complaints***

A 76-year-old White male was referred for esophagogastroduodenoscopy (EGD) after an episode of upper gastrointestinal bleeding.

***History of present illness***

The patient reported recurrent epigastric pain, transient fatigue and melena.

***History of past illness***

The patient's comorbidities were type 2 diabetes mellitus, arterial hypertension and benign prostatic hyperplasia. Past medical history was relevant for coronavirus disease

2019, ischemic stroke, appendectomy, viscerocranial abscess and surgically-treated cataract.

### **1** *Personal and family history*

The patient had a history of smoking in the past (30 pack-years). However, he had not smoked for 4 years and denied drinking alcohol. There was no relevant family history.

### *Physical examination*

The patient's height was 183 cm, weight was 80 kg, and body mass index was 23.89. Vitals upon admission were: heart rate, 50 beats/min; blood pressure, 118/48 mmHg; respiratory rate, 14/min; and body temperature, 36 °C. There was no abdominal tenderness and no peripheral edema.

### *Laboratory examinations*

Laboratory results were not relevant. Serum protein or albumin levels were not tested because Ménétrier's disease was not suspected at the time.

### *Endoscopic examination*

EGD revealed a polypoid mass (4 cm × 1 cm) with enlarged mucosal folds in the body of the stomach between the lesser curvature and posterior wall (Figure 1A). The mass was cohesive and somewhat stiff in contact with the forceps. A small ulcer at the distal end of the mass was identified as the source of the bleeding (Figure 1B). Standard and deep biopsy were taken from the distal end of the mass, and both were negative for neoplasia. Except for the mass, the mucosa was normal, and gastric folds were not enlarged.

### *Imaging examinations*

Computed tomography of the abdomen with contrast enhancement showed a submucosal lipoma (49 mm × 19 mm) in the body of the stomach, elevating the mucosa

(Figure 2). The stomach was otherwise normal. There was no visible infiltration of surrounding tissue and no enlarged lymph nodes.

### **FINAL DIAGNOSIS**

The final diagnosis of Ménétrier's disease and submucosal lipoma was determined by pathological examination of the resected specimen (Figure 3). Upon macroscopic examination, the gastric mucosa was found to be focally thickened (up to 1.5 cm in width) with tortuous folds and elevation of the surface, which gave the mucosa cobblestone or cerebriform appearance (Figure 4 and Figure 5). Histologically, the dominant feature was foveolar hyperplasia of gastric glands (Figure 6). The surface and glandular mucous cells were elongated, cystically dilated and tortuous, which can be described as a "corkscrew-like appearance" (Figure 4B, Figure 5A, and Figure 7A). Additionally, cystic dilation of the deep glands was observed (Figure 4A). Foveolar hyperplasia was accompanied by oxyntic atrophy with the loss of chief and parietal cells, especially in the area adjacent to cystically dilated deep glands. Muscularis mucosae was focally thickened and branched out to the lamina propria with vertical strands of smooth muscles (Figure 5B). Among microscopic changes of the mucosa, predominant chronic inflammatory infiltrate of low intensity with some scattered eosinophils was present in the lamina propria (Figure 5C). Moreover, a lipoma was identified in the submucosal layer (Figure 5 and Figure 7). This benign lesion was located within the submucosal border without breaching the muscularis mucosae. It simultaneously lifted the mucosal layer, described as an elevation of the surface during the macroscopic examination. The immunohistochemical tests showed no *Helicobacter pylori* (*H. pylori*) infection.

### **TREATMENT**

The mass was removed *en bloc via* tunneling ESD (Figure 8).

### **OUTCOME AND FOLLOW-UP**

The patient's symptoms subsided after the intervention, and he was scheduled for follow-up EGD.

## DISCUSSION

Clinical symptoms of Ménétrier's disease are nonspecific and include abdominal pain, nausea, vomiting, asthenia, anorexia, weight loss and peripheral edema<sup>[1,2]</sup>. Among these, our patient presented only with recurrent abdominal pain. He was older than most patients at the time of diagnosis since the disease is most often diagnosed between the age of 30 and 60 years. It is diagnosed more frequently in males<sup>[1,2]</sup>.

The etiology of Ménétrier's disease in most cases is unknown. It is generally considered to be acquired, but a rare familial form has been reported in siblings. Some cases have been linked to *H. pylori* with regression after treatment of the infection. In our patient, the immunohistochemical test for *H. pylori* was negative. There is also a subtype occurring in children, associated with cytomegalovirus infection<sup>[1,2]</sup>.

The definite pathophysiology of Ménétrier's disease is still being investigated. One of the theories is linked to increased production of transforming growth factor-alpha (TGF- $\alpha$ ) and as a consequence increased signaling of the epidermal growth factor receptor (EGFR). One consequence of TGF- $\alpha$  overexpression is cellular proliferation, which may trigger neoplastic transformation. Studies on mice have shown that TGF- $\alpha$  overexpression in the stomach mucosa showed changes characteristic of Ménétrier's disease<sup>[4-6]</sup>. Furthermore, studies on Ménétrier's disease patients demonstrated a similar mechanism<sup>[7,8]</sup>. Increased overexpression of TGF- $\alpha$  causes increased signaling of EGFR, a transmembrane receptor with tyrosine kinase activity that further triggers an intracellular signaling cascade, expanding the cell's proliferation. Immunohistochemical reactions using TGF- $\alpha$  and EGFR are not routinely performed during the diagnostic process as they are not a requirement for the diagnosis of Ménétrier's disease. However, in the future, it will be worth focusing on the study of the TGF- $\alpha$  and EGFR pathways in order to understand its pathophysiology and consequences.

Initially, Ménétrier's disease was not suspected in our patient. His symptoms (epigastric pain, fatigue and melena) were not typical for this disease. Gastroscopic and imaging results did not indicate Ménétrier's disease either. Gastric folds are usually enlarged in the whole body and fundus of the stomach, with antrum spared, although a localized form of the disease has been reported<sup>[1,3,9]</sup>. In this case, gastric folds were enlarged only on the surface of the mass in the body of the stomach. Biopsy of the affected mucosa usually confirms the diagnosis of Ménétrier's disease, but in our case it did not show any significant changes in the mucosa. Nevertheless, it helped differentiate the origin of the mass.

Differential diagnosis of Ménétrier's disease involves a broad spectrum of conditions and requires analysis of clinical symptoms, gastroscopy, imaging and histological results. Ménétrier's disease should be differentiated from hypertrophic lymphocytic gastritis, hypertrophic hypersecretory gastropathy, Zollinger-Ellison syndrome, hyperplastic or hamartomatous polyps, gastric carcinoma, lymphoma and amyloidosis<sup>[1,2]</sup>.

Upper gastrointestinal bleeding has been reported as a rare manifestation of Ménétrier's disease. The bleeding may present as hematemesis or, like in this case, as melena<sup>[10,11]</sup>. One patient developed deep vein thrombosis and received anticoagulation therapy, which led to gastrointestinal bleeding<sup>[12]</sup>. Iron deficiency anemia in patients with Ménétrier's disease could be a sign of occult bleeding, but iron malabsorption should also be considered<sup>[13,14]</sup>.

Hypoalbuminemia is present in the majority of patients with Ménétrier's disease (85%), and in some cases causes peripheral edema<sup>[1]</sup>. Ménétrier's disease should be considered in differential diagnosis of protein-losing gastropathy/enteropathy, and certain interventions may be necessary to normalize albumin level, such as *H. pylori* eradication, proton pump inhibitors, H2-blockers, anticholinergic drugs, corticosteroids or octreotide<sup>[15]</sup>. In this case, albumin level was not obtained during the diagnostic process or preoperative laboratory evaluation. It should be tested if Ménétrier's disease is suspected or the patient presents with peripheral edema.

Treatment of Ménétrier's disease usually includes a high-protein diet and supportive medication, but severe cases may require total gastrectomy<sup>[1]</sup>. Partial gastrectomy has also been performed in selected patients<sup>[9,16,17]</sup>. The discovery of the role of TGF- $\alpha$  and EGFR overexpression in the pathogenesis of Ménétrier's disease resulted in experimental treatment with monoclonal antibodies, such as cetuximab<sup>[18-20]</sup>. To our knowledge, localized Ménétrier's disease with an underlying submucosal lipoma has never been reported. Tunneling ESD was used for the first time to remove localized Ménétrier's disease.

Increased risk of gastric cancer in patients with Ménétrier's disease contributes to increased mortality in this group. In a case-control study of 76 patients by Almazar *et al*<sup>[3]</sup>, 8.9% of patients with Ménétrier's disease developed gastric cancer 10 years after the diagnosis *vs* 3.7% in the control group. The 5-year and 10-year survival rates were 72.7% and 65.0%, respectively (*vs* 100% in the control group). The authors suggest annual screening for cancer with EGD. Gastrectomy remains the primary treatment option for patients who developed gastric cancer. Recently, two curative endoscopic interventions for early-stage gastric cancer in patients with Ménétrier's disease have been reported: endoscopic mucosal resection and standard ESD<sup>[21,22]</sup>.

## **CONCLUSION**

We report a highly unusual case of localized Ménétrier's disease coexisting with a submucosal lipoma, which created a polypoid mass in the stomach. Successful resection was achieved with tunneling ESD.

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## Figure Legends

### **Figure 1 Polypoid mass found in the stomach during esophagogastroduodenoscopy.**

A: A mass (4 cm × 1 cm) with enlarged mucosal folds in the body of the stomach between the lesser curvature and posterior wall; B: A small ulcer at the distal end of the mass.

### **Figure 2 Computed tomography of the abdomen with contrast enhancement.**

A: A submucosal lesion in the stomach. Mean density of -89 HU suggested a submucosal lipoma; B: Length, 4.86 cm; C: Width, 1.96 cm.

### **Figure 3 Resected specimen.**

A: Immediately after resection, enlarged gastric folds were observed on the surface; B: Intersected specimen in the Pathology Department. Yellow tissue of the submucosal lipoma was observed.

### **Figure 4 Histological changes in Ménétrier's disease.**

A: Low magnification; B: Cystic dilation of deep glands with foveolar hyperplasia; C: Foveolar hyperplasia with tortuous glands; D: Foveolar hyperplasia with dilation of the glands and oxyntic atrophy.

### **Figure 5 Submucosal lipoma and accompanying changes in the course of Ménétrier's disease.**

A: Low magnification; B: Foveolar hyperplasia; C: Foveolar hyperplasia with a corkscrew morphology; D: Foveolar hyperplasia with tortuous glands and mild inflammation in lamina propria.

### **Figure 6 Histological changes in the course of Ménétrier's disease: foveolar hyperplasia, proliferation of muscularis mucosae and mild inflammation of lamina propria.**

A: Low magnification; B, C and D: Representative images taken at high magnification.

### **Figure 7 The mucosa with changes in the course of Ménétrier's disease and the adjacent submucosal lipoma.**

The lipoma was adjacent to the mucosa without crossing its borders. A: Low magnification; B, C and D: Representative images taken at high magnification.

### **Figure 8 Resection of the mass *via* tunneling endoscopic submucosal dissection.**

A: A tunnel was created in the submucosal layer beneath the mass; B: Dissection was

performed on both sides of the tunnel; C: Muscular defects were closed, and mucosal margins approximated with clips.

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