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CASE REPORT | STOMACH

A Concurrent Case of Ménétrier's Disease and Signet Ring Carcinoma

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ABSTRACT

Ménétrier's disease, also known as hyperplastic protein-losing gastropathy, is a rare, idiopathic, acquired, premalignant condition associated with gastric carcinoma. Its association with signet ring cell cancer of the stomach has been previously reported only twice. We present the third case of histologically confirmed concurrent Ménétrier's disease with signet ring carcinoma of the stomach, interrogated by esophagogastroduodenoscopy and endoscopic ultrasound.

INTRODUCTION

Ménétrier's disease (MD), also known as hyperplastic protein-losing gastropathy, is a rare idiopathic condition characterized by diffuse hypertrophy of gastric mucosa and giant gastric rugae. Patients with MD appear to be at an increased risk of traditional gastric adenocarcinoma.[1] The association of MD with signet ring cell carcinoma (SRCC) of the stomach is much less studied, with only two previously reported cases in literature.

CASE REPORT

A 64-year-old man presented with a 2-month history of epigastric pain, nausea, and 9-kg weight loss. Physical examination revealed thin body habitus but was otherwise unremarkable. Total protein and albumin were 6.4 g/dL and 4.2 g/dL, respectively. Mild normocytic anemia was noted (hematocrit 38%). Bilirubin and liver-associated enzymes were within normal limits.

On esophagogastroduodenoscopy (EGD), a copious amount of mucus was noted in the stomach. Prominent gastric rugae were observed, persisting despite repetitive insufflation (Figure 1). The mucosa was diffusely edematous in appearance with mosaic patterning (Figure 2). Endoscopic ultrasound (EUS) revealed diffuse thickening of the gastric wall and gastric folds from the body to the fundus, with associated perigastric lymphadenopathy (Figure 3). Areas of increased thickening with nodularity were observed.

Multiple gastric biopsies were obtained, demonstrating extensive foveolar hyperplasia (Figure 4). On one biopsy sample, SRCC was seen, leading to the concurrent diagnosis of MD and SRCC of the stomach. Of note, the biopsies were negative for cytomegalovirus (CMV) and *Helicobacter pylori*.

DISCUSSION

Ménétrier's disease, named after French pathologist Pierre Ménétrier, was first reported in 1888 and is characterized by diffuse hypertrophy of the gastric rugae.[2] Bimodal age distribution is classically described, occurring in childhood and mid-to-late adulthood (mean age, 55 years).[3] A male predilection is often reported. Most commonly, patients with MD present with non-specific abdominal pain, vomiting, diarrhea, and weight loss. In severe cases,

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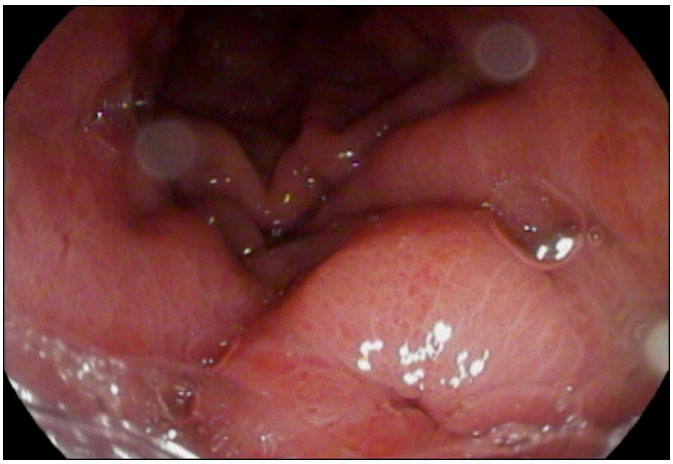

Figure 1. EGD showing abnormal appearance of the mucosa and prominent gastric rugae despite repetitive insufflation.

peripheral edema secondary to hypoproteinemia may be observed. When the 4 classic signs and symptoms of MD are considered (abdominal pain, nausea, vomiting, and edema), the majority of patients will describe only one (44%) or two (32%).[4] Due to its rarity, with an incidence of less than 1 in 200,000, the exact pathoetiology remains to be elucidated. CMV and *H. pylori* have been implicated as possible causative agents.[5,6] The disease is characterized by enlarged gastric folds within the body and fundus. While laboratory findings are typified by anemia, low serum albumin, high gastric pH, and normal to mildly elevated serum gastrin, a range of values have been reported and diagnosis should be considered in conjunction with the clinical, endoscopic, and pathological data.[4] Histology demonstrates mucosal hypertrophy, foveolar hyperplasia, and glandular atrophy. In a diagnostic algorithm proposed by Rich et al., MD may be distinguished from its mimics (such as polyposis syndromes, proton pump inhibitor effect, infiltrative disease, and Zollinger-Ellison syndrome) by

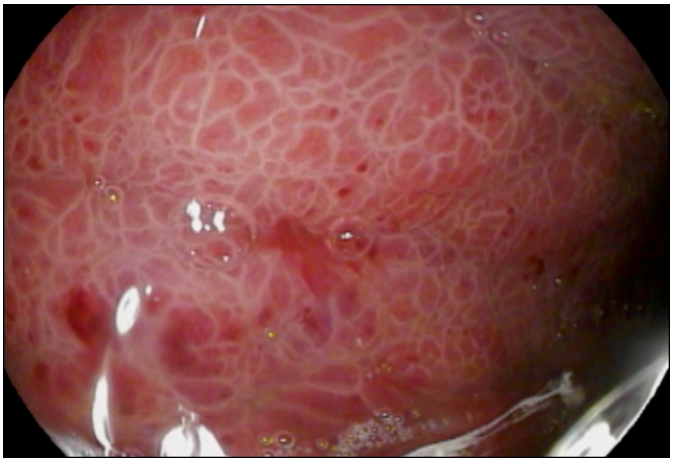

Figure 2. EGD showing diffusely edematous appearance of the gastric mucosa, which exhibits a mosaic pattern.

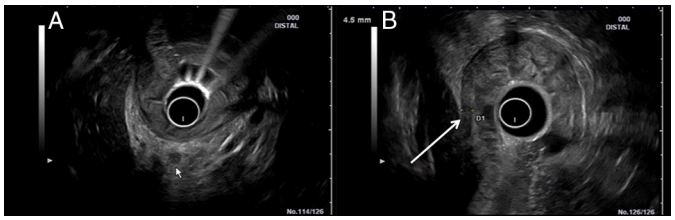

Figure 3. EUS demonstrating (A) diffuse thickening of the gastric wall and (B) perigastric lymph nodes (arrow) with a thickened gastric wall.

the presence of foveolar hyperplasia, retained orderly architecture/glandular parallelism, and a decreased number of parietal cells.[4]

While the association of traditional gastric adenocarcinoma with MD is increasingly recognized, there has been little research on the incidence of concurrent MD and SRCC. SRCC is a rare subtype of gastric malignancy with distinct clinicopathological features.[7] The overall incidence of gastric cancer within the United States has decreased over the past 30 years, but a recent review has demonstrated a 998% increase in the incidence of SRCC over the past few decades, although this may be complicated by change in the classification paradigm.[8] Perhaps more importantly, SRCC has been shown to be a major and independent predictor of poor prognosis.[9] Thus, differentiation of SRCC from traditional gastric adenocarcinoma is of clinical relevance.

The risk factors of SRCC have not been well examined. The role of *H. pylori* in the pathogenesis of SRCC is being questioned. In a Japanese study of *H. pylori*-negative gastric cancer, 40% of the *H. pylori*-negative cases without gastric atrophy were SRCC.[10] The roles of other traditionally

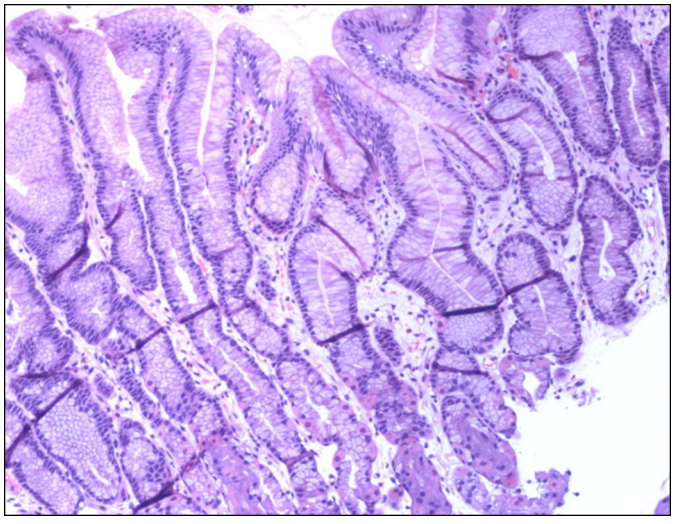

Figure 4. Hematoxylin and eosin stain of the gastric biopsy demonstrating relative preservation of mucosal architecture with foveolar hyperplasia and maintained parallelism, consistent with Ménétrier's disease. Foci of signet ring cell adenocarcinoma are also seen.

recognized risk factors of gastric cancer, such as salt-preserved food, smoking, gastritis, and obesity, remain poorly studied in this area.[11] To date, genetic mutation of the *CDH1*/E-cadherin pathway is the only firmly established risk factor of SRCC.[12] Prognosis depends heavily on the timing of diagnosis. It is known that depth of tumor invasion but not tumor size is predictive of lymph node metastasis of SRCC in early gastric cancer.[13]

An English-language MEDLINE search for "Ménétrier's disease" and "signet ring" from 1966 to the present revealed only two previously reported cases.[14,15] Including our case, all patients were male and presented in their 50s or 60s with midepigastric abdominal pain. Due to the rarity of MD, controlled studies on intervention and surveillance have not been performed, and evidence-based guidelines are unlikely to be established. In cases where suspected causative factors exist, treatment should be attempted. Cetuximab, a monoclonal antibody against the epidermal growth factor receptor, has recently been proposed as first-line therapy for MD following successful treatment in a small group of patients.[16,17] On the basis of our review of the limited available literature, we suggest close (at least yearly) surveillance of patients with MD as proposed by others.[18] EGD, EUS, and generous biopsies may prove invaluable for follow-up.

In cases where SRCC is found, literature suggests early gastric cancer without nodal metastasis or suspicious features (such as ulceration, size greater than 3 cm, or invasion) may be amenable to endoscopic resection. Otherwise, surgical resection may be a more appropriate option. While the role of chemotherapy has yet been fully investigated, it should be noted that the chemosensitivity profile of SRCC likely differs from that of non-SRCC. For further details on therapeutic treatment, Pernot et al. provided a more detailed discussion on therapeutic strategies and challenges in their review.[11]

DISCLOSURES

Author contributions: All authors wrote and edited the manuscript and performed the literature search. N. Martinez is the article guarantor.

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REFERENCES

1. Scharschmidt BF. The natural history of hypertrophic gastrophy (Ménétrier's disease): Report of a case with 16 year follow-up and review of 120 cases from the literature. *Am J Med*. 1977;63(4):644–52.
2. Ménétrier P. Des polyadenomes gastriques et de leurs rapports avec le cancer de l'estomac. *Arch Physiol Norm Pathol*. 1888;1(32–55):236–62.
3. Lambrecht NW. Ménétrier's disease of the stomach: A clinical challenge. *Curr Gastroenterol Rep*. 2011;13(6):513–7.
4. Rich A, Toro TZ, Tanksley J, et al. Distinguishing Ménétrier's disease from its mimics. *Gut*. 2010;59(12):1617–24.
5. Bayerdörffer E, Ritter M, Hatz R, Brooks W, Stolte M. Ménétrier's disease and *Helicobacter pylori*. *N Engl J Med*. 1993;329(1):60.
6. Sferra TJ, Pawel BR, Qualman SJ, Li B. Ménétrier's disease of childhood: Role of cytomegalovirus and transforming growth factor alpha. *J Pediatr*. 1996;128(2):213–9.
7. Kim J, Kim S, Yang H. Prognostic significance of signet ring cell carcinoma of the stomach. *Surg Oncol*. 1994;3(4):221–7.
8. Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973–2000: Increase in the signet ring cell type. *Arch Pathol Lab Med*. 2004;128(7):765–70.
9. Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. *Ann Surg*. 2009;250(6):878–87.
10. Kato S, Matsukura N, Tsukada K, et al. *Helicobacter pylori* infection-negative gastric cancer in Japanese hospital patients: Incidence and pathological characteristics. *Cancer Science*. 2007;98(6):790–4.
11. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. *World J Gastroenterol*. 2015;21(40):11428.
12. Charlton A, Blair V, Shaw D, Parry S, Guilford P, Martin IG. Hereditary diffuse gastric cancer: Predominance of multiple foci of signet ring cell carcinoma in distal stomach and transitional zone. *Gut*. 2004;53(6):814–20.
13. Lee J, Choi I, Kook M, Nam B, Kim Y, Ryu K. Risk factors for lymph node metastasis in patients with early gastric cancer and signet ring cell histology. *Br J Surg*. 2010;97(5):732–6.
14. Hsu C, Ito M, Kawase Y, Sekine I, Ohmagari T, Hashimoto S. Early gastric cancer arising from localized Ménétrier's disease. *Gastroenterol Jpn*. 1991;26(2):213–7.
15. Yukawa M, Fujimori T, Tabata T, et al. A small gastric cancer in association with Ménétrier's disease. *Digestive Endoscopy*. 1991;3(3):378–81.
16. Fiske WH, Tanksley J, Nam KT, et al. Efficacy of cetuximab in the treatment of Ménétrier's disease. *Sci Transl Med*. 2009;1(8):8ra18.
17. Settle SH, Washington K, Lind C, et al. Chronic treatment of Ménétrier's disease with erbitux: Clinical efficacy and insight into pathophysiology. *Clin Gastroenterol Hepatol*. 2005;3(7):654–9.
18. Bayless TM, Diehl AM. Chronic gastritis: Ménétrier's disease. In: *Advanced Therapy in Gastroenterology and Liver Disease*. PMPH-USA; 2005, p. 181.