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Curative resection with endoscopic submucosal dissection of early gastric cancer in *Helicobacter pylori*-negative Ménétrier's disease: A case report

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Abstract

BACKGROUND

Adult-onset Ménétrier's disease is strongly associated with *Helicobacter pylori* (*H. pylori*) infection and an elevated risk of carcinogenesis. Cases of early-stage gastric cancer developed in *H. pylori*-negative Ménétrier's disease are extremely rare. We report a case of early gastric cancer in *H. pylori*-negative Ménétrier's disease that was curatively resected with endoscopic submucosal dissection (ESD).

CASE SUMMARY

A 60-year-old woman was referred to our hospital after her medical examination detected anemia. Contrast-enhanced upper gastrointestinal (UGI) radiography revealed translucency of the nodule-aggregating surface with giant rugae. Blood tests showed hypoproteinemia and were negative for serum *H. pylori* immunoglobulin G antibodies. The ^{99m}Tc-DTPA-human serum albumin scintigraphy showed protein loss from the stomach. UGI endoscopy showed a 40-mm protruding erythematous lesion on giant rugae of the greater curvature of lower gastric body, suggesting early-stage gastric cancer due to Ménétrier's disease. *En bloc* resection with ESD was performed for diagnosis and treatment. Histology of ESD showed well-differentiated tubular adenocarcinoma. The cancer was confined to the mucosa, and complete curative resection was achieved. Foveolar hyperplasia and atrophy of the gastric glands were observed in non-tumor areas, histologically corresponding to Ménétrier's disease. Three years after ESD, gastric cancer had not recurred, and Ménétrier's disease remained in remission with spontaneous regression of giant gastric rugae.

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CONCLUSION

Complete curative resection was achieved through ESD in a patient with early-stage gastric cancer and *H. pylori*-negative Ménétrier's disease.

Key Words: Ménétrier's disease; *Helicobacter pylori*; Gastric cancer; Endoscopic resection; Endoscopic submucosal dissection; Case report

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Core Tip: We reported an extremely rare case of gastric cancer as a complication of *Helicobacter pylori*-negative Ménétrier's disease. The cancer was early-stage, and a minimally invasive curative resection was achieved with endoscopic submucosal dissection (ESD). There was no recurrence, and the patient's course was extremely good. This case also highlights that when endoscopic biopsy tissue from a cancer-suspected lesion showed atypical glands in Ménétrier's disease, total biopsy with ESD can be useful for diagnosis as well as treatment. ESD seems to be a beneficial therapy for early-stage gastric cancer in Ménétrier's disease because of its low invasiveness and high complete curative resection rate.

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INTRODUCTION

Ménétrier's disease (discovered in 1888) is a relatively rare gastric disease[1] characterized by giant rugae in the stomach accompanied by hypoproteinemia. Adult-onset Ménétrier's disease is strongly associated with *Helicobacter pylori* (*H. pylori*) infection and an elevated risk of carcinogenesis[2]. Our literature review suggests that *H. pylori*-negative cases of early-stage gastric cancer are extremely rare[3,4].

We report the first case of *H. pylori*-negative Ménétrier's disease with early gastric cancer in which complete curative resection was achieved through endoscopic submucosal dissection (ESD).

CASE PRESENTATION

Chief complaints

A 60-year-old woman was referred to our hospital for examination and treatment of anemia.

History of present illness

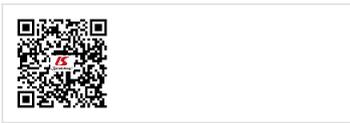
After observing transient melena, the patient's previous doctor conducted a medical examination and detected severe anemia (blood hemoglobin 6.1 g/dL).

History of past illness

The patient had undergone successful treatment of chronic hepatitis C with interferon therapy performed by a previous doctor.

Personal and family history

The patient had no history of smoking or drinking alcohol. There was no relevant family history.



Physical examination

On admission, the patient's temperature was 36.7 °C, heart rate was 81 bpm, blood pressure was 128/80 mmHg. There was conjunctival pallor and no spontaneous abdominal pain or no tenderness.

Laboratory examinations

The blood test revealed hypoproteinemia (serum albumin, 3.4 g/dL), and the serum *H. pylori* immunoglobulin G antibody level was negative (< 3).

Imaging examinations

Computed tomography (CT) of the abdomen revealed marked mucosal thickening of the body of the stomach, with no enlarged lymph nodes around the stomach (Figure 1A). Upper gastrointestinal (UGI) radiograph showed giant gastric rugae[5] and translucency of the nodule-aggregating surface in the greater curvature of the lower gastric body (Figure 1B). The ^{99m}Tc-DTPA-human serum albumin (HSA-D) scintigraphy showed protein loss from the stomach after 24 h (Figure 1C).

Endoscopic examination

UGI endoscopy revealed giant rugae in the gastric body, similar to contrast-enhanced radiographic findings (Figure 2A). A 40-mm broad-based, protruding erythematous lesion with lobular surface was observed on the giant rugae of the gastric body (Figure 2B). UGI endoscopy showed no evidence of atrophic gastritis and intestinal metaplasia.

Endoscopic ultrasonography (EUS) demonstrated the five layers of the gastric wall. In the lesion area, hypertrophy was observed in the first two layers (equivalent to the mucosa and the muscularis mucosae); however, no noticeable structural changes were evident in the third layer (equivalent to the submucosal layer) or deeper (Figure 2C). These findings were consistent with early tumor confined to the mucosal layer.

Low-magnification narrow-band imaging (NBI) showed granular surfaces with various sizes/forms and dilated vessels (Figure 2D). High-magnification NBI demonstrated irregular microstructures of various forms and tortuous microvessels with changes in caliber (Figure 2E).

Histopathological findings

Histological diagnosis based on endoscopic biopsy was Group 2 (non-tumorous changes suspected, though tumorous lesions cannot be ruled out)[6]. Considering the tumor size and high probability of a cancerous lesion based on the endoscopic images, *en bloc* resection with ESD was performed for definitive diagnosis and treatment (Figure 3A). Loupe image showed that the well-differentiated tubular adenocarcinoma was confined to the mucosal layer, with no lymphovascular invasion (ly0/v0) or ulceration (UL0), and both the lateral and vertical margins were negative (Figure 3B).

Histology of ESD specimens also showed proliferation of atypical cells with an irregular glandular structure (Figure 4A and B). Additionally, scattered p53 protein-positive cells were observed (Figure 4C). Based on these findings, the atypical glands were diagnosed with early gastric cancer of a well-differentiated tubular adenocarcinoma. Foveolar hyperplasia and atrophy of the proper gastric glands were observed in the non-tumor areas, a histological image corresponding to Ménétrier's disease (Figure 4D).

Immunohistochemical staining showed that the tumor cells were diffusely positive for MUC5AC (Figure 5A) and partially positive for MUC6 (Figure 5B), and negative for MUC2 (Figure 5C) and CD10 (Figure 5D). *H. pylori* were not observed in any biopsy or ESD specimens.

FINAL DIAGNOSIS

The final diagnosis of the presented case was early-stage gastric cancer and *H. pylori*-negative Ménétrier's disease.

TREATMENT

The patient underwent ESD.

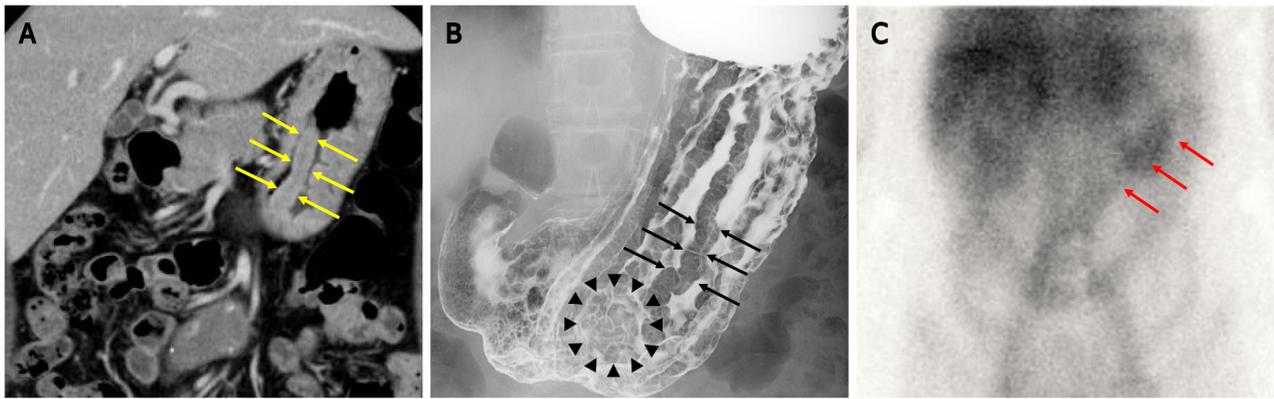


Figure 1 Images of computed tomography scan, upper-gastrointestinal radiograph and scintigraphy. A: Computed tomography scan revealed marked mucosal thickening of the body of the stomach (yellow arrow); B: The double-contrast technique shows remarkably enlarged fold width > 10 mm (black arrow) and translucency of nodule aggregating surface at the greater curvature in the lower gastric body (black arrowhead); C: ^{99m}Tc -DTPA-human serum albumin (HSA-D) scintigraphy: The arrows indicate accumulation in the stomach (red arrow).

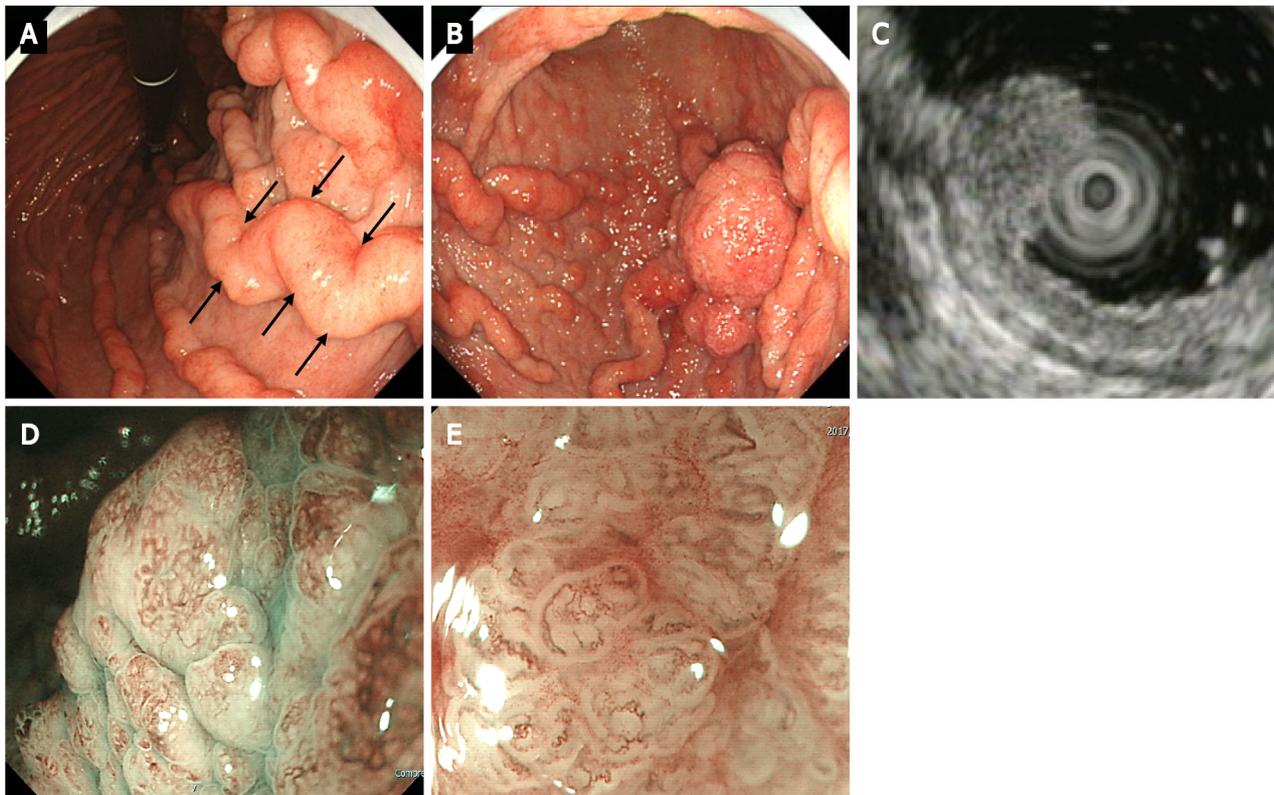


Figure 2 Upper gastrointestinal endoscopy. A: Upper gastrointestinal endoscopy shows marked fold enlargement from the ventricular angle to the fundus (black arrow); B: A 40-mm broad-based protruding lesion is observed near the posterior wall of the greater curvature of the lower gastric body; C: Endoscopic ultrasonography shows the five layers of the gastric wall. In the lesion area, hypertrophy was observed in the first two layers. No noticeable structural changes were evident in the third layer or deeper; D: Low-magnification narrow-band imaging (NBI) shows granular surfaces with various sizes/forms and dilated vessels; E: High-magnification NBI demonstrates irregular microstructures with various forms and tortuous microvessels with changes in caliber.

OUTCOME AND FOLLOW-UP

Histology of ESD specimens showed complete curative resection. Endoscopic follow-up was performed twice a year for 3 years after ESD, and no recurrence was detected (Figure 6). Even though no therapeutic agents were administered specifically for Ménétrier's disease, the giant rugae regressed spontaneously, hypoproteinemia and anemia improved gradually, and the remission was maintained until the last surveillance endoscopy.

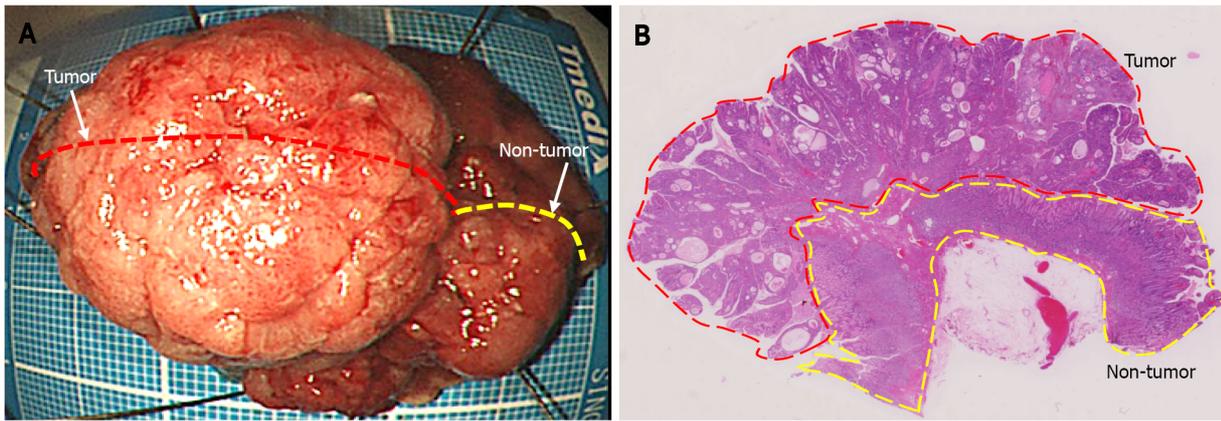


Figure 3 Endoscopic submucosal dissection specimen. A: 45 mm × 38 mm resection specimen comprising a broad-based protruding lesion with nodular surface and uninvolved (non-tumor) tissue with giant rugae; B: Loupe image shows that the well-differentiated tubular adenocarcinoma was confined to the mucosal layer, with no lymphovascular invasion (ly0/v0) or ulceration (ULO), and both the lateral and vertical margins were negative.

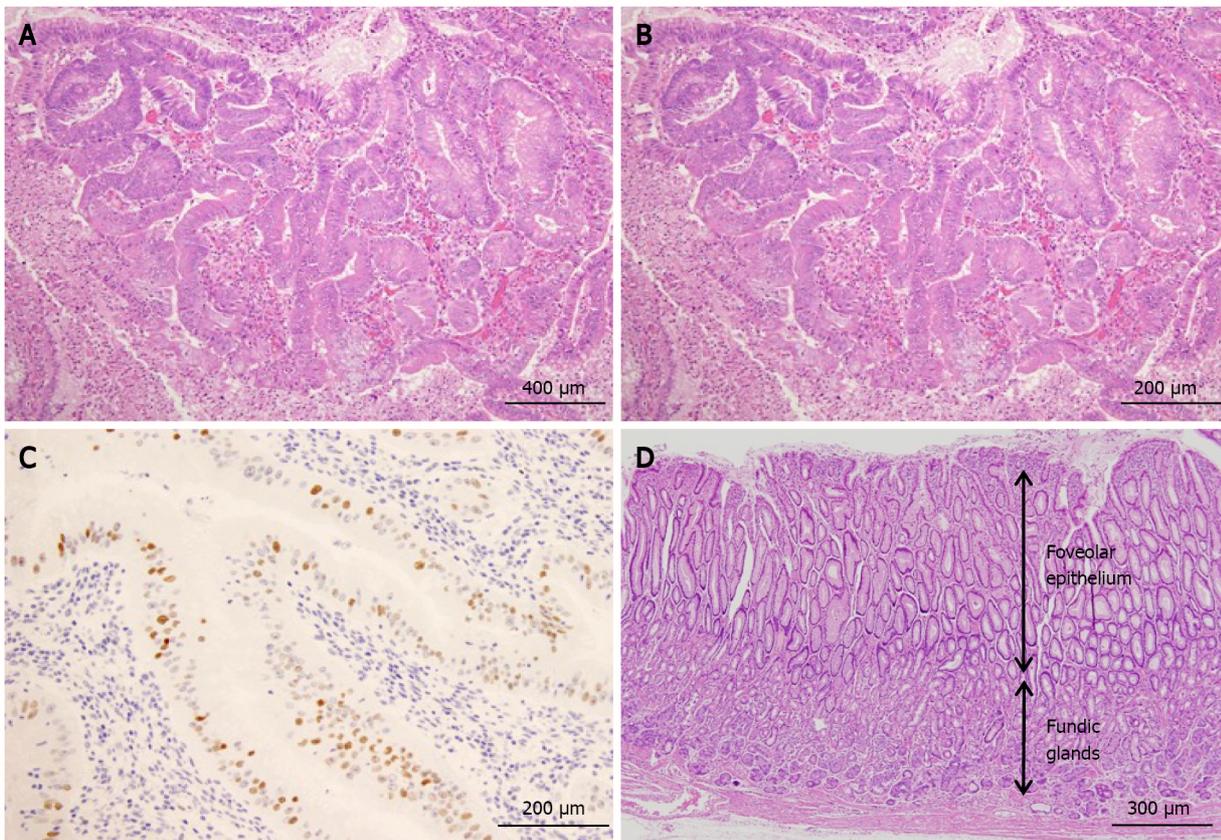


Figure 4 Histological findings. A: The protruding lesion exhibits proliferation of atypical glands with irregular tubular structures (HE; × 20); B: High magnification shows proliferation of atypical cells and enlarged nuclei (irregular or oval-shaped) in the irregular tubular structure (HE; × 20); C: Scattered positive image (in nuclei) in the region (p53; × 20); D: Foveolar hyperplasia and atrophy of the proper gastric glands in non-cancerous area, consistent with Ménétrier's disease (HE; × 20).

DISCUSSION

We reported an extremely rare case of early gastric cancer as a complication of *H. pylori*-negative Ménétrier's disease. We succeeded in curative resection of the cancerous lesion with ESD. Three years after the ESD, there was no recurrence of gastric cancer and Ménétrier's disease regressed spontaneously and had maintained regression for about 30 mo.

Although the present case was *H. pylori*-negative, there have been two reports of close associations between adult-onset Ménétrier's disease and *H. pylori* infection[7,8].

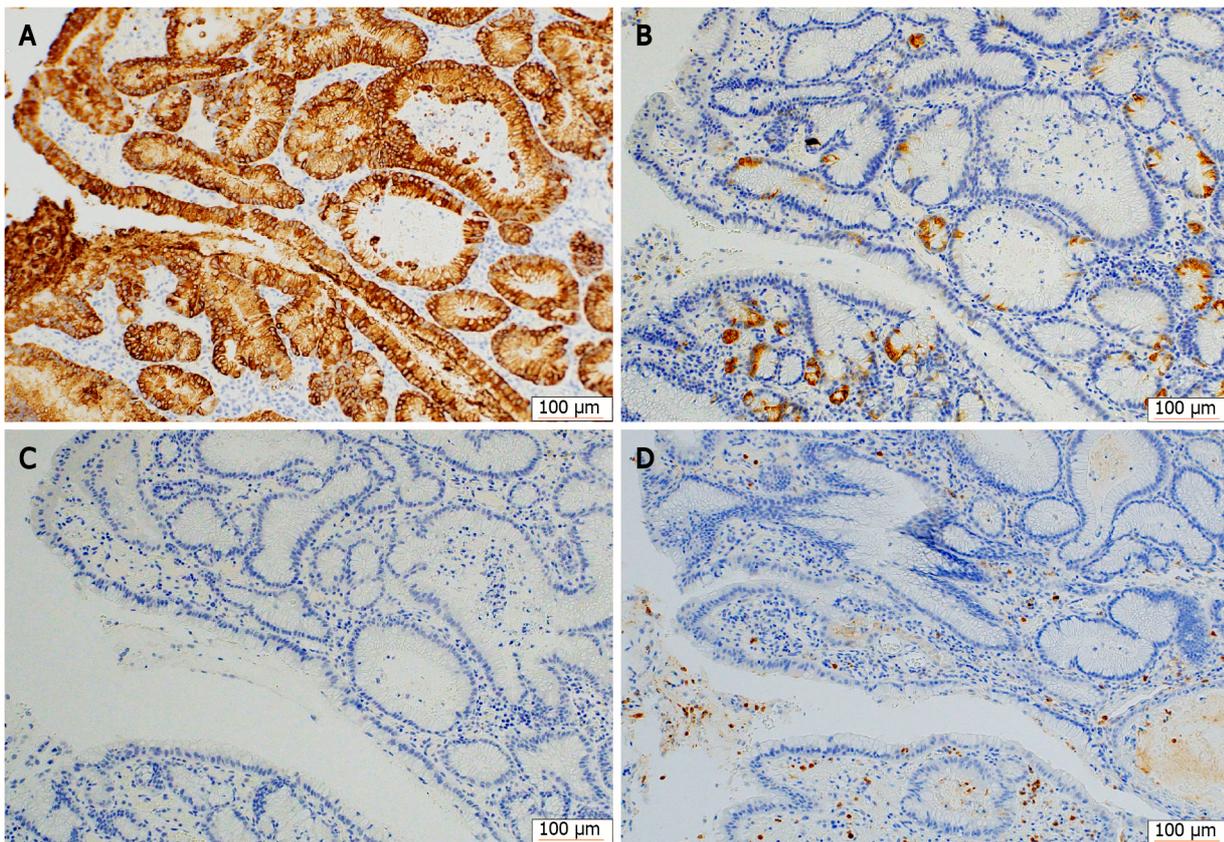


Figure 5 Immunohistochemical staining for mucin phenotypes. The tumor cells were diffusely positive for MUC5AC and partially positive for MUC6, and negative for MUC2 and CD10. A: MUC5AC; B: MUC6; C: MUC2; D: CD10.

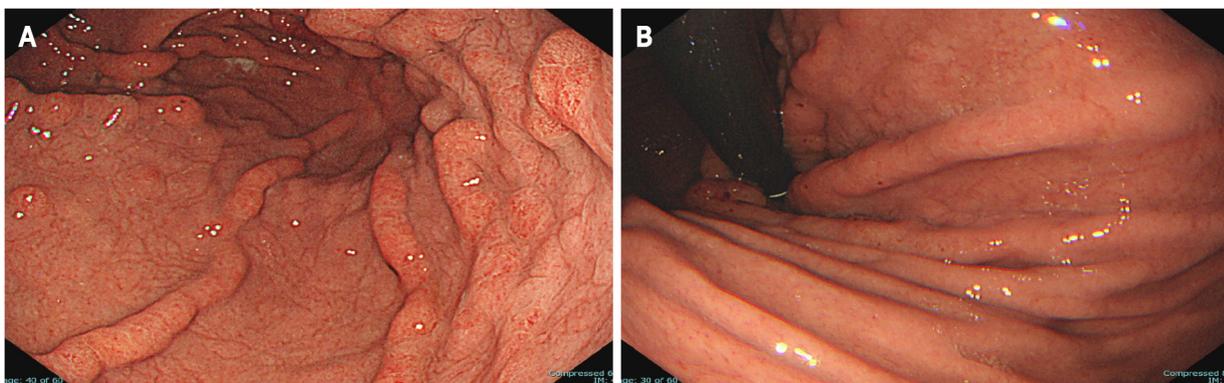


Figure 6 Upper-gastrointestinal endoscopy 3 yr after endoscopic submucosal dissection. A: Endoscopic submucosal dissection scar but no recurrence of tumor; B: The giant rugae with erythematous and edema has regressed spontaneously. Ménétrier's disease has remained in remission for the past 3 yr.

It has been reported that Ménétrier's disease with hypertrophic gastropathy increases the risk of gastric carcinogenesis[9]; however, the association between gastric carcinogenesis and *H. pylori* infection in Ménétrier's disease remains unclear.

There have been about 80 case reports on gastric cancer (including advanced cancer) in adult-onset Ménétrier's disease, though few have reported early-stage cancers. Our literature search found four case reports of Ménétrier's disease with early gastric cancer and recorded endoscopic findings and *H. pylori* infection status (Table 1); two of these cases were *H. pylori*-positive[10,11], and three cases, including the present one, were *H. pylori*-negative[3,4]. Our case was the second early gastric cancer to undergo endoscopic resection and the first resection with ESD instead of conventional endoscopic mucosal resection. Macroscopically, all the lesions of early gastric cancer were of protruding-type[12] and located on the oral side of the ventricular angle (corpus/fundus region)[13]. Hypoalbuminemia was observed in three cases and was

Table 1 Case reports on early-stage gastric cancer in patients with Ménétrier's disease

Ref.	Age	Gender	Hypoalbuminemia ¹ (g/L)	<i>H. pylori</i>	Differentiation	Tumor invasion depth	Macroscopic types	Tumor location	Therapy	Outcome
Raderer <i>et al</i> [10]	79	F	Present (1.5)	Positive (Hp IgG-Ab)	Well	M	0-Is	Fundus	EMR	No recurrence for 3 yr
Johnson <i>et al</i> [11]	73	M	Present (2.4)	Positive (histology)	Well	SM	0-IIa + IIc	Corpus	TG	Unknown
Ozawa <i>et al</i> [3]	48	F	Present (1.5)	Negative (Hp IgG-Ab)	Poor	M	0-Is	Corpus to Antrum	TG	No recurrence for 2 yr
Charton-Bain <i>et al</i> [4]	62	F	Unknown	Negative (histology)	Well	M	0-Is	Corpus	TG	Death on the 7 th day post-operation ²
Present case	60	F	Present (3.4)	Negative (Hp IgG-Ab)	Well	M	0-Is	Corpus	ESD	No recurrence for 3 yr

¹Hypoalbuminemia defined with less than 3.4 g/L.

²Death of pneumonia and liver failure.

EMR: Endoscopic mucosal resection; TG: Triglyceride; ESD: Endoscopic submucosal dissection; IgG: Immunoglobulin G.

unclear in one case.

These findings (protruding lesions located in the corpus or fundus region and hypoalbuminemia) may depict the clinicopathological features of Ménétrier's disease-associated early gastric cancer.

Ménétrier's disease generally presents with hypertrophic gastropathy, primarily in the fundic gland region, which may explain the tendency for Ménétrier's disease-associated early-stage gastric cancer to occur in this region[14]. Endoscopic gastric cancer screening of patients with Ménétrier's disease should focus on two characteristics: The location (corpus or fundus) and the macroscopic type.

In the present case, cancer could not be confirmed by preoperative biopsy; therefore, a definitive diagnosis of cancer was made using the specimen from the endoscopic resection specimen. Based on histopathological findings, Ménétrier's disease is considered a chronic inflammatory disease[15], making it difficult to differentiate between inflammatory atypia and neoplastic atypia *via* small tissue biopsy alone, as in the present case. When endoscopic biopsy tissue from a superficial tumor-like lesion exhibits atypical glands in patients with Ménétrier's disease, total biopsy with *en bloc* ESD can be useful for definitive diagnosis as well as treatment including complete curative resection, such as in this case.

Severe Ménétrier's disease cases with clinical symptoms such as abdominal pain and vomiting require total gastrectomy to control severe hypoalbuminemia[16,17]. Besides the present patient, the two other patients with *H. pylori*-negative early-stage cancer underwent total gastrectomy. There was one case of surgery-related death. Therefore, if Ménétrier's disease is not severe and the stomach can be preserved, ESD seems a beneficial therapy for early-stage gastric cancer, especially for mucosal cancer, because of its low invasiveness and high complete curative resection rate.

The mucin phenotype of the early gastric cancer in this case was gastric type with strongly positive for MUC5AC and low expression of MUC6. These suggest the gastric-type mucin of foveolar-dominant type. In the non-tumor area involved by Ménétrier's disease, although p53 staining was negative and Ki-67 index was low, significant hyperplasia of foveolar epithelium was shown in the fundic gland region. We deduced that early cancer in the present case could be developed from a polypoid lesion with foveolar hyperplasia along hyperplasia-dysplasia-carcinoma sequence [18], even though the mechanism of gastric cancer development in Ménétrier's disease is unknown.

CONCLUSION

To our knowledge, this is the first report of an extremely rare case of early-stage

gastric cancer detected in a patient with *H. pylori*-negative Ménétrier's disease in which complete curative resection was achieved with ESD.

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