

## Responses to reviewers' comments

Reviewer #1: This is the first report 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. This case is very rare and interesting. However, I have some contents that you should add it. I write below some comment.

1. You performed only serum IgG antibodies about inspection of the *H.pylori*. When it is only one method, there is possibility of the false-negative. You should add another method to clarify *H. pylori* negative.

Response:

There was no endoscopic atrophy or intestinal metaplasia, no history of *H. pylori* eradication, no *H. pylori* presence observed during histopathological examination of resected and biopsied specimens, and a negative blood test for *H. pylori*-IgG antibody (<3). These findings strongly suggest that the patient had

*H. pylori*-negative Ménétrier's disease.

We have revised the manuscript as follows:

UGI endoscopy showed no evidence of atrophic gastritis and intestinal metaplasia. (Page 6, Lines 4-5).

*H. pylori* were not observed in any biopsy or ESD specimens. (Page 6, Lines 3-4).

2. The histological diagnosis from biopsy was Goup2, but you suspected a cancer endoscopically. You might observe the lesion by NBI. Please add the views if you observed it by NBI.

Response:

We have added the endoscopic images of magnified NBI in Figure 2. We have also revised the descriptions of the figure legend in Figure 2 as follows:

Low-magnification narrow-band imaging (NBI) showed granular surfaces with various sizes/forms and dilated vessels (Figure 2D). High-magnification NBI demonstrated irregular microstructures with various forms and tortuous microvessels with changes in caliber (Figure 2E). (Page 6, Lines 10-13).

3. Please add the existence of lymphovascular invasion and UL in histological result of ESD.

Response:

We have added a statement regarding the presence of lymphovascular invasion and UL as follows:

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). (Page 6, Lines 20-23).

4. This case is very rare. I want to know whether this tumor is gastric type or intestinal type. You had better add the immunostaining of mucin phenotype. (For example, MUC2, MUC5AC, MUC6)

Response:

We performed the additional immunohistochemical staining for the mucin phenotype in the ESD specimens. The staining for gastric phenotype comprised: MUC5AC, positive; MUC6, positive; MUC2, negative; and CD10, negative; as

described in the text. We deduced the carcinogenesis of the present case and made the following revisions:

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.

(Page 7, Lines 1-4).

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<sup>[18]</sup>, even though the mechanism of gastric cancer development in Ménétrier's disease is unknown.

(Page 9, Lines 13-20).

Reviewer #2: I enjoyed reading this study entitled "Curative resection with endoscopic submucosal dissection of early gastric cancer in Helicobacter pylori-negative Ménétrier's disease: A case report". Several comments are as follows:

(1) Computed tomography of the abdomen findings about the protruding lesion in stomach and whether there were enlarged lymph nodes around should be described.

Response:

We have revised the manuscript as follows:

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).

(Page 5, Lines 23-25).

( 2 ) I would like to know if the patient had any gastroscopy or barium examination results before the disease occurred.

Response:

The patient had never undergone endoscopy or barium examination before the disease occurred.

( 3 ) I wonder to know whether the causes of the Ménétrier's disease, such as autoimmunity, virus infection or parasite, had been excluded.

Response:

Unfortunately, we did not inspect autoimmunity and viral/parasitic infection, Hence, we cannot deny that these factors may be Ménétrier's disease in the present case.

( 4 ) During the follow-up period, whether the patient's anemia symptoms improved should be described.

Response:

After ESD, the anemia gradually improved. We have made the following revisions in the manuscript:

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. (Page 7, Lines 16-19).

( 5 ) As for the outcome, the giant rugae regressed spontaneously and hypoproteinemia improved gradually after ESD with no special therapeutic agents treatment, whether it means that the giant rugae and hypoproteinemia were caused by the protuberant lesions which was finally confirmed as early gastric cancer.

Response:

We do believe that the protuberant lesion associated with early cancer was responsible for the hypoproteinemia. However, the non-cancerous part, such as the giant rugae, was much larger than that of the protuberant lesion of early cancer, and the size of the giant rugae diminished gradually as

hypoproteinemia improved. We deduced that the protein leakage was caused primarily by non-cancerous sites associated with Ménétrier's disease.

- (6) In figure 4, a magnification bar should be included in the photos.

Response:

Thank you for your suggestion. We have added magnification bars in all histopathological images of Figures 4 and Figure 5.

- (7) In figure 5, Picture A and B should be described separately.

Response:

As per your suggestion, we have separated the images in Figure 5. (Page 15, Lines 5-7).

Reviewer #3: The authors describe a case of H. pylori-negative Ménétrier's disease with early gastric cancer, in which complete curative resection was achieved through endoscopic submucosal dissection. Although there have been

about 80 case reports on gastric cancer in adult-onset Ménétrier's disease, few have reported early-stage cancers. Our literature search found four case reports of Ménétrier's disease with early gastric cancer that recorded endoscopic findings and *H. pylori* infection status (two cases were *H. pylori* positive and three, including the present one, *H. pylori* negative). The case report is well written and of clinical relevance. No specific comment.

Response:

Thank you so much for your kind comments.