

Case Report

A Case of Grade 3 Gastric Neuroendocrine Tumor with Glandular Formation: Diagnosis and Differentiation from Gastric Mixed Neuroendocrine–Non-Neuroendocrine Neoplasm

Makiko Kurata¹, Takuma Tajiri¹, Masataka Ueda¹, Chie Inomoto¹,
Tomoko Sugiyama¹, Takayoshi Suzuki², Hideki Izumi³, Junichi Kaneko³,
Eiji Nomura³, Naoya Nakamura⁴ and Yohei Masugi⁴

¹Department of Diagnostic Pathology, Tokai University Hachioji Hospital, Tokyo, Japan

²Department of Gastroenterology, Tokai University Hachioji Hospital, Tokyo, Japan

³Department of Surgery, Tokai University Hachioji Hospital, Tokyo, Japan

⁴Department of Pathology, Tokai University School of Medicine, Kanagawa, Japan

A 78-year-old man was diagnosed as having a submucosal gastric mass (diameter 4 cm). Preoperative findings from endoscopic ultrasound-guided fine needle aspiration suggested a diagnosis of gastric neuroendocrine neoplasm. Total gastrectomy with excision of a metastatic liver lesion and dissection of gastric lymph nodes was performed. Analysis of frozen sections indicated adenocarcinoma of the peritoneum, which suggested the possibility of a mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN), based on the presence of solid tubules, metastatic spread, and lymphovascular invasion. However, the smooth gastric mucosal surface, organoid architecture with rare atypia or necrosis, immunopositivity for neuroendocrine markers, a Ki-67 index of 21%, and the presence of somatostatin receptor 2 expression confirmed a final pathological diagnosis of grade 3 gastric neuroendocrine tumor (NETG3) with glandular formation. NETG3 with glandular formation can be difficult to distinguish from MiNEN because their histological features overlap. However, gastric NETG3 with glandular formation is distinguishable from MiNEN by the presence of a submucosal tumor with a histological organoid pattern without frequent mitoses and/or necrosis, immunopositivity for neuroendocrine markers, and the absence of an adenocarcinoma or neuroendocrine carcinoma component within the tumor, as determined by immunohistochemistry for somatostatin receptor 2 expression, Ki-67, and Rb1.

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Introduction

Gastric neuroendocrine neoplasm (g-NEN) is histomorphologically classified as a gastric neuroendocrine tumor (g-NET) or gastric neuroendocrine carcinoma (g-NEC)¹. g-NETs are further classified as Grade 1, 2, or 3 on the basis of the Ki-67 index and/or mitotic index. g-NECs are composed of cells with severe atypia and are classi-

fied as a small-cell or large-cell carcinoma that frequently contains an adenocarcinoma or squamous cell carcinoma component plus areas of NEC cells.

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) comprise neuroendocrine and non-neuroendocrine component(s), such as adenocarcinoma or squamous cell carcinoma, with each making up >30%

Correspondence to Takuma Tajiri, takumatajiri1003@yahoo.co.jp

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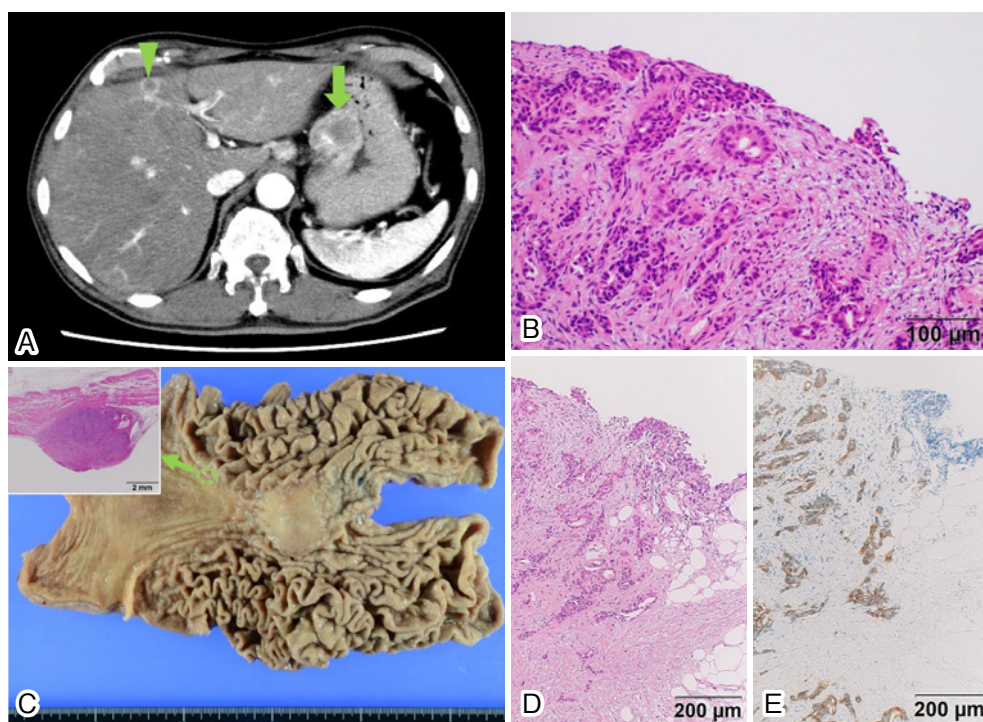


Figure 1 Diagnostic abdominal imaging (A), intraoperative histology of frozen section (B), macroscopic appearance of gastric mucosa (C) and histology of serosal area (C; inset), histology of permanent section (D), and immunohistochemistry of permanent section (E)

(A) Abdominal enhanced CT (early phase) revealed ring-enhancing lesions in the gastric body (arrow) and in segment 4 of the liver (arrowhead). (B) Histologically, the intraoperative frozen section of peritoneal masses was composed of atypical glands with solid features, suggesting a diagnosis of adenocarcinoma. (C) Note the smooth mucosal surface of the submucosal mass. (Inset) Note the subserosal dissemination of the nodule (green dotted circle) from the submucosal mass. (D) Permanent section revealed atypical glands admixed with solid features. (E) Synaptophysin was positive, leading to a final diagnosis of disseminated NETG3.

of the tumor volume¹. Thus, MiNENs may contain components of NET, NEC, and other non-neuroendocrine components of carcinoma cells, including mixed adenoneuroendocrine carcinoma (MANEC) or mixed adenocarcinoma-NETs. Mixed adenocarcinoma-NET is often associated with autoimmune chronic atrophic gastritis^{2,3}.

Although gastroenteropancreatic NETG3 and NEC are now recognized as separate entities, it can be difficult to distinguish NETG3 with glandular formation from MiNEN or NEC because their histological features overlap^{4,5}. g-NETG3 with glandular formation is characterized by mucin production in the lumen of glands, which is not a feature of NET.

Here, we report a case of g-NETG3 with glandular formation in which histological morphology and immunohistochemistry allowed us to distinguish the neoplasm from MiNEN.

Case Report

A 78-year-old Japanese man was referred by his local physician to our Department of Gastroenterology for assessment of a single submucosal mass measuring 4 cm in diameter at the posterior wall of the lesser curvature of the middle stomach on upper gastrointestinal endoscopy. The patient's past medical history included urinary bladder carcinoma at age 76 years, and his family history was unremarkable. Physical examination and laboratory tests on admission to our hospital were within normal limits. Abdominal enhanced CT scans showed double ring-enhancing lesions in the gastric submucosa (31 mm × 43 mm; **Figure 1A**, arrow) and in segment 4 of the liver (20 mm; **Figure 1A**, arrowhead), and two enlarged left gastric lymph nodes. Positron emission tomography (PET) showed no apparent accumulation in any other organ, apart from the stomach and liver. These findings suggested a tentative clinical diagnosis of gastric submucosal tumor with liver and lymph node metastases.

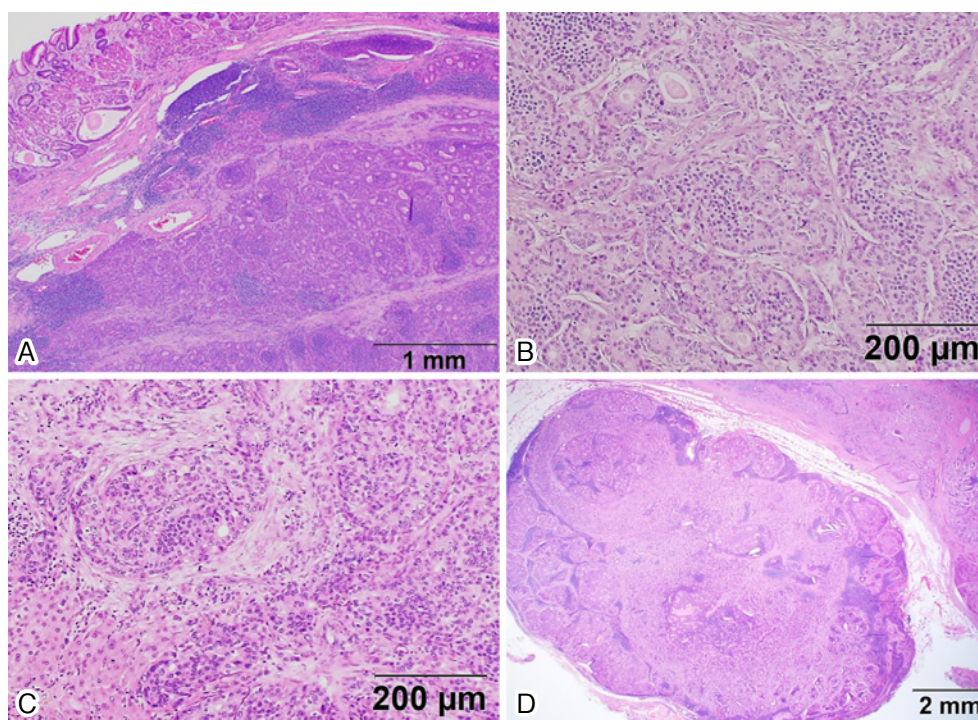


Figure 2 Results of histological examination of the gastric submucosal tumor (A) and (B), metastasis of the liver (C), and lymph nodes (D)

(A) A low-power view showing a submucosal tumor-like lesion surrounded by lymphocyte aggregation. (B) A high-power view of a histological section of the gastric lesion showing neoplastic cells in an organoid fashion and forming solid tubules. The cytoplasm of the cells making up the tubules was eosinophilic, and the cell nuclei were uniform. Atypia of the neoplastic cells was not as pronounced as in adenocarcinoma. (C) The liver exhibited the same appearance as the gastric submucosal tumor, which was consistent with metastasis from the gastric submucosal tumor. (D) Neoplastic cells almost completely occupied the lymph node tissue.

Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) Biopsy and Cytological Findings

Histological examination of the EUS-FNA biopsy specimen of the submucosal mass revealed aggregations of small, round cells with uniform nuclei in a hemorrhagic background. Immunohistochemically, the neoplastic cells expressed pan-cytokeratin AE1/3, synaptophysin, and chromogranin A in the cytoplasm, and CD56 on the cell membrane. However, the neoplastic cells were negative for carcinoembryonic antigen (CEA). The Ki-67 index was 21.2%. EUS-FNA cytology revealed a cluster of tumor cells that had round nuclei with smooth contours and abundant cytoplasm, indicating a Papanicolaou class of IV.

After preoperative diagnosis of g-NEN with lymph node and liver metastases, laparoscopic total gastrectomy plus excision of the metastatic liver lesion and dissection of lymph nodes was scheduled. The surgeon incidentally found several white masses in the peritoneum during surgery, and the intraoperative pathological diagnosis of the frozen sections was adenocarcinoma (Figure 1B).

During surgery, the surgeon and pathologist discussed the discrepancy between the intraoperative and preoperative diagnoses of g-NEN. The pathologist advised the surgeon of the several phenotypic variants of g-NEN and that the final pathological diagnosis could change during immunohistochemical analysis of a permanent section. Because the peritoneal dissemination was localized, the surgery was changed to abdominal open total gastrectomy with excision of the metastatic liver lesion and resection of lymph node metastasis.

Macroscopic and Histological Findings

The submucosal mass measured 55 mm × 38 mm (Figure 1C). The gastric mucosa was intact. The gastric tumor extended from the submucosa (Figure 2A) into the subserosa, and a small nodule associated with the submucosal mass was observed on the serosal surface of the stomach (Figure 1C, inset, green dotted circle). The tumor comprised solid tumor cell nests in the central area surrounded by glandular structures; some tumor cells were aligned in a palisade pattern at the periphery. The solid

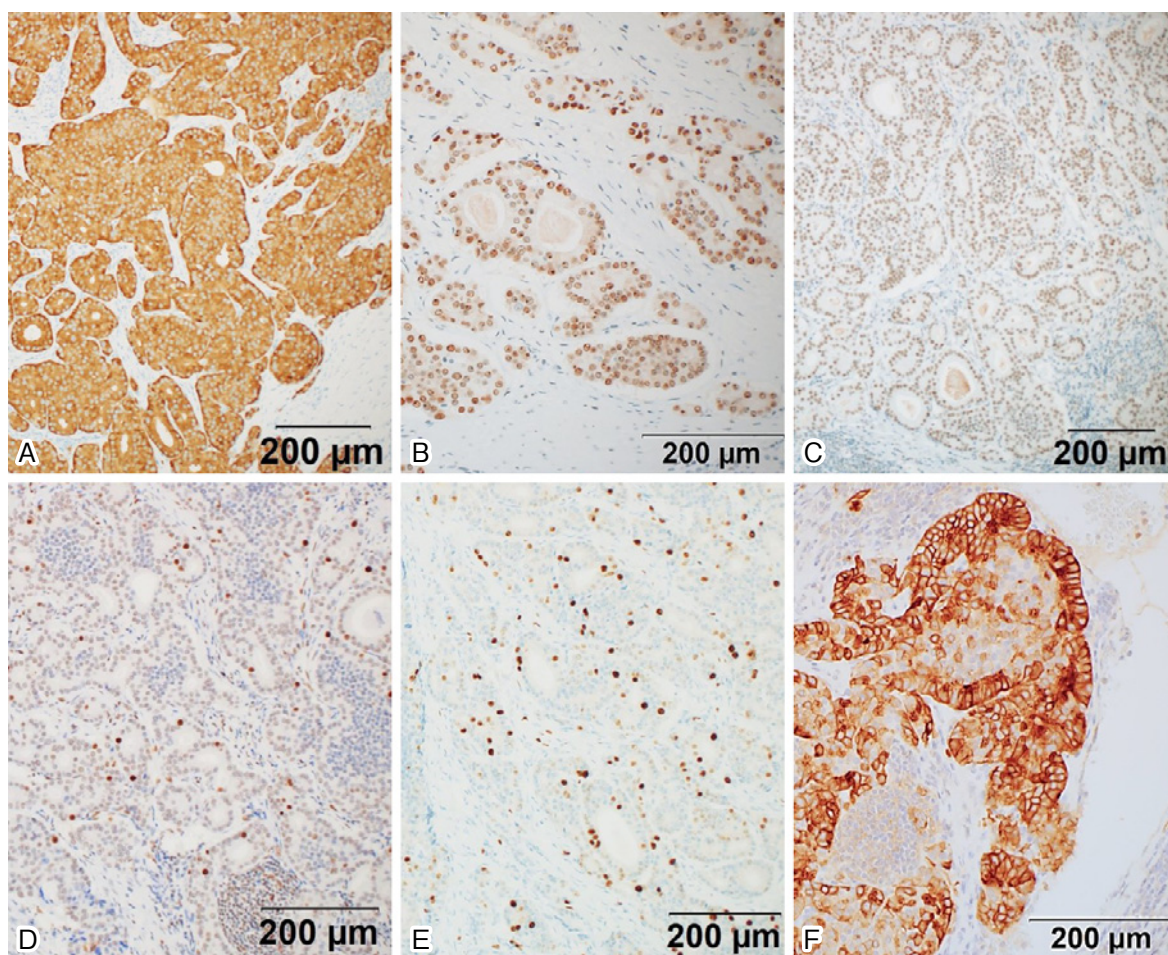


Figure 3 Immunohistochemistry findings for the gastric submucosal tumor

(A) The cytoplasm of the neoplastic cells of the solid tubules was diffusely immunoreactive for synaptophysin. (B) The nuclei of the neoplastic cells were diffusely immunoreactive for insulinoma-associated protein 1. (C) The neoplastic cells showed weak but diffuse nuclear staining for α -thalassemia/mental retardation syndrome X-linked. (D) Note the strong but patchy nuclear staining for Rb1. (E) The nuclei of the neoplastic cells were positive for Ki-67. (F) Somatostatin receptor 2 was expressed in the cell membrane and in the cytoplasm of neoplastic cells.

and mucin-producing glandular components of the gastric tumor were occasionally mingled (**Figure 2B**). The tumor exhibited monotonous round nuclei, but histologic atypia was not as pronounced as in an adenocarcinoma. Vascular invasion and perineural invasion were evident, and metastatic spread to the liver (**Figure 2C**) and two gastric lymph nodes (**Figure 2D**) were confirmed. There was no atrophy of the oxyntic mucosa and no evidence of autoimmune gastritis³.

Immunohistochemistry

NET was distinguished from adenocarcinoma by performing immunohistochemistry for CEA and multiple neuroendocrine markers (chromogranin-A, synaptophysin, CD56, and insulinoma-associated protein 1) (**Figure 3A and 3B**). NETG3 was distinguished from NEC by immunohistochemistry for α -thalassemia/mental retar-

dation syndrome X-linked (ATRX) (**Figure 3C**), Rb1 (**Figure 3D**), Ki-67, and somatostatin receptor 2 (SSTR-2) (**Table 1**). The Ki-67 index was 21.2% in hot spots in the gastric submucosal tumor and 37% in the liver metastasis (**Figure 3E**). In addition, there was no evidence of an adenocarcinoma component within the tumor. SSTR-2 expression was noted in neoplastic cells in the cell membranes of the glandular formations, which was consistent with a Volante score of 2 (**Figure 3F**)⁶.

Although the peritoneal mass was diagnosed intraoperatively as adenocarcinoma on the basis of the frozen sections, the ultimate diagnosis was dissemination from g-NET with glandular formation, based on the histological features of an organoid pattern with little necrosis or mitosis (**Figure 1D**), as well as neuroendocrine marker immunostaining findings (**Figure 1E**) that were similar to those of the main gastric submucosal tumor.

Table 1 Results of Immunohistochemistry

Biomarker	Staining	Localization
PAS	+	Neoplastic tubules, apical surface
d-PAS	+	Neoplastic tubules, apical surface
MUC-1	+	Neoplastic tubules, apical surface
Pancytokeratin AE1/3	++/diffuse	Cytoplasm
CEA	–	–
CK7	++/diffuse	Cytoplasm
CK20	–	–
Chromogranin-A	+/diffuse	Cytoplasm
Synaptophysin	++/diffuse	Cytoplasm
CD56	+/focal	Membrane
INSM-1	++/diffuse	Nucleus
p53	+/patchy	Focally nucleus
Rb1	++/diffuse	Nucleus
ATRX	++/diffuse	Nucleus
DAXX	++/diffuse	Nucleus
P16	–	–
TTF-1	–	–
SSTR-2	++/diffuse	Membrane and cytoplasm
Ki-67 index	Stomach: 21.2%, Liver: 37%	

– negative; + moderately positive; ++ strongly positive.

Ap, apical surface; CEA, carcinoembryonic antigen; INSM-1, insulinoma-associated protein; PAS, periodic acid-Schiff; d-PAS, periodic acid-Schiff with diastase; SSTR-2, somatostatin receptor-2; TTF-1 thyroid transcription factor; ATRX, α -Thalassemia/mental retardation syndrome X-linked; DAXX, Death-Domain Associated Protein.

Differential Diagnosis and Final Histopathological Diagnosis

We considered three other possibilities: (i) gastric MiNEN (MANEC or mixed adenocarcinoma-NET), (ii) metastatic MiNEN from another organ, and (iii) g-NET arising from ectopic pancreatic tissue.

Gastric MiNEN was excluded because mucosal damage was absent and because the histological organoid pattern giving rise to solid tubules without frequent mitoses or necrosis resembled NET. We excluded MANEC because there was no evidence of an NEC component, such as nuclear loss of ATRX and Rb1. We also excluded mixed adenocarcinoma-NET because the neoplastic cells with solid and tubular features were diffusely stained for neuroendocrine markers but not stained for CEA, indicating no evidence of an adenocarcinoma component within the tumor. In addition, our patient did not have autoimmune gastritis.

Metastatic MiNEN originating from another organ was excluded because the growth pattern appeared organoid, with little atypia or necrosis, and PET/CT hot spots were observed only in the stomach and liver.

g-NET arising from ectopic pancreatic tissue was excluded because of the absence of histological evidence of pancreatic tissue in the surgically resected tissue. Thus,

the final pathological diagnosis of this patient was g-NET (NETG3; pT4, N1, M1a; Stage IV).

Octreotide, a long-acting somatostatin analogue (SSA), was administered for tumor control. The patient continued with SSA treatment for 12 months after surgery. However, when abdominal MRI detected metastasis/recurrence in the liver and lymph nodes after temporary discontinuation of SSA for 3 months, SSA was again administered for an additional 3 months. However, enlargement of the liver metastasis was remarkable, and tumor control was difficult. Treatment was thus changed to the molecular-targeted drug everolimus. The patient is alive at this writing, 51 months after surgery.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki (1975) and was approved by the Institutional Review Board of Tokai University (Approval no. 22J011). This patient provided written informed consent for the procedure and for anonymized use of his clinical information for study purposes.

Discussion

We described the diagnostic process to differentiate

NETG3 with glandular formation from MiNEN (including MANEC and mixed adenocarcinoma-NET). Because of the morphological varieties of NETs, it was difficult to differentiate NETG3 with glandular formation from adenocarcinoma during intraoperative analysis of frozen sections without performing immunohistochemistry. Thus, during intraoperative diagnosis, pathologists sometimes mistake g-NET with glandular formation for g-MiNEN/MANEC with an adenocarcinoma component. We considered the possibility of g-NET at the EUS-FNA biopsy before surgery. However, the aggressive biological behavior of the gastric mass with peritoneal dissemination, and the lymph node and liver metastases, led us to initially mistake NETG3 with glandular formation for MiNEN when the intraoperative frozen sections of peritoneal masses were diagnosed morphologically as adenocarcinoma. Kasajima et al.⁵ described the histological differences between NETG3 and NEC or most MiNEN/MANECs: the defining criteria were organoid versus diffuse architecture, scant versus widespread necrosis, and moderate-grade versus high-grade cellular atypia. The median Ki-67 index value can be used to distinguish NETG3 from NEC or MiNEN/MANEC (30% versus 60%, respectively)⁵. Further, NETG3 shows no evidence of loss of nuclear expression of Rb1, whereas NECs and MiNEN/MANEC exhibits loss of nuclear expression of ATRX and Rb1^{5,7}.

A recent report showed that the expression pattern of SSTR-2 in NET differs from that of NEC⁸, which may be helpful in distinguishing a NET component from that of NEC within a tumor when considering a differential diagnosis of NET, MiNEN/MANEC, or NEC. SSTR-2 expression in the cell membrane is detected in approximately 80% of NETs and is usually strongly positive in NETs but focal and weak to absent in most NECs⁵. Although no standard therapy has been established for NETG3⁸, SSA hormone therapy (octreotide), radionuclide-labeling peptide therapy, and everolimus and other molecular target drugs have been used to treat NETG3⁹. SSTR-2 status in NET cells, as evaluated by immunohistochemistry, was reported to be associated with the therapeutic efficacy of SSAs¹⁰; however, there is no documented evidence of the effect and predictive response to SSAs¹¹. In contrast, patients with NEC or MiNEN/MANEC initially treated with platinum-based combination cytotoxic chemotherapy developed severe side effects. Hijioka et al.⁷ reported that 49 patients with NEC exhibited loss of Rb immunolabeling (54.5% of patients) and/or KRAS mutation (48.7% of patients), each of

which was associated with a good response to platinum-based chemotherapy⁷. Thus, it is important to distinguish components of NET, including NETG3, from that of NECs, including MANEC or mixed adenocarcinoma-NETs. SSTR-2 expression may serve as a differential marker in the presence of a NET component, as well as for therapeutic management.

The present case of submucosal tumor without mucosal invasion exhibited less atypia and necrosis histologically, along with immunopositivity for neuroendocrine markers, which are not characteristic of adenocarcinoma. Immunohistochemistry revealed expression of SSTR-2, a Ki-67 index of 20–30%, and no nuclear loss for ATRX and Rb1, confirming a final diagnosis of g-NETG3¹⁰. As MiNEN/MANEC and MiNEN/mixed adenocarcinoma-NET include an adenocarcinoma component, absence of adenocarcinoma within the tumor should be confirmed before diagnosing NET with glandular formation.

In conclusion, g-NETG3 with glandular formation can be distinguished from MiNEN by (i) examining the macroscopic features of the submucosal tumor, (ii) ruling out any carcinoma component, based on a histological organoid structure with less atypia or necrosis, (iii) confirming tumor immunopositivity for neuroendocrine markers, and (iv) identifying any NEC components within the tumor by immunohistological evaluation of SSTR-2, Ki-67 index, and Rb1^{12,13}.

Author Contributions: Makiko Kurata and Takuma Tajiri contributed to the execution of the study and writing of the manuscript. Masataka Ueda, Chie Inomoto, Tomoko Sugiyama, Naoya Nakamura, and Yohei Masugi participated in the execution of the study and reviewed the manuscript. All authors have read and approved the final manuscript.

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References

1. La Rosa Sallás B, Rindi G, Solicía E, Tang LH. Classification of neuroendocrine neoplasms of the digestive systems. Gastric neuroendocrine neoplasms. In: WHO Classi-

- fication of Tumours Editorial Board, editor. Digestive system tumors: WHO classification of tumours. 5th ed. Geneva: World Health Organization; 2019. p. 104–9.
2. Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Geneva: World Health Organization; 2010.
 3. Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. *Clin Exp Gastroenterol*. 2017 Feb;10:19–27.
 4. Konukiewicz B, Jesinghaus M, Kasajima A, Kloppel G. Neuroendocrine neoplasms of the pancreas: diagnosis and pitfalls. *Virchows Arch*. 2022 Feb;480(2):247–57.
 5. Kasajima A, Konukiewicz B, Schlitter AM, Weichert W, Kloppel G. An analysis of 130 neuroendocrine tumors G3 regarding prevalence, origin, metastasis, and diagnostic features. *Virchows Arch*. 2022 Feb;480(2):359–68.
 6. Volante M, Brizzi MP, Faggiano A, et al. Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy. *Mod Pathol*. 2007 Nov; 20(11):1172–82.
 7. Hijioka S, Hosoda W, Matsuo K, et al. Rb loss and KRAS mutation are predictors of the response to platinum-based chemotherapy in pancreatic neuroendocrine neoplasm with Grade 3: a Japanese multicenter pancreatic NEN-G3 study. *Clin Cancer Res*. 2017 Aug 15;23(16):4625–32.
 8. Popa O, Taban SM, Pantea S, et al. The new WHO classification of gastrointestinal neuroendocrine tumors and immunohistochemical expression of somatostatin receptor 2 and 5. *Exp Ther Med*. 2021 Oct;22(4):1179.
 9. Ito T, Masui T, Komoto I, et al. JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. *J Gastroenterol*. 2021 Nov;56(11):1033–44.
 10. Watanabe H, Fujishima F, Komoto I, et al. Somatostatin receptor 2 expression profiles and their correlation with efficacy of somatostatin analogues in gastrointestinal neuroendocrine tumors. *Cancers (Basel)*. 2022 Feb 2;14(3):775.
 11. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumors. *Aliment Pharmacol Ther*. 2010;31(2):169–88.
 12. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol*. 2022 Mar;33(1):115–54.
 13. Pavel M, Oberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020 Jul;31(7):844–60.