



## CASE REPORT

# Mixed neuroendocrine–non-neuroendocrine neoplasm associated with autoimmune gastritis

Naoko Mori<sup>1</sup> | Masanori Hongo<sup>1</sup> | Shizuki Takemura<sup>2</sup> | Yoshihiko Sugitani<sup>1</sup> | Fumiyasu Nakamura<sup>1</sup> | Masaji Tani<sup>3</sup> | Atsushi Nishida<sup>4</sup>  | Osamu Inatomi<sup>4</sup> | Akira Andoh<sup>4</sup> | Hiromitsu Ban<sup>1</sup> 

<sup>1</sup>Division of Gastroenterology, Omi Medica Center, Shiga, Japan

<sup>2</sup>Division of Pathology, Omi Medica Center, Shiga, Japan

<sup>3</sup>Department of Surgery, Shiga University of Medical Science, Shiga, Japan

<sup>4</sup>Department of Medicine, Shiga University of Medical Science, Shiga, Japan

## Correspondence

Hiromitsu Ban, Division of Gastroenterology, Omi Medica Center, Yabase-chou 1660, Kusatsu, Shiga 525-8585, Japan.

Email: hban@seikoukai-sc.or.jp

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## Abstract

A 60-year-old woman presented with a protruding tumor at the anterior wall of the middle gastric body, and she was positive for anti-parietal cells antibodies with elevated serum gastrin level. Final diagnosis was a mixed neuroendocrine–non-neuroendocrine neoplasm consisting of adenocarcinoma (tub1) and neuroendocrine tumor G2 with autoimmune gastritis.

## KEYWORDS

adenocarcinoma, autoimmune gastritis, endoscopic submucosal dissection, mixed neuroendocrine–non-neuroendocrine neoplasms

## 1 | INTRODUCTION

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) are a rare neoplasm consisting of two histologically and immunohistochemically distinct components (neuroendocrine and non-neuroendocrine), with the constitution of each component more than 30% of the neoplasm.<sup>1</sup> Although the vast majority of neuroendocrine neoplasms (NEN) are classified into a well-differentiated neuroendocrine tumor (NET) and a poorly differentiated neuroendocrine carcinoma (NEC), MiNENs are not pure NEN and are composed of both well or poorly differentiated both neuroendocrine and non-neuroendocrine components.<sup>2</sup>

Autoimmune gastritis (AIG) is caused by an autoimmune response that disrupts the oxyntic mucosa of the proximal stomach via autoantibodies against parietal cells and intrinsic factor.<sup>3</sup> The incidence of gastric neoplasms including adenocarcinoma and NEN is higher in patients with AIG than the general population.<sup>4</sup> Incidences of gastric cancer and gastric NET have been reported to be 0.9%–9% and 4%–9% of patients with autoimmune gastritis, respectively.<sup>5</sup> However, gastric MiNEN associated with AIG is extremely rare, and there have been no published reports as far as we can ascertain. Here, we report a case of MiNEN associated with AIG which showed a characteristic histological feature (coexistence of adenocarcinoma and NET G2).

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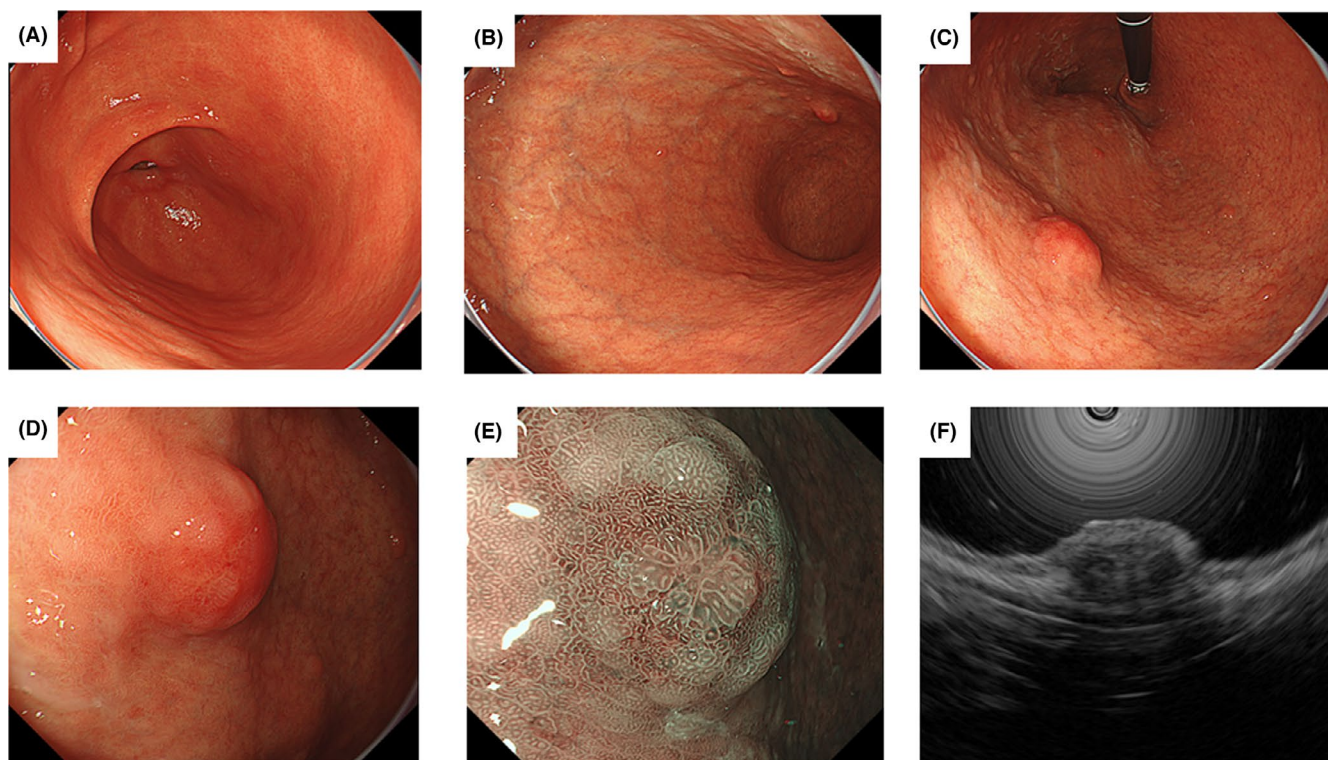
## 2 | CASE REPORT

A 60-year-old woman underwent a screening esophago-duodenoscopy (EGD) at a former clinic, which revealed a gastric tumor. She had no symptoms. She was referred to our hospital for further examination and treatment. Physical examination revealed no abnormalities. EGD at our hospital revealed a marked mucosal atrophy with a prominent vascular visibility of the gastric body but no atrophic finding of the antrum (Figure 1A and B). At this time, she was positive for anti-parietal cell antibodies ( $\times 160$ ; normal  $< \times 10$ ) but negative for anti-*Helicobacter (H) pylori* IgG antibodies. The serum gastrin level was elevated to 2870 pg/ml (normal range, 37–172 pg/ml), and serum vitamin B12 level was reduced to 190 pg/ml (normal range, 249–938 pg/ml). She was not taking any gastric acid suppressors. These findings led to a diagnosis of AIG.

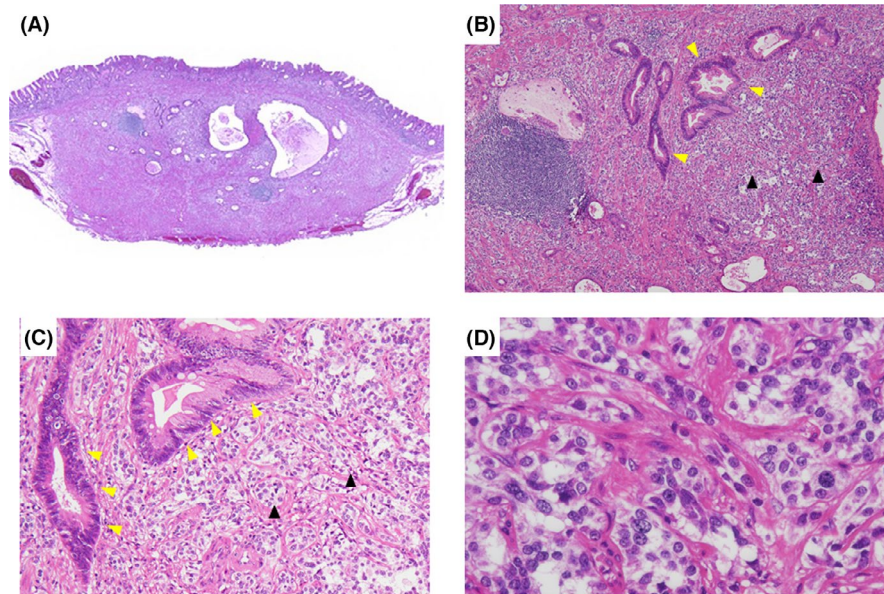
EGD also revealed multiple small polypoid lesions at the gastric body (Figure 1C). Among them, an approximately 10-mm protruding tumor with slight redness was observed at the anterior wall of the middle body (Figure 1C). This was covered by an intact mucosa (Figure 1D), and a magnified endoscopy with narrow-band imaging (M-NBI)

revealed a regular microsurface pattern without a demarcation line (Figure 1E). A scar from a previous biopsy at the former clinic could also be seen (Figure 1E). An endoscopic ultrasonography (EUS) showed a low and heterogeneous echoic mass raised from the second and third layers (Figure 1F). The deep part of the third layer was intact (Figure 1F). A computed tomography (CT) scan revealed no signs of extraluminal extension and metastasis. For a definitive diagnosis, an endoscopic submucosal dissection (ESD) was performed.

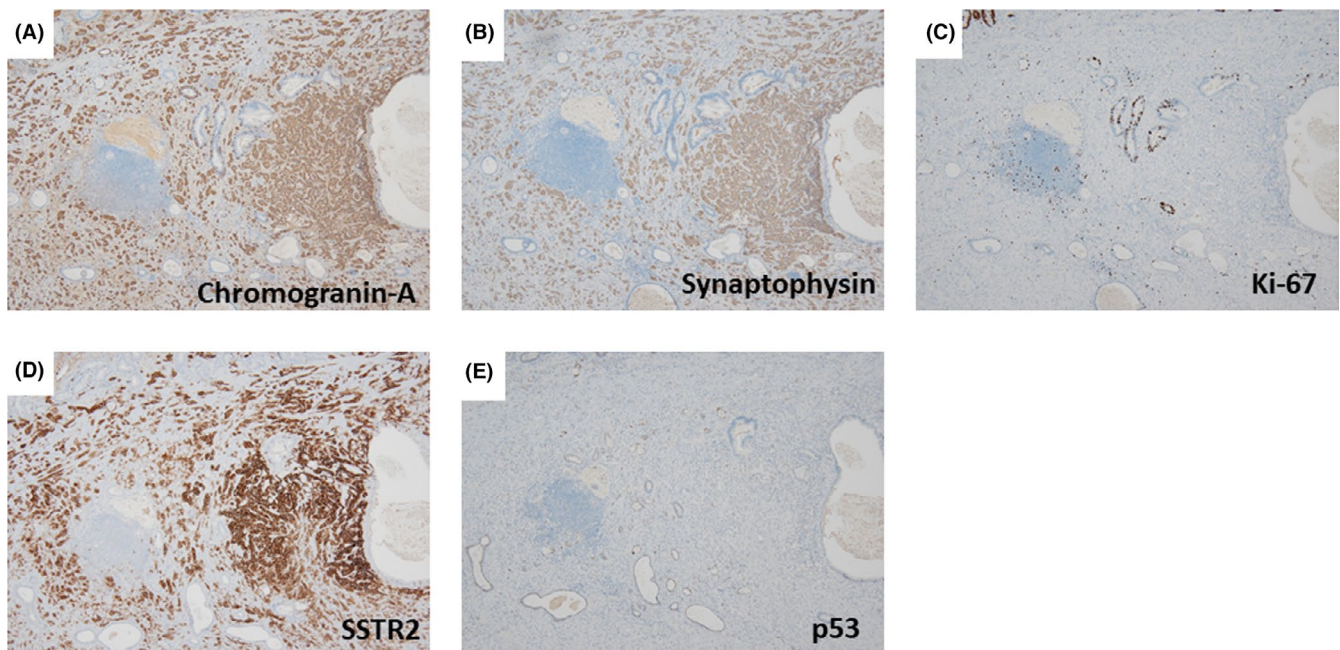
The resected specimen showed a 10  $\times$  12-mm submucosal tumor (Figure 2A). Histologically, the tumor consisted of two components with a fibrotic change and dilated cystic structures (Figure 2B). One component was a glandular structure with irregularly shaped ducts, and this was diagnosed as well-differentiated tubular adenocarcinoma (tub1) (Figure 2C). The other component was composed of small-to-large round cells with hyperchromatic nuclei forming solid nests (Figure 2C, D). As shown in Figure 3, these cells were positive for neuroendocrine markers such as chromogranin A, synaptophysin, and somatostatin receptors 2 (SSTR2)<sup>2,6,7</sup> and the Ki67 proliferation index was 3.8% of the cells (Figure 3C). P53 staining was negative



**FIGURE 1** Endoscopic findings of gastric mixed neuroendocrine-non-endocrine neoplasm with autoimmune gastritis. (A) Esophagogastroduodenoscopy (EGD) revealed a normal mucosa of the gastric antrum. (B) EGD revealed a marked mucosal atrophy of the gastric body. (C and D) EGD showed an approximately 10-mm protruding tumor with slight redness at the anterior wall of the middle gastric body. Several small polypoid lesions were also detected. (E) Magnified endoscopy with narrow-band imaging showed a normal pit pattern with a scar from a previous biopsy at the former clinic. There were some bumps on the surface of the tumor. (F) Endoscopic ultrasound image shows a mass consisting of low- and heteroechoic lesions raised from the second and the third layer of gastric wall. The deep part of the third layer was intact



**FIGURE 2** Histological findings of the resected sample by endoscopic submucosal dissection. (A) The tumor was a 10 × 12-mm submucosal tumor consisting of two components with a fibrotic change and dilated cystic structures. (B, C and D) One component was a glandular structure with irregularly shaped ducts (yellow arrow heads), and this was diagnosed as well-differentiated tubular adenocarcinoma (tub1). The other component was composed of small-to-large round cells with hyperchromatic nuclei forming solid nests (black arrow heads), suggesting a neuroendocrine neoplasm. Original magnification: A ×20, B ×40, C ×100, D ×400



**FIGURE 3** Immunohistochemical staining of the tumor. The cells of neuroendocrine components were positive for neuroendocrine markers such as chromogranin A, synaptophysin, and somatostatin receptors 2 (SSTR2), and the Ki67 proliferation index was 3.8%. These cells were negative for p53 staining

(Figure 3E) The luminal surface of the tumor was covered by a non-neoplastic epithelium, and adenocarcinoma was detected from the deep mucosa to the submucosa. The background mucosa of the resected sample revealed characteristics of AIG, such as intestinal metaplasia and

pseudopyloric metaplasia. According to the 2019 World Health Organization (WHO) classification,<sup>2,8</sup> the patient's gastric lesion was diagnosed as MiNEN and a distal gastrectomy was performed according to the patient's request after detail explanation of therapeutic options. The final

diagnosis was a MiNEN [mixed adenocarcinoma (tub1) and NET(G2), pT1b(SM), pLy0, pV0, pHM0, and pVM0]. Two other small polypoid lesions were diagnosed as NET G1, which revealed a Ki67 positive rate <1%. EGD and CT examination performed six months later revealed no signs of recurrence.

### 3 | DISCUSSION

MiNENs were proposed in the 2019 WHO classification of tumors of the digestive system.<sup>1,2,8</sup> MiNENs are defined as mixed epithelial neoplasms composed of both neuroendocrine and non-neuroendocrine components. Since MiNEN is a new term and a rare disease, there have as yet been no reports of gastric MiNEN associated with AIG.

AIG is characterized by mucosal atrophy in the body and fundus of the stomach.<sup>9</sup> Chronic autoimmune inflammation induces a loss of parietal cells and chief cells in the fundic glands, which are replaced by goblet cells (intestinal metaplasia), pyloric glands, and/or pseudopyloric glands.<sup>9,10</sup> These changes induce hypergastrinemia as a feedback to reduced gastric acid secretion and vitamin B12 malabsorption due to decreased secretion of intrinsic factor.<sup>9</sup> This patient was diagnosed as AIG based on the laboratory data (presence of anti-parietal cell antibodies, elevated serum gastrin levels, and reduced serum vitamin B12 levels), endoscopic findings (atrophic gastritis restricted in the body), and histology (intestinal metaplasia and pseudopyloric metaplasia).

In AIG patients, adenocarcinoma of the intestinal phenotype develops with intestinal and/or pyloric/pseudopyloric metaplasia in the body or fundus.<sup>9,10</sup> Incidence of gastric NENs is also higher in patients with AIG due to increased gastrin secretion which stimulates and promotes a proliferation of enterochromaffin-like cells in the body.<sup>11</sup> NENs in the background of AIG have been reported to be multiple but usually small (<20 mm) and low malignancy.<sup>11</sup> In this case, polypoid lesions, except MiNEN, were immunohistochemically diagnosed as NET G1 (Ki67 proliferation index <1%). Thus, the lesions observed in this case matched the previously reported characteristics of NENs developed in the background of AIG.

The MiNEN of this patient had unique histological features. The adenocarcinoma component was located in the deep layer of the mucosa to the submucosa, and the luminal surface of the tumor was completely covered by non-tumorous cells. Although most of the neuroendocrine component of gastric MiNENs have been reported to be a poorly differentiated phenotype (NEC) and only rarely NET,<sup>12,13</sup> the neuroendocrine component in this case was a well-differentiated phenotype (NET G2). In addition, previous studies have suggested that the

neuroendocrine component (NEC) might develop from non-neuroendocrine neoplasms (adenocarcinoma) via accumulation of additional molecular aberrations.<sup>13-15</sup> In this case, the NET occupied a major part of the tumor and adenocarcinoma was observed as a relatively minor component. The borders of the two components were continuous. Furthermore, this patient showed hypergastrinemia which might play an important role in the development of the NET component. These findings raised three possible pathological mechanisms in this rare case: (a) adenocarcinoma originating from the initially developed well-differentiated neuroendocrine component (NET), (b) adenocarcinoma partially differentiated into the NET component, and (c) adenocarcinoma and the NET independently developed and coexisting. We think that the first hypothesis is most likely, since it is hard to consider that adenocarcinoma transformed into a well-differentiated NET instead of a NEC.

The precise pathophysiology of MiNENs still remains unclear. Although there is a possibility that neuroendocrine and non-neuroendocrine components independently originate from different progenitor cells, recent genetic studies have demonstrated that both tumor components of MiNENs were differentiated from a common multipotent stem cell.<sup>16</sup> This is supported by the recent discovery of an overlapping mutational profile in both cell varieties that make up the MiNEN.<sup>15</sup> This patient presented with a rare case of MiNEN composed by adenocarcinoma and NET in the background of hypergastrinemia and AIG. In this rare case, molecular analysis of each component might provide a clue to its pathophysiology.

Due to its low incidence, the prognosis of patients with MiNEN remains controversial.<sup>17</sup> MiNEN patients may have a worse prognosis than those with isolated gastric adenocarcinoma and neuroendocrine carcinoma.<sup>17</sup> Furthermore, a recent study revealed that the clinical features of gastric MiNENs largely depend on the proportion of neuroendocrine components.<sup>18</sup> The WHO previously recommended that MiNEN should be treated as adenocarcinoma, but a recent study recommended that treatment should be based on the most aggressive histologic component.<sup>19</sup> In this case, the neuroendocrine component was a NET, adenocarcinoma invasion was limited to the submucosa and there was no lymph node and vascular invasion in the resected sample.

In consultation with an oncologist, we did not perform adjuvant chemotherapy after surgery but strictly followed up by CT and endoscopy.

In conclusion, this was an extremely rare case of gastric MiNEN composed of NET and adenocarcinoma in the AIG background. Molecular analysis of each component of the NET and adenocarcinoma will be helpful to define the pathogenesis of this rare gastric MiNEN.

## ACKNOWLEDGMENT

None.

## CONFLICT OF INTEREST

The authors declare that they have no competing interest.

## AUTHOR CONTRIBUTIONS

All authors contributed to the design of this manuscript. NM, AA, and HB wrote the first draft. ST made a pathological diagnosis. MT performed distal gastrectomy. MH, YS, FN, AN, and OI scientifically reviewed the manuscript. AA and BH wrote the final version.

## CONSENT

Written informed consent for publication (including images) has been obtained from the patient.

## DATA AVAILABILITY STATEMENT

The data are available with the correspondence author and can be achieved on request.

## ORCID

Atsushi Nishida  <https://orcid.org/0000-0002-1288-3272>

Hiromitsu Ban  <https://orcid.org/0000-0002-5782-9210>

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