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Single Case

A Gastric Intramucosal Mixed Adenocarcinoma-Neuroendocrine Tumor

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Keywords
Stomach · Composite tumor · Mixed adenocarcinoma-neuroendocrine tumor · Endoscopic submucosal dissection

Abstract
Gastric mixed adenocarcinoma-neuroendocrine tumor (NET) is a rare composite tumor, and a limited number of studies have reported on it. A 77-year-old man was admitted to our hospital because of acute cholecystitis. He underwent a cholecystectomy. Esophagogastroduodenoscopy during his admission revealed a slightly elevated tumor, and biopsy demonstrated a well-differentiated tubular adenocarcinoma. The tumor was resected completely by endoscopic submucosal dissection. Histological findings showed that it measured 9 mm in diameter, was located within the mucosa, and consisted of well-differentiated tubular adenocarcinoma and a NET G1. The NET was covered with adenocarcinoma and both components exhibited histological continuity. The NET and a part of the adenocarcinoma component showed a positive

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reaction for chromogranin A and synaptophysin. Neither enterochromaffin-like cell hyperplasia nor endocrine cell micronest surrounded the tumor. The diagnosis was gastric mixed adenocarcinoma-NET. The histological continuity between the two components can be likened to the same histogenesis.

Introduction

Gastric neuroendocrine tumors (NETs) are mainly derived from enterochromaffin-like (ECL) cell hyperplasia stimulated by increased serum gastrin [1], whereas gastric adenocarcinoma is associated with chronic gastritis caused by *Helicobacter pylori* infection [2]. Although the tumorigenesis of gastric NETs is entirely different from that of gastric adenocarcinoma, a tumor comprising adenocarcinoma and NET components rarely develops [3, 4]. When both tumor components show various admixtures, the tumor is regarded as a composite tumor, as stated by Lewin in 1987 [5]. Cases of mixed adenoneuroendocrine carcinoma, which belong to composite tumors, were included in the World Health Organization (WHO) 2010 classification [6]. Nevertheless, the concept of mixed adenoneuroendocrine carcinoma was extended and the revised term "mixed neuroendocrine-non-neuroendocrine neoplasm" (MiNEN) is now recommended by the WHO (2019 classification) for cases of tumors with various combinations of neuroendocrine and non-neuroendocrine neoplasms in the digestive organs [7]. Here, we report the case of a patient with gastric MiNEN showing intramucosal mixed adenocarcinoma-NET and discuss his clinical, endoscopic, and histopathological findings in detail.

Case Report

A 77-year-old man was admitted to our hospital with a complaint of right hypochondriac pain. Personal history revealed bronchial asthma, hypertension, diabetes mellitus, atrial fibrillation, renal failure, and hearing impairment in the right ear. He had a habit of drinking 1 L of distilled spirits daily since he was 20 years old. Abdominal computed tomography (CT) examination showed acute cholecystitis with a gallstone (Fig. 1a). No gastric wall thickening or perigastric lymphadenopathy (Fig. 1a, b) was seen. He underwent a cholecystectomy after receiving percutaneous transhepatic gallbladder drainage and was relieved from right hypochondriac pain after the treatment. During his admission, esophagogastroduodenoscopy showed a slightly elevated gastric tumor. Biopsy revealed a well-differentiated tubular adenocarcinoma. A second esophagogastroduodenoscopy detected a 9-mm, slightly elevated 0–IIa type gastric tumor that was located in the middle third of the stomach under chromoendoscopy (Fig. 2a) [8]. Magnifying narrow-band imaging (NBI) revealed a demarcation line and an irregular structure pattern with low-power view (Fig. 2b). The high-power view revealed an irregular vascular pattern in the large white zone, which indicated differentiated-type gastric cancer (Fig. 2c). Laboratory examination results included a hemoglobin level of 11.0 g/dL, a creatinine level of 1.37 mg/dL, a fasting blood glucose level of 141 mg/dL, and tumor

markers (including CEA, CA19-9, and AFP) within normal limits. Serum anti-*H. pylori* antibody test results were negative. The serum gastrin level was 695 pg/mL (normal 42–200 pg/mL), and both antiparietal cell and anti-intrinsic factor antibody results were negative. There was no evidence of autoimmune gastritis.

The patient successfully underwent complete tumor resection by endoscopic submucosal dissection (ESD). He was discharged 8 days after ESD. From histological findings, the size of the tumor was 9 mm. The tumor was located within the mucosa without venous or lymphatic infiltration and contained a well-differentiated tubular adenocarcinoma and NET showing trabecular, ribbons, and tubular structure, with eosinophilic granules in the cytoplasm. The adenocarcinoma was located in the superficial part of the mucosa, while the NET was in the basal part (Fig. 3a). Both components exhibited histological continuity through the transitional area (Fig. 3b). Although the NET and the lower part of the adenocarcinoma were positive for chromogranin A (Fig. 3c) and synaptophysin on immunohistochemistry, the NET component was more diffusely positive than the adenocarcinoma component. The histological distinction between adenocarcinoma and NET components was based on morphology, regardless of immunohistochemical findings. As the NET component immunohistochemically showed a low Ki-67 index of <1%, the component was regarded as a NET G1 (Fig. 3d). Each component constituted ≥30% of the neoplasm. This tumor was diagnosed as a mixed adenocarcinoma-NET. Neither ECL cell hyperplasia nor endocrine cell micronest (ECM) was detected, although intestinal metaplastic change was observed in the mucosa surrounding the tumor. Esophagogastroduodenoscopy and abdominal CT examinations revealed no recurrence or metastasis 3 years after ESD.

Discussion

Both gastric adenocarcinoma and NETs are common epithelial neoplasms in the gastrointestinal tract. The carcinogenesis of gastric carcinomas is associated with *H. pylori* infection as one of the main environmental factors [2]. Infection causes atrophic gastritis and metaplastic gastritis to the gastric mucosa, making it a risk for neoplastic development. In addition, typical gastric NETs are derived from ECL gastric mucosa cells with increased serum gastrin as a primary stimulus. They form ECL cell hyperplasia and progress to NETs [1]. Increased gastrin is caused by several factors, such as autoimmune chronic atrophic gastritis, *H. pylori* infection, and gastrinoma.

The histological definition of NETs was unclear because conventional NETs included both NETs and neuroendocrine carcinomas (NECs), as stated by the WHO in 1980 [6]. Subsequently, these neoplasms were graded based on their proliferative activity, such as mitotic rate and Ki-67 proliferation index. According to the WHO classification of digestive system tumors in 2019 [7], neuroendocrine neoplasms are classified into NETs, NECs, and MiNENs. NETs are well-differentiated and NECs are poorly differentiated, classified according to the histomorphological findings. NETs are divided into three groups (G1, G2, and G3) based on their mitotic rate and Ki-67 index. A mitotic rate <2 per 10 high-power fields and a <3% Ki-67 index belongs to G1. MiNENs require that each component constitutes ≥30% of the neoplasm.

In 1987, Lewin [5] classified pure and mixed endocrine tumors into carcinoid, collision, and amphicrine tumors, composite glandular endocrine cell carcinoma, and adenocarcinoma. Composite carcinoma contains various admixtures of endocrine and nonendocrine epithelial cells, whereas the two cell types of collision tumors are not individually intermixed. In our case, the NET G1 component exhibited continuity with the adenocarcinoma component through the transitional area. A mixed adenocarcinoma-NET is considered a composite tumor. Histogenesis of the composite tumor is suggested as either the respective neoplastic change of two different stem cells or proliferation of a pluripotent stem cell into two different cellular types [9]. We found two case reports via PubMed: composite tumors formed by adenocarcinoma and a NET in the stomach (Table 1) [3, 4]. There were six pure NETs and a large number of ECMs on the atrophic oxyntic mucosa with gastrin-containing G-cell hyperplasia in case 1, while hypergastrinemia with no pure NETs or ECMs was found in case 2. Both cases inferred that the adenocarcinoma and the NET component were derived from common histogenesis because of the histological continuity between the two components. Although our patient had increased serum gastrin and metaplastic gastritis, the stomach revealed neither ECL cell hyperplasia nor ECMs surrounding the tumor. Therefore, it was unlikely that the increased serum gastrin brought the NET component's development in this composite tumor. We consider that this tumor was also derived from pluripotent stem cells in the gastric mucosa because of the histological continuity between the two components and positive reaction for chromogranin A and synaptophysin in both components. The pluripotent stem cell may give rise to both well-differentiated adenocarcinoma towards the superficial part of the mucosa and the NET G1 towards the basal part.

We could not recognize the NET G1 by magnifying NBI before ESD. Although magnifying NBI is a very useful technology for detecting changes in the surface structure of the mucosa [10], the penetrating depth of the narrow-band illumination is 150 μm from the surface of the mucosa [11]. The illumination could not reach the NET G1, which was morphologically located in the basal part of the mucosa. According to previous case reports, as both of the two NET G1 components were located in the basal part of the mucosa as well, it might not be easy to detect an intramucosal NET G1 component through magnifying NBI (Table 2) [3, 4].

The therapeutic strategy for gastric intramucosal differentiated adenocarcinoma without lymphovascular infiltration and ulceration recommends endoscopic treatment [2]. Currently, the therapeutic strategy for gastric MiNEN within the mucosa is not clear. In this case, as the well-differentiated tubular adenocarcinoma with NET was located within the mucosa without lymphovascular infiltration and ulceration, we considered that complete resection of the tumor by ESD was an appropriate treatment. However, the patient should undergo follow-up examinations using esophagogastroduodenoscopy and CT examinations postoperatively because NET of mixed adenocarcinoma-NET has not been evaluated as an exacerbation prognosis factor. It is necessary to establish a therapeutic strategy for gastric MiNEN by endoscopic resection in the future.

In conclusion, gastric intramucosal mixed adenocarcinoma-NET G1 with histological continuity is rare. We suggest that this type of tumor was derived from the same histogenesis as intramucosal mixed adenocarcinoma-NET.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y. Sano wrote the article. S. Saito, H. Kawachi, and J. Fujisaki reviewed and edited the manuscript. J. Tsutsumi supervised the writing of the manuscript.

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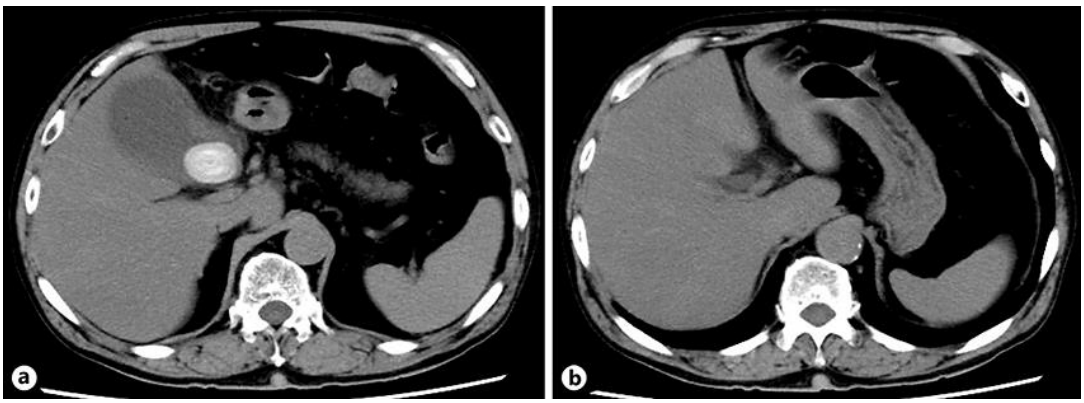

Fig. 1. Abdominal computed tomography examination. **a** Acute cholecystitis with a gallstone. **b** No gastric wall thickening or perigastric lymphadenopathy was seen.

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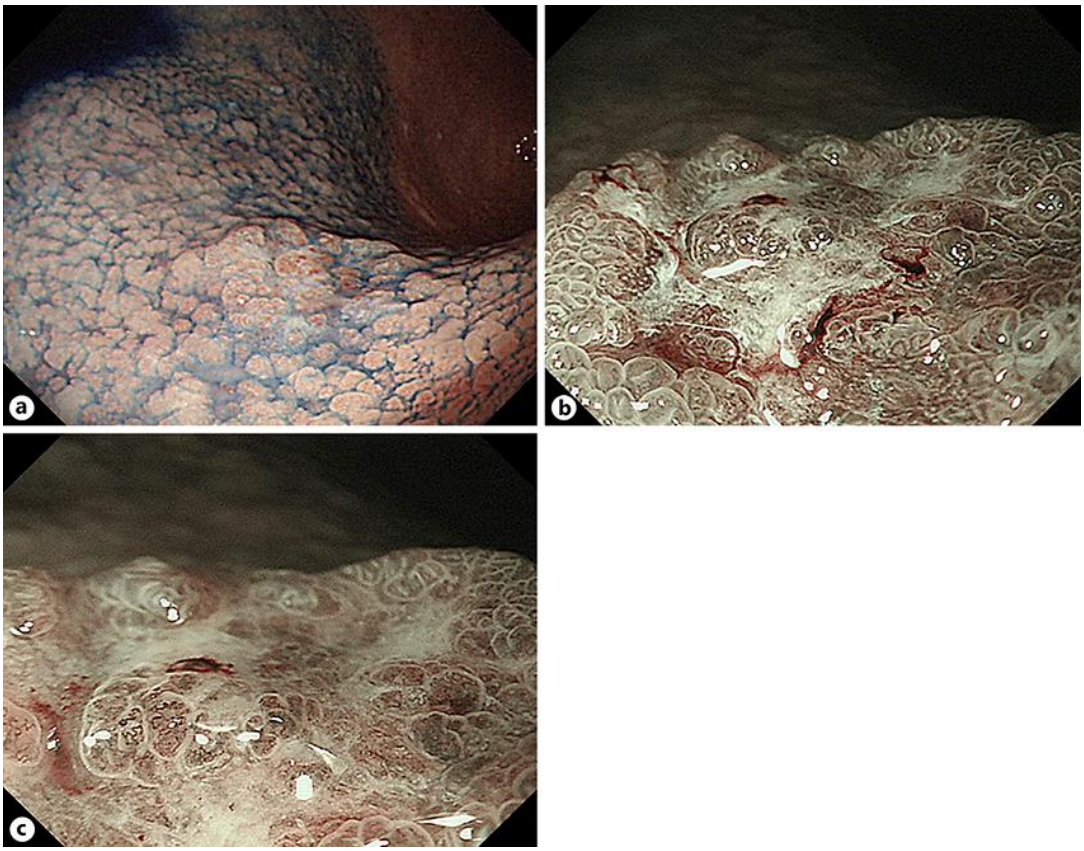

Fig. 2. Endoscopic images. **a** Esophagogastroduodenoscopy revealing a 9-mm, slightly elevated 0–IIa type gastric tumor under chromoendoscopy. **b** Magnifying NBI showing a demarcation line and an irregular structure pattern with low-power view. **c** The high-power view of magnifying NBI revealing an irregular vascular pattern in the large white zone. NBI, narrow-band imaging.

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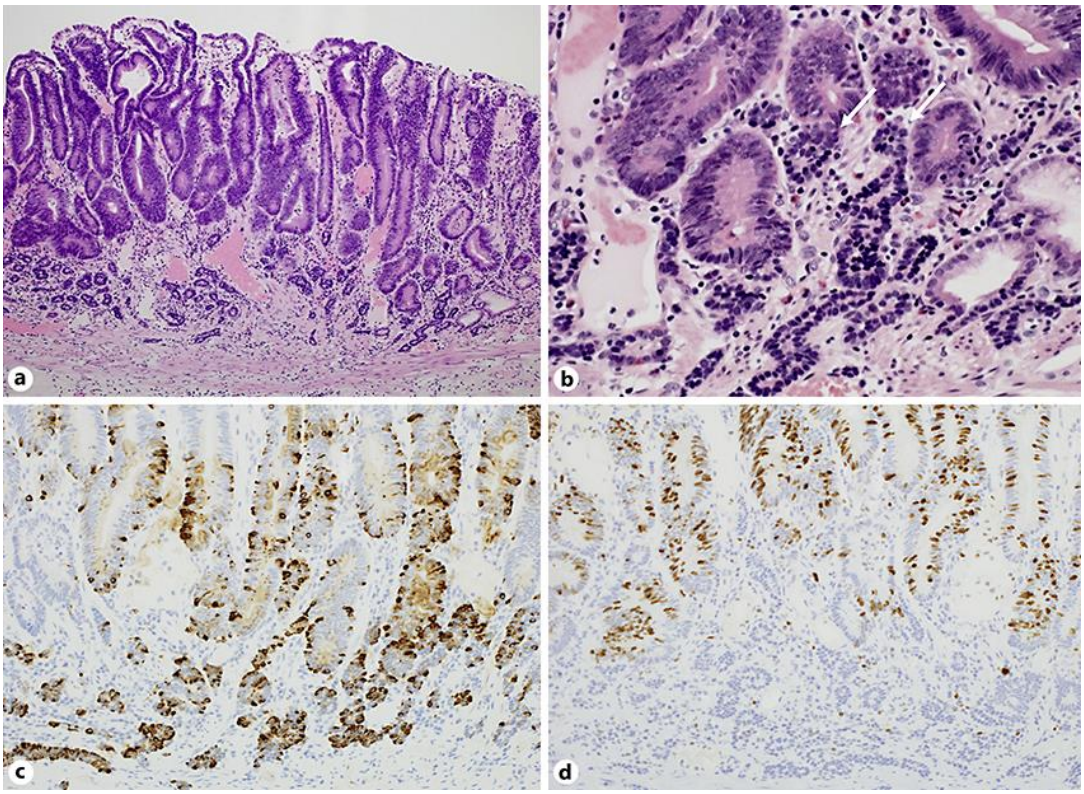

Fig. 3. Microscopic findings of the mixed adenocarcinoma-NET of the stomach. **a** The adenocarcinoma was located in the superficial part of the mucosa, while the NET was in the basal part (H&E staining, ×100). **b** The adenocarcinoma component and the NET component exhibited histological continuity through the transitional area (white arrows) (H&E staining, ×400). **c** The NET component was more diffusely positive for chromogranin A than the lower part of the adenocarcinoma components (×200). **d** The NET component showed a low Ki-67 index of <1% by immunohistochemistry using MIB1 antibody (×200). H&E, hematoxylin and eosin; NET, neuroendocrine tumor.

Table 1. Case reports of gastric composite tumor consisting of adenocarcinoma and NET using PubMed

Reference	Year	Age	Sex	Location	Size, mm	Type	Depth	Adenocarcinoma	NET	ECL cell hyperplasia or ECMs	Number of pure NETs	Treatment	Gastrin status	AIG
Caruso et al. [3]	1989	53	f	U	15	0–I	pT1b	tub1	G1	a large number	6	TG	not evaluated[1]	+
Kubo et al. [4]	2018	80	m	M	25	0–IIa	pT1a	tub1	G1	not detected	not detected	ESD	hypergastrinemia	–
Our case	2021	77	m	M	9	0–IIa	pT1a	tub1	G1	not detected	not detected	ESD	hypergastrinemia	–

AIG, autoimmune gastritis; ECL, enterochromaffin-like; ECMs, endocrine cell micronests; ESD, endoscopic submucosal dissection; M, middle third; NET, neuroendocrine tumor; pT1a, tumor confined to the mucosa; pT1b, tumor confined to the submucosa; TG, total gastrectomy; tub1, well-differentiated tubular adenocarcinoma; U, upper third. [1] Histological G-cell hyperplasia.

Table 2. Location of each component of the gastric composite tumor within the mucosa, according to the previous case report

Reference	Type	Depth	Morphological location within the mucosa	
			adenocarcinoma component	NET component
Caruso et al. [3]	0–I	pT1b	basal part	basal part
Kubo et al. [4]	0–IIa	pT1a	superficial part	basal part
Our case	0–IIa	pT1a	superficial part	basal part

NET, neuroendocrine tumor; pT1a, tumor confined to the mucosa; pT1b, tumor confined to the submucosa.