Gastric Mixed Adenoneuroendocrine Carcinoma with a Good Prognosis

Nobuhiko Fukuba¹, Takafumi Yuki², Shunji Ishihara¹, Hiroki Sonoyama¹, Yasumasa Tada¹, Ryusaku Kusunoki¹, Akihiko Oka¹, Naoki Oshima¹, Ichiro Moriyama¹, Kousaku Kawashima¹ and Yoshikazu Kinoshita¹

Abstract

A flat, elevated lesion measuring 5 mm in diameter was found in the gastric body of an 80-year-old man. A biopsy showed moderately differentiated adenocarcinoma, and endoscopic ultrasonography revealed a hypoechoic mass located in the submucosa. Endoscopic submucosal dissection was subsequently performed, and a pathological examination revealed a tumor composed of adenocarcinoma and neuroendocrine carcinoma with submucosal infiltration. The pathological diagnosis was gastric mixed adenoneuroendocrine carcinoma (MANEC). An additional gastrectomy procedure was performed, and no recurrence was noted for at least three years. This case is interesting with respect to the carcinogenesis of endocrine cell carcinoma and MANEC.

Key words: gastric cancer, good prognosis, mixed adenoneuroendocrine carcinoma

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Introduction

A mixed adenoneuroendocrine carcinoma (MANEC) is a tumor composed of both adenocarcinoma and neuroendocrine carcinoma (NEC) components, with each comprising at least one-third of the lesion, as defined by the World Health Organization (WHO) classification of neuroendocrine neoplasms in 2010 (1). There are few reports of MANEC cases, as it is a comparatively new disease concept. On the other hand, gastric NEC is known to be a rare and progressive tumor with a poor prognosis compared with that of gastric adenocarcinoma. Several previous reports have noted the coexistence of NEC with small adenocarcinomas. Hence, there may be a relationship between NEC and MANEC with respect to carcinogenesis. In this report, we describe an interesting case of a gastric MANEC associated with a good prognosis. We also consider the carcinogenesis of MANEC and NEC of the stomach.

Case Report

A flat, elevated lesion measuring 5 mm in diameter was found in the gastric upper body of an 80-year-old man on an endoscopic checkup. The lesion was raised smooth, with a reddish area of erosion exhibiting an irregular edge (Fig. 1a, b). An upper gastrointestinal series of images showed findings similar to the endoscopic results (Fig. 1c), while a biopsy demonstrated moderately differentiated tubular adenocarcinoma. In addition, endoscopic ultrasonography (EUS) revealed a hypoechoic mass with a maximum diameter of 7.8 mm located in the submucosa under the mucosal lesion (Fig. 2); the submucosal hypoechoic lesion was distinguished from the first and second layers. There were no endoscopic findings indicating submucosal invasion, and the submucosal hypoechoic mass was distinguished from the mucosal layer; therefore, we suspected that the adenocarcinoma was located in the mucosal layer, while the submucosal hypoechoic mass constituted another lesion. The pa-
Helicobacter pylori antibodies was positive. The titer of anti-gastrin, including the serum gastrin level, were normal, although the patient displayed no symptoms, and a physical examination showed no abnormalities. Furthermore, laboratory findings, such as an NEC. The echogenicity of the submucosal mass corresponded to the reddish area of erosion observed on endoscopy, classified as moderately tubular adenocarcinoma, and a deep side corresponding to the hypoechoic submucosal lesion detected on EUS, classified as a high cellularity tumor with necrosis, such as an NEC. The echogenicity of the submucosal mass potentially reflected the cellularity of the NEC component. The immunohistological findings showed the NEC component to be weakly positive for chromogranin A and neural cell adhesion molecule (NCAM) (Fig. 4a, b). In addition, the nuclei of the tumor cells were large and some had a polygonal shape. The mitotic activity was >20/10 high-power field (HPF) and the Ki-67 index was >90% in the NEC component (Fig. 4c). Therefore, the diagnosis was MANEC according to the WHO classification presented in 2010. Although the surgical margins were negative, the post-endoscopic submucosal dissection (ESD) pathological diagnosis was early gastric cancer, Type 0-IIa, approximately 10×9 mm, mixed adenoneuroendocrine carcinoma, see description, depth T1b2(SM2), UL(+), v(+), pHM0(4 mm), pVM0. An additional laparoscopic proximal gastrectomy procedure with lymph node dissection was performed, although no remnant tissue or lymph node metastasis were observed. The pathological progress classification was pT1bN0M0, pStage IA. The patient’s postoperative recovery was uneventful, and he was discharged on postoperative day 7; he did not wish to receive postoperative chemotherapy due to his advanced age. No recurrence was noted at an examination conducted three years after the surgery.

Discussion

A new classification system of digestive neuroendocrine tumors (NETs) was formulated and presented in the 2010 revision of the WHO classification of digestive tumors (1). This system recognizes three main categories according to the Ki-67 index: NET G1, NET G2 and NEC. The submucosal component in the present case corresponded to NEC. The original definition of mixed endocrine-exocrine carcinoma (MEEC) was incorporated into the WHO classification of gastroenteropancreatic endocrine tumors in 2000, which states that an MEEC is a tumor with two different cell populations, each of which composes at least one-third of the tumor area. Thereafter, the new WHO classification proposed the term MANEC to classify this type of tumor based on similar criteria (1). In the present case, each of the NEC and adenocarcinoma components accounted for nearly half of the tumor; thus, the lesion was consistent with the defini-

Figure 1. Images of gastric mixed adenoneuroendocrine carcinoma. (a) A flat, elevated lesion was detected in the upper gastric body exhibiting a reddish area of erosion and a smooth edge. (b) The structure of the surface was clearly visualized with the application of indigo carmine dye. (c) An upper gastrointestinal series of images revealed the lesion (arrowheads).

Figure 2. EUS showed a hypoechoic mass located in the submucosa with a maximum diameter of 7.8 mm and an irregular and distinguishable border.
Figure 3. (a) Distribution map of the two tumor components. The yellow line indicates the distribution of the NEC component along the cut lines, and the green line indicates the adenocarcinoma component. (b) Loupe images of slices #9 on the map. Hematoxylin and Eosin staining sections showed the shallow side of the lesion to be moderately tubular adenocarcinoma (green), while the deep side was similar to neuroendocrine carcinoma (yellow). The two components were continuous. (c) An enlarged view of the NEC component. (d) An enlarged view of the adenocarcinoma component.

Figure 4. Immunohistological appearance of the submucosal lesion: (a) chromogranin A, (b) NCAM, (c) Ki-67. The NEC component was weakly positive for chromogranin A and NCAM. The mitotic activity was >20/10 HPF and the Ki-67 index was >90% in the NEC component.

Gastric NETs containing a so-called carcinoid are increasingly being recognized due to expanding indications for upper gastrointestinal endoscopy examinations. These lesions usually present as well-differentiated non-functioning neoplasms derived from enterochromaffin-like (ECL) cells. Gastric NETs are comprised of three distinct tumor types: type I, associated with autoimmune chronic atrophic gastritis; type II, associated with multiple endocrine neoplasia type 1 (MEN1) and Zollinger-Ellison syndrome; and type III, which are sporadic (2). Recently, the category of ‘type IV gastric NET’ was proposed to include all poorly differenti-
ated gastric NETs consisting of other than ECL gastric endocrine cells (producing serotonin or gastrin) and also MANEC, a very rare type of gastric malignancy (3).

The carcinogenesis of MANEC is unclear. Previous reports have noted the coexistence of gastric NEC with a scant amount of adenocarcinoma tissue. Nishikura et al. noted that 70.6% of gastric NEC cases include an adenocarcinoma component in the mucosa and/or submucosa (4). Gastric NECs are considered to arise predominantly from endocrine precursor cell clones that develop in the preceding adenocarcinoma component rather than ECL cells. These clones transform into NEC lesions during rapid clonal expansion, while NEC tumors develop rapidly in the submucosal and deeper layers (4, 5). In the present case, the endoscopic findings showed a reddish area of erosion, which corresponded to the adenocarcinoma component, and endoscopic ultrasonography revealed a hypoechoic mass in the submucosal layer, which reflected the NEC component. Furthermore, the NEC component was seen pushing up the mucosal lesion along with the peripheral mucosa. Since the NEC was located on the basal side of the mucosal or submucosal layer, its origin may have been endocrine cell clones derived from the deep portion of the preceding adenocarcinoma component. When the tumor was resected, the NEC and adenocarcinoma components were each found to occupy approximately half of the tumor. Since NECs typically grow rapidly compared with adenocarcinomas, the NEC portion would have accounted for most of the tumor if not resected, and the diagnosis may have been advanced NEC rather than MANEC. Although we diagnosed the tumor as MANEC according to the WHO classification presented in 2010, we speculate that it was in a stage prior to developing into NEC.

Gastric NEC is believed to be a rapidly growing lesion, with nearly all patients exhibiting a poor prognosis (6, 7). NEC is known to frequently invade the lymphatic and vascular lumen and subsequently metastasize to the lymph nodes and liver, even during the early stages, due to its aggressive biological behavior. In the present case, the findings of a histological examination performed after endoscopic therapy showed submucosal invasion. Hence, we also performed total gastrectomy and lymph node dissection, although no metastasis was observed in the resected specimen or local remnant. The patient displayed no evidence of recurrence at an examination performed three years after surgery. Nevertheless, it is necessary to watch for recurrence, as there are reports of gastric endocrine cell carcinoma and/or MANEC tumors requiring resection at an early stage. In the current case, a good prognosis is anticipated, since adequate treatment was administered early in the disease course.

The authors state that they have no Conflict of Interest (COI).

References