Intramucosal Gastric Mixed Adenoneuroendocrine Carcinoma Completely Resected with Endoscopic Submucosal Dissection

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Abstract

Composite tumors in the stomach composed of adenocarcinoma and neuroendocrine carcinoma are rare. We herein report a case of intramucosal gastric mixed adenoneuroendocrine carcinoma (MANEC) that was treated with endoscopic submucosal dissection (ESD). A 77-year-old man who had previously received ESD for early gastric adenocarcinoma underwent esophagogastroduodenoscopy for screening, which showed a depressed lesion on the lesser curvature of the antrum. The tumor was removed en bloc via ESD and pathologically diagnosed as MANEC. The tumor was located within the mucosal layer, and no lymphovascular invasion was evident. Seven months after the ESD procedure, the patient is currently feeling well without recurrence or metastasis.

Key words: mixed adenoneuroendocrine carcinoma, adenocarcinoma, endoscopic submucosal dissection

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Introduction

Composite tumors in the stomach composed of adenocarcinoma and neuroendocrine carcinoma are rare, although these carcinomas are considered to occur in against a common background of atrophic gastritis (1, 2). According to the World Health Organization (WHO) 2010 classification, neuroendocrine tumors are primarily classified according to the mitotic count and Ki-67 index, which reflect the proliferative activity of the tumor, as follows: neuroendocrine tumors are graded as G1 or G2, neuroendocrine carcinoma is graded as G3 and mixed adenoneuroendocrine carcinoma (MANEC) is identified as a composite tumor with two distinct components, adenocarcinoma and neuroendocrine carcinoma. In order to qualify for the definition of MANEC, each component must represent at least 30% of the tumor (1). In general, neuroendocrine carcinoma is considered to grow rapidly and have a poor prognosis (3), whereas MANEC tumors grow based on the component with greater malignant potential (4). Most neuroendocrine carcinomas, including MANEC lesions, are diagnosed at an advanced stage and mainly treated with surgical resection or chemotherapy.

We herein report a case of intramucosal gastric MANEC that was removed en bloc via endoscopic submucosal dissection (ESD).
A 77-year-old Japanese man underwent esophagogastroduodenoscopy (EGD) as follow-up after treatment for early gastric cancer. He had received surgery for metachronous early gastric cancers with ESD two and nine years previously. The histology of both gastric cancers was differentiated adenocarcinoma. The patient’s past medical history also included chemoradiation therapy for left lung squamous cell carcinoma nine years previously and resection of right lung adenocarcinoma one year previously. He had neither a genetic predisposition to malignancy nor family history of cancer.

Blood tests revealed no leukocytosis or anemia, and the results of liver and renal function tests were normal. The serum levels of tumor markers, including carcinoembryonic antigen, squamous cell carcinoma-related antigen and cytokeratin 19 fragment, were within the normal limits. Serum IgG antibodies to Helicobacter pylori (H. pylori) were negative, as H. pylori had been eradicated one year earlier. A contrast-enhanced computed tomography (CT) scan revealed no remarkable lymph node metastasis, although scarring of the lung as a result of earlier treatment was apparent.

EGD showed a slightly red depressed lesion 5 mm in size on the lesser curvature of the antrum (Fig. 1A). A diagnosis of moderately differentiated tubular adenocarcinoma was made based on an examination of the biopsy specimen. A second EGD procedure using magnifying endoscopy with narrow-band imaging (NBI) showed an unclear line of demarcation between the normal mucosa and a depressed area containing an irregular microstructure pattern (the power of magnification with NBI was not adequately high). The irregular microstructure pattern was characterized by the presence of an irregular network, whereas the background normal mucosa exhibited regular tubular or granular structures (Fig. 1B). Chromoendoscopy with an acetic acid-indigo carmine mixture showed the border of the lesion more clearly than did white light endoscopy (Fig. 1C). We diagnosed the lesion as intramucosal gastric cancer. The tumor met the general indications for ESD, including intramucosal differentiated-type adenocarcinoma measuring less than 2 cm in size with no ulceration. ESD was performed using the IT-Knife2 (Olympus, Tokyo, Japan) and Dual Knife (Olympus), and en bloc resection was achieved without adverse events.

Macroscopically, the tumor was a 10×6-mm depressed lesion with a negative margin (Fig. 2). Microscopically, routine hematoxylin-eosin stained sections of the tumor showed two distinct components (Fig. 3): the major component was moderately differentiated tubular adenocarcinoma, while the minor component was neuroendocrine carcinoma with pali-sading and budding nested patterns. The latter component comprised more than 30% of the tumor and exhibited a high number of mitoses, >20/10 high power fields (HPF). Most of the neuroendocrine carcinoma component was covered by non-neoplastic mucosa. The tumor was located within the mucosa, although it had grown into the muscular layer of the mucosa. No lymphovascular or perineural invasion was noted on D2-40 and Elastica van Gieson staining. According to immunohistochemical staining, the neuroendocrine carcinoma component was positive for chromogranin A and synaptophysin (Fig. 4). In addition, part of the tumor was positive for both chromogranin A and MUC 6, an exocrine marker. Based on these findings, we diagnosed the tumor as MANEC.

The patient’s post-ESD course was uneventful, and he was discharged on the eighth day postoperatively. We considered applying adjuvant treatment; however, we decided against it taking into consideration the prognosis of the lung cancer. Seven months after the ESD procedure, CT and EGD have continued to show no evidence of recurrence or metastasis.

Discussion

Although composite tumors of the gastrointestinal tract composed of adenocarcinoma and neuroendocrine carcinoma in the appendix have been previously reported, such tumors in the stomach, esophagus and colon are rare (1). Most re-
ported cases were advanced, and, although the prognosis of advanced MANEC remains unknown, it is thought to depend on the component with greater malignant potential (4). Composite tumors have been renamed several times. In 1987, mixed adeno-endocrine cell tumors were identified and classified into three groups as mixed glandular-endocrine cell carcinomas (composite tumors), amphicrine tumors and collision tumors, respectively (5). In 2000, the WHO classification defined composite tumors as mixed exocrine-endocrine tumors. In 2010, the most recent WHO classification defined such tumors as MANEC (1).

The carcinogenic pathway of MANEC is unclear. Two major hypotheses have been proposed: 1. adenocarcinoma cells dedifferentiated to neuroendocrine cells during tumor progression (4) and 2. monoclonal pluripotent epithelial stem cells differentiated into two components (6). The first hypothesis is supported by a report in which the adenocarcinoma component of the composite tumor displayed intraglandular endocrine cell hyperplasia and extraglandular budding nests of endocrine cells suggestive of dedifferentiation to neuroendocrine cells (5). Furthermore, the phenotypic expression of the neuroendocrine component was almost identical to that of the adenocarcinoma component (4). In the present case, budding nested patterns were demonstrated in the MANEC; this finding appears to support the first hypothesis. The second hypothesis is supported by a report in which a microallelotyping analysis of polymorphic microsatellite markers covering chromosomes 3, 5q, 6, 11, 17 and 18 in six gastrointestinal composite or collision carcinomas showed common genetic alterations in both the adenocarcinoma and neuroendocrine carcinoma components (6). Moreover, a gastric MANEC composed of three histologically distinct components has been reported, including a neuroendocrine component and two different exocrine components with adenocarcinoma and squamous cell carcinoma (7). However, the common carcinogenic pathway of MANEC currently remains unclear, and several carcinogenic pathways may be associated with the onset of MANEC.

Although the early detection and treatment of gastric tumors has increased in accordance with the progression of endoscopic techniques, the early detection of MANEC is extremely rare. Even in the early stage of the disease, the neuroendocrine carcinoma component is detected in the deeper portion of the mucosal or submucosal layers (8-10), suggesting that most cases of MANEC are diagnosed as advanced carcinoma. In the current case, biopsy specimens of
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the tumor showed only adenocarcinoma, as the neuroendocrine carcinoma component was primarily located in the deeper portion of the mucosal layer and the superficial layer of the neuroendocrine carcinoma was covered with non-neoplastic mucosa or adenocarcinoma. These findings made it difficult to predict the existence of the neuroendocrine carcinoma component. Hence, obtaining an early diagnosis of composite tumors with a neuroendocrine carcinoma component is difficult. Most previously reported MANECs were diagnosed after total resection of the tumor (7), and there are currently no recommended therapeutic strategies. However, surgical resection is indicated in patients without metastasis as a therapeutic option (1). In contrast, in those with distant metastasis, chemotherapy for neuroendocrine carcinoma has been reported to be the treatment of choice (7).

Adjuvant therapy for early gastric MANEC is controversial. Three patients with early gastric MANEC treated with ESD have been reported in Asian countries (8-10). In each case, all tumors had invaded the submucosal layer. One patient underwent additional distal gastrectomy and exhibited no recurrence for 10 months after surgery, while another received no adjuvant therapy and displayed no recurrence for 12 months after ESD. The third patient refused additional treatment and developed liver metastasis and peritoneal dissemination 14 months after surgery.

To the best of our knowledge, this report describes the first case of intramucosal early gastric MANEC. Further case accumulation is required to establish the standard therapy for early gastric MANEC. The current case shows that MANEC lesions can occur within the mucosal layer at an extremely early stage. This observation may help to elucidate the carcinogenic pathway of MANEC.

In conclusion, we herein reported a case of an intramucosal gastric MANEC tumor successfully treated with en bloc resection via ESD. As diagnostic endoscopic technology progresses, the diagnosis of early gastric MANEC may increase in the future. There is thus a need to develop therapeutic strategies and clarify the prognosis of early gastric MANEC.

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

References


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