[CASE REPORT]

Lymph Node Metastasis of Mixed Adenoneuroendocrine Carcinoma after Curative Resection Using the Expanded Criteria for Early Gastric Cancer

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Abstract:
Endoscopic submucosal dissection (ESD) of lesions using expanded indications for early gastric cancer (EGC) has been accepted as an alternative treatment for cases without lymph node metastasis. We herein report a rare case of metastatic lymph node tissue in mixed adenoneuroendocrine carcinoma (MANEC) after curative ESD using the expanded pathological criteria. A 70-year-old man underwent ESD for two EGC lesions. A pathological examination revealed lesions that required curative resection based on the expanded pathological criteria of the Japanese classification of gastric carcinoma. However, lymph node metastasis was detected at 26 months after ESD. Additional surgical resection was performed and MANEC was pathologically diagnosed in the metastatic lymph node. The patient subsequently underwent additional chemotherapy and remains alive at 2 years after surgery. Even though MANEC is a rare tumor, this case suggests that periodic follow-up is important when patients undergo curative resection by ESD based on the expanded indications because of the high malignant potential and the poor prognosis.

Key words: neuroendocrine, MANEC, endoscopic submucosal dissection, recurrence

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Introduction

Endoscopic submucosal dissection (ESD) using the expanded indications for lesions of early gastric cancer (EGC) based on retrospective examinations of surgically resected cases has been reported to be useful for patients without lymph node metastasis (1-3).

We herein report a rare case of lymph node metastasis of mixed adenoneuroendocrine carcinoma (MANEC) that was discovered after curative ESD using the expanded pathological criteria (differentiated gastric cancer without an ulceration scar with <500 μm invasion of the submucosa from the muscularis mucosa [SM1]).

Case Report

A 70-year-old man with a history of hypertension and no history of other malignancy was admitted to our hospital after two EGC lesions were detected on screening esophagogastroduodenoscopy. A physical examination and laboratory analysis, which included an analysis of the patient’s tumor marker levels, revealed no abnormalities. One lesion was a 15-mm depressed lesion (type 0-IIc) without ulceration that was located on the lesser curvature of the antrum and which was limited to the mucosa (Fig. 1a, c and d)). The other was a 25-mm depressed lesion (type 0-IIc) without ulceration that was located on the

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greater curvature of the middle corpus of the stomach and which was limited to the mucosa (Fig. 1b). Each biopsy specimen was diagnosed as well-differentiated adenocarcina-

oma. Because no lymph node or distant metastasis was detected by computed tomography (CT), the lesions were re-

sected en bloc by ESD. In the pathological examination, im-

munohistochemical staining with Desmin, D2-40, and Victo-

ria blue, revealed that the smaller lesion was a well-
differentiated tubular adenocarcinoma of 17 mm × 9 mm in size with an invasion depth of SM1 (43 μm from the muscu-

laris mucosa), and that the larger lesion was a well-
differentiated tubular adenocarcinoma of 25 mm × 14 mm in size located in the intra-mucosa. The horizontal and vertical margins were negative for each tumor, and there was no lymphovascular invasion or ulceration of the lesions. Thus, the resection was considered to be curative based on the expanded pathological criteria of the Japanese classification of gastric carcinoma.

Thereafter, enhanced abdominal CT was performed every 6 months and no metastasis was observed. EGD was also performed annually. At 26 months after ESD, enhanced ab-

dominal CT showed enlargement of an infrapyloric (no. 6) lymph node (Fig. 2a). 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) showed the abnor-

mal accumulation of FDG in the same spot (Fig. 2b). The patient’s carcinoembryonic antigen (CEA) level remained within the normal range after ESD, but had increased to 9.8 U/mL at 25 months after treatment. Because no metastatic or primary lesions were found in any organ by 18F-FDG PET/CT, the diagnosis was metastasis of ESD-treated EGC. Laparoscopic distal gastrectomy was performed with D2 lymph node dissection, and a postoperative pathological ex-

amination revealed no local recurrent tumor at the site of ESD in the stomach. A histopathological examination re-

vealed that the tumor consisted of endocrine cell carcinoma and adenocarcinoma. Adenocarcinoma cells were predomi-

nant in the metastatic lymph node (Fig. 3a, b and c). The neuroendocrine markers (chromogranin A, synaptophysin,

and CD56) were all immunohistochemically positive, the Ki-67 index was 90%, and the metastatic tissue had signifi-

cant adenoneuroendocrine components, which comprised > 30% of the tumor (Fig. 3d, e and f). Thus, the diagnosis was MANEC. The initial ESD specimens were reviewed be-

cause the histological type was different from that of the metastatic lymph node and because broken glandular structures were detected in part of the mucosa of the lesser cur-

vature of the antrum (Fig. 4a, b and c). A neuroendocrine marker examination indicated that the patient was negative for chromogranin A and synaptophysin but partially positive for CD56 (Fig. 4d, e and f). The Ki-67 index of the broken
glandular structures was 25%. However, broken glandular structures were not observed in the mucosa of the greater curvature of the middle corpus. The patient was also negative for all neuroendocrine markers. Thus, it was suggested that carcinoma had differentiated into neuroendocrine carcinoma in the adenocarcinoma component. However, it is considered difficult to predict lymph node metastasis of MANEC after ESD. Adjuvant chemotherapy (irinotecan, cisplatin) was administered for 4 months, and S-1 was administered for eight months. At the 28-month follow-up examination, the patient was well with no evidence of recurrence.

**Discussion**

The Gastric Cancer Treatment Guideline specifies that the pathological criteria for curative endoscopic resection of EGC have been expanded to include other lesions with a negligible risk of lymph node metastasis (3). These expanded criteria include larger lesions, lesions with ulceration, and lesions that invade the submucosa by <500 μm (SM1), and are based on retrospective examinations of the expanded criteria for surgical resection of EGC determined to have a negligible risk of lymph node metastasis (1, 2). Recently, a prospective, multicenter study (JCOG0607) showed that favorable long-term outcomes were achieved...
using the expanded criteria, with no recurrence observed among patients who underwent curative resection according to the expanded criteria (4). However, a large, multicenter questionnaire study revealed three cases of recurrence (0.2%) in patients who underwent curative resection using the expanded criteria (5, 6). One case involved a patient with predominant differentiated adenocarcinoma, SM1, with poorly differentiated components and ulceration, one case fulfilled the expanded curative criteria for SM1, and one case involved a large mucosal differentiated carcinoma without ulceration but with poorly differentiated components (7).

The present case fulfilled the expanded criteria for curative resection (SM1 without ulceration). Abe et al. reported that differentiated-type gastric cancer of ≤3 cm with an invasion depth of SM1 had higher potential for lymph node metastasis based on a retrospective analysis of an observational study of a series of cases treated by surgical dissection or ESD (8).

The Japanese classification of gastric carcinoma recommends that EGD be performed annually or every 6 months and that abdominal CT be performed every 6 months (3, 9).

In this case, we detected lymph node metastasis at 26 months after ESD and an increased CEA level at 25 months after ESD, because EGD was performed annually while abdominal CT and the evaluation of tumor marker levels were performed twice per year. Although favorable long-term outcomes have been reported, CT scans and the analysis of tumor marker levels should be performed periodically to detect metastasis in differentiated-type gastric cancer of ≤3 cm in size and an invasion depth of SM1 (20).

MANEC is a rare tumor of the gastrointestinal tract (10-12). Neuroendocrine carcinoma was reported in approximately 0.6% of all gastric cancers. This tumor shows dual adenomatous and neuroendocrine differentiation, with each component representing at least 30% of the tumor according to the 2010 World Health Organization (WHO) classification (13). Each component comprises <30% of the tumor, and the diagnosis is mainly based on the components. Using this classification, neuroendocrine tumors (NETs) are classified by the mitotic counts per 10 high power fields and the Ki-67 index. Grade 3 (neuroendocrine carcinoma) characteristics include 10 high power fields, mitotic count >20, and Ki-67 index >20%. Although the carcinogenic pathway of neuroendocrine carcinoma has not been fully clarified, there are four accepted types of outbreak. The first type involves adenocarcinoma cells. The second type involves carcinoid cells. The other two types involve cells with multiple differentiation potency or immature neuroendocrine cells. Recently, it has been hypothesized that neuroendocrine carcinoma predominantly arises from endocrine precursor cell clones that are dedifferentiated from adenocarcinoma components (14-18). In the present case, the primary tissue of the EGC was mainly differentiated adenocarcinoma. However, the metastatic tissue had significant neuroendocrine components. In addition, the Ki-67 index was high in the metastatic lymph node, whereas it was lower in small areas of the ESD-resected specimen. Thus, in the present case, it was considered that sampling detected an initial transition from adenocarcinoma to neuroendocrine carcinoma and supported the abovementioned hypothesis.
Although the early detection and treatment for gastric neoplasms has increased in accordance with the progression of endoscopic techniques, the early detection of MANEC is extremely rare. Some patients who have undergone ESD for early-stage gastric MANEC were diagnosed with MANEC based on a pathological examination after ESD (11, 12, 14, 18). However, in the present case, because the neuroendocrine carcinoma components were extremely small throughout the lesion, we could not identify them in the pathological examination after ESD. If immunohistochemical staining had been performed to detect neuroendocrine carcinoma, it might have been possible to identify neuroendocrine carcinoma components during the pathological examination. However, it is impractical to perform immunohistochemical staining to evaluate all cases of ESD. In addition, neuroendocrine cells are not always immunoreactive to specific markers, with reported positivity rates being 60-70% for chromogranin A, 75-90% for synaptophysin, and 50% for CD56.

Neuroendocrine carcinoma is extremely malignant, and the 5-year survival rate is approximately 25% (10-12, 17). Because components of neuroendocrine cells are often located in the submucosal layer or deeper layers, neuroendocrine carcinoma is often found at an advanced clinical stage. Neuroendocrine carcinoma that has invaded the submucosal layer or deeper tissues is reported to develop rapidly and metastasize in 50-100% of cases (12). Importantly, lymph node metastasis is more likely to occur in tumors with higher malignancy (17). A few cases of lymph node metastasis have been reported in patients with early-stage disease (11, 12, 14, 15). Because it frequently involves vascular invasion, metastasis occurs in the lymph nodes or the liver, even during the early stages of the disease. In one case involving a patient who was diagnosed with MANEC after ESD, the patient died at 18 months after ESD due to multiple lymph node and distant metastases (19). In that case, the invasion of neuroendocrine carcinoma components into the submucosal layer, positive lymphovascular invasion, and a Ki-67 index of >30% were observed. In contrast, neuroendocrine carcinoma components were only present in the mucosal layer and there was no lymphovascular invasion in our case. If a pathological examination of the ESD specimen shows that the tumor consists of endocrine cells, then multimodal therapy, including additional surgical resection and chemotherapy, is recommended. The optimal chemotherapy regimen has not been established; however, combination chemotherapy is generally used for small cell cancer (10-12). Regardless, in our case, it was difficult to identify the neuroendocrine component after ESD and it the risk of metastasis was assumed to be low; however, lymph node metastasis occurred at 26 months after ESD.

In conclusion, we encountered a rare case of lymph node metastasis of MANEC that was discovered after curative ESD using the expanded pathological criteria. MANEC was considered to be difficult to diagnose in the postoperative pathological examination and to predict lymph node metastasis. Similar cases—especially cases involving differentiated-type gastric cancer, SM1—should therefore be followed while using CT and carefully evaluating the tumor marker levels.

**Author's disclosure of potential Conflicts of Interest (COI).**

**References**


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