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

Tadashi Ochiai, Masaki Ominami, Yasuaki Nagami, Shusei Fukunaga, Takahiro Toyokawa, Hirokazu Yamagami, Tetsuya Tanigawa, Toshio Watanabe, Masaichi Ohira, Masahiko Ohsawa and Yasuhiro Fujiwara

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

(Intern Med 57: 2837-2842, 2018)
DOI: 10.2169/internalmedicine.0311-17)
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 adenocarcinoma. Because no lymph node or distant metastasis was detected by computed tomography (CT), the lesions were resected en bloc by ESD. In the pathological examination, immunohistochemical staining with Desmin, D2-40, and Victoria 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 muscularis 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 abdominal CT showed enlargement of an infrapyloric (no. 6) lymph node (Fig. 2a). 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) showed the abnormal 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 examination revealed no local recurrent tumor at the site of ESD in the stomach. A histopathological examination revealed that the tumor consisted of endocrine cell carcinoma and adenocarcinoma. Adenocarcinoma cells were predominant in the metastatic lymph node (Fig. 3a-c). The neuroendocrine markers (chromogranin A, synaptophysin, and CD 56) were all immunohistochemically positive, the Ki-67 index was 90%, and the metastatic tissue had significant adenoneuroendocrine components, which comprised >30% of the tumor (Fig. 3d-f). Thus, the diagnosis was MANEC. The initial ESD specimens were reviewed because 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 curvature of the antrum (Fig. 4a-c). A neuroendocrine marker examination indicated that the patient was negative for chromogranin A and synaptophysin but partially positive for CD56 (Fig. 4d-f). The Ki-67 index of the broken glandular structures was 25%. How-

Figure 1. a: Esophagogastroduodenoscopy showed a 15-mm depressed lesion (type 0-IIc) limited to the mucosa without ulceration located on the lesser curvature of the antrum. b: Esophagogastroduodenoscopy showed a 25-mm depressed lesion (type 0-IIc) limited to the mucosa without ulceration located on the greater curvature of the middle corpus of the stomach. c, d: Magnified endoscopy with narrow band imaging showed a well-demarcated line with irregular microvascular and microsurface patterns.
Figure 2. a: Abdominal computer tomography detected enlargement of the infrapyloric (no. 6) lymph node at 26 months after endoscopic submucosal dissection. b: $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography showed abnormal accumulation in the same spot.

Figure 3. a: The macroscopic appearance of the metastatic lymph node. b: The adenocarcinoma component in the metastatic lymph node. c: The endocrine cell carcinoma component in the metastatic lymph node. d: The specimen was immunohistochemically positive for synaptophysin. e: The specimen was immunohistochemically positive for chromogranin A. f: The specimen was also immunohistochemically positive for CD56.

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 $<500 \, \mu m$ (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 predominantly differentiated adenocarcinoma, SM1, with poorly differentiated components and ulceration, one case fulfilled the expanded 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 (10).

MANEC is a rare tumor of the gastrointestinal tract (11-13). 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 (14). 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 (15-19). 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 tissue, 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 (12, 13, 15, 19). 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% (11-13, 18). 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 (13). Importantly, lymph node metastasis is more likely to occur in tumors with higher malignancy (18). A few cases of lymph node metastasis have been reported in patients with early-stage disease (12, 13, 15, 16). 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 (20). 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 (11-13). 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).

Tetsuya Tanigawa: Employment, EA Pharma. Toshio Watanabe: Employment, EA Pharma. Yasuhiro Fujiwara: Employment, EA Pharma; Research funding, Ono.

References
1. Gotoda T, Yanagisawa A, Sasaki M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 3: 219-225, 2000.
2. Hiratsuka T, Gotoda T, Miyata S, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 12: 148-152, 2009.
3. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 20: 1-19, 2017.
4. Hashi N, Ono H, Boku N, et al. A non-randomized confirmatory trial of an expanded indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a): the Japan Clinical Oncology Group study (JCOG0607). Gastric Cancer 21: 114-123, 2018.
5. Oda I, Oyama T, Abe S, et al. Preliminary results of multicenter questionnaire study on long-term outcomes of curative endoscopic submucosal dissection for early gastric cancer. Dig Endosc 26: 214-219, 2014.
6. Suzuki H, Oda I, Abe S, et al. High rate of 5-year survival among patients with early gastric cancer undergoing curative endoscopic submucosal dissection. Gastric Cancer 19: 198-205, 2016.
7. Oya H, Gotoda T, Kinjo T, et al. A case of lymph node metastasis following a curative endoscopic submucosal dissection of an early gastric cancer. Gastric Cancer 15: 221-225, 2012.
8. Abe S, Oda I, Nakajima T, et al. A case of local recurrence and distant metastasis following curative endoscopic submucosal dissection of early gastric cancer. Gastric Cancer 18: 188-192, 2015.
9. Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 14: 101-112, 2011.
10. Martelli D, Pineto E, De Stefano A, et al. Clinical utility of CEA, CA 19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer. Am J Surg 181: 16-19, 2001.
11. Levi Sandri GB, Carboni F, Vallee M, Visca P, Garofalo A. Mixed adenoneuroendocrine gastric carcinoma: a case report and review of the literature. J Gastric Cancer 14: 63-66, 2014.
12. Fukuba N, Yuki T, Ishihara S, et al. Gastric mixed adenoneuroendocrine carcinoma with a good prognosis. Intern Med 53: 2585-2588, 2014.
13. Yamasaki Y, Nasu J, Miura K, et al. Intramucosal gastric mixed adenoneuroendocrine carcinoma completely resected with endoscopic submucosal dissection. Intern Med 54: 917-920, 2015.
14. Neuroendocrine neoplasms. In: WHO classification of tumours of the digestive system. 4th ed. Bosman FT, Carneiro F, Hruban RH, Theise ND, Eds. International Agency for Research on Cancer, Lyon, 2010: 64-68.
15. Sakatani A, Shinzaki S, Hayashi Y, et al. A case of gastric mixed adenoneuroendocrine with difficulty in diagnosis before endoscopic submucosal dissection. Nihon Shokakibyo Gakkai Zasshi 113: 1909-1915, 2016 (in Japanese, Abstract in English).
16. Muto M, Muto M, Ichiki K, et al. A case of mixed adenoneuroendocrine carcinoma of the stomach. Nihon Shokakibyo Gakkai Zasshi 113: 1769-1776, 2016 (in Japanese, Abstract in English).
17. Nishikura K, Watanabe H, Iwafuchi M, et al. Carcinogenesis of gastric endocrine cell carcinoma: analysis of histopathology and p53 gene alteration. Gastric Cancer 6: 203-209, 2003.

18. Shen C, Chen H, Chen H, et al. Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. BMC Gastroenterol 16: 111, 2016.

19. Takeshita H, Sakuramoto S, Takee K, et al. Diminutive type III gastric carcinoid with regional lymph node metastasis: a case report. Journal of Kyoto Prefectural University of Medicine 123: 355-361, 2014 (in Japanese, Abstract in English).

20. Higuchi T, Koyanagi K, Aiura K, et al. A case of mixed adenoneuroendocrine carcinoma of the stomach. Progress of Digestive Endoscopy 82: 140-141, 2013.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).