

Metachronous liver and bone metastasis from small early gastric carcinoma without lymph node involvement: A case report

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Abstract. A 65-year-old man was referred to our Hospital for examination of gastric cancer initially diagnosed by medical check-up. Esophagogastroduodenoscopy demonstrated a superficial depressed-type gastric cancer in the antrum, and abdominal computed tomography showed no evidence of distant metastases. A tumor measuring 11 mm in diameter was removed by endoscopic submucosal dissection (ESD). Since histological examinations of ESD specimens showed a well-differentiated adenocarcinoma invading the submucosal layer with lymphatic invasion, the patient subsequently underwent laparoscopy-assisted distal gastrectomy with regional lymph node dissection, resulting in no residual carcinoma and no lymph node metastasis. The patient developed solitary liver metastasis one year later and was treated with trastuzumab plus capecitabine/cisplatin since results of the immunohistochemical analysis of the resected specimens demonstrated overexpression of the human epidermal growth factor receptor 2 (HER2). The patient was alive 12 months after surgical resection of the liver metastasis and subsequently developed bone metastasis. Controversy remains over the role of HER2 status as a prognostic factor in gastric cancer. However, it has been generally reported that HER2 overexpression correlates with aggressive biological behavior and poor prognosis. HER2 overexpression is a potentially useful predictive factor for tumor recurrence and poor prognosis even in early gastric cancer cases.

Introduction

Early gastric cancer (EGC) is defined as the presence of a lesion confined to the mucosa or submucosa, regardless of the presence of regional lymph node metastasis, and has a

good prognosis with appropriate treatment (1). Although the outcome of patients with EGC following curative surgery is excellent, cancer recurrence is a rare event and could occur even after curative gastrectomy with an incidence of 1.4-2.7% (2-5).

Endoscopic resection with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is widely accepted as the standard treatment for EGC without lymph node metastasis and enables a clinician to resect a target lesion en bloc (6,7). Most EGC confined to the mucosa can be curatively treated by endoscopic resection, since lymph node metastasis is rare in such cases. Endoscopic resection is currently considered appropriate for the treatment of intestinal-type gastric cancer cases without central ulceration that are <2 cm in diameter, according to guidelines for EMR/ESD established by the Japanese Gastric Cancer Association (7). However, gastrectomy with lymph node dissection should be performed in patients with submucosal invasion with or without margin involvement following endoscopic resection (8,9).

In this study, a case of metachronous liver and bone metastasis after laparoscopy-assisted distal gastrectomy is described, following initial treatment by ESD for small EGC without lymph node metastasis, showing human epidermal growth factor receptor 2 (HER2) overexpression. All diagnostic procedures and therapy concerning the patient were performed after obtaining written informed consent.

Case report

A 65-year-old man was referred to our hospital for examination of gastric cancer initially diagnosed by medical check-up. The patient's medical and family history were unremarkable. The laboratory findings were almost within normal range, as were levels of serum carcinoembryonic antigen and cancer antigen 19-9. Esophagogastroduodenoscopy (EGD) demonstrated a superficial depressed-type gastric cancer in the antrum that proved to be a well-differentiated adenocarcinoma on biopsy (Fig. 1). Abdominal computed tomography (CT) demonstrated no evidence of distant metastases and endoscopic ultrasound (EUS) identified tumor invasion of the antral mucosa.

Following a clinical diagnosis of EGC confined to mucosa, ESD was performed. The macroscopic findings of the resected specimen showed that the tumor was an irregularly shaped

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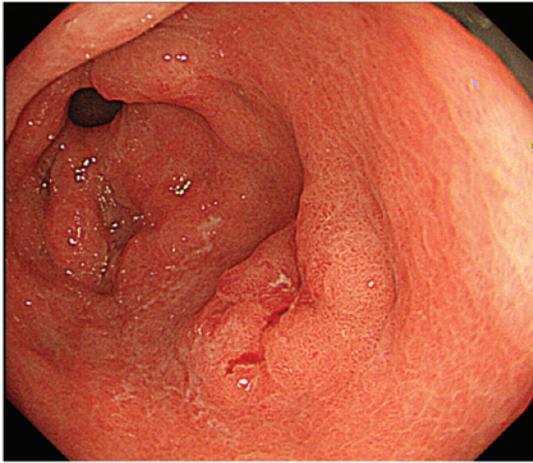


Figure 1. Esophagogastroduodenoscopy showing a small superficial depressed lesion in the antrum of the stomach.

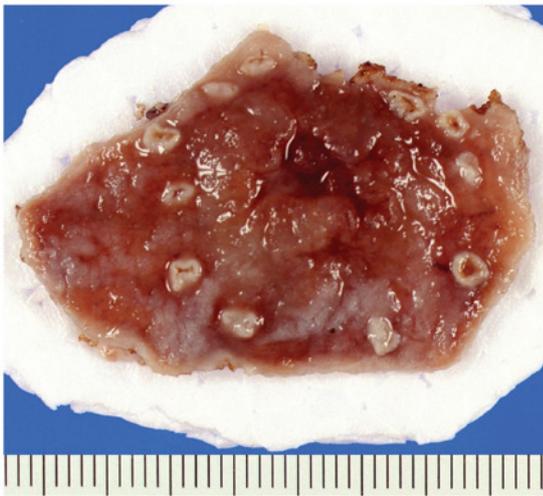


Figure 2. Macroscopic appearance of the resected specimen by endoscopic submucosal dissection showing an irregularly shaped depressed lesion, 11 mm in diameter.

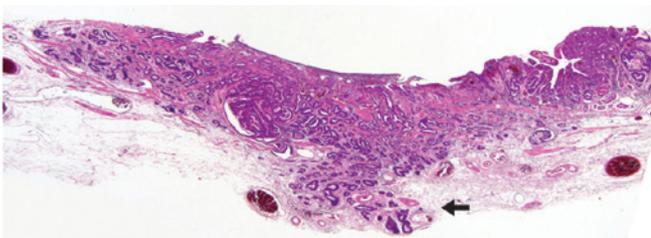


Figure 3. Hematoxylin and eosin-stained section of the gastric tumor demonstrating deep submucosal invasion of a well-differentiated adenocarcinoma in the center of the lesion (arrow).

depressed lesion, 11 mm in diameter (Fig. 2). Histological analyses revealed that the tumor was a well-differentiated adenocarcinoma that had invaded the submucosal layer to a depth of $>500 \mu\text{m}$ at the center of the lesion with positive lymphatic and negative venous invasion (Fig. 3). Therefore, according to the extended criteria for endoscopic resection,



Figure 4. Abdominal computed tomography scan showing a 4.8-cm mass in the liver, which demonstrated strong enhancement following intravenous administration of contrast material (arrow).

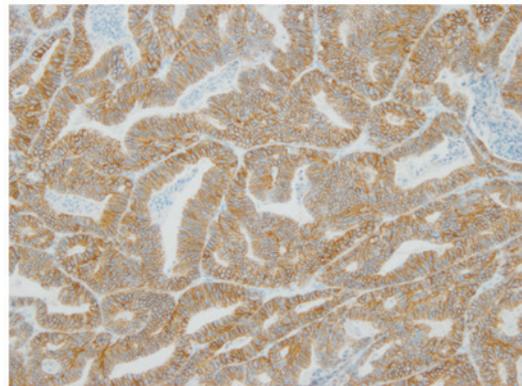


Figure 5. Specimen of the metastatic liver tumor showing strong basolateral membranous HER2 immunoreactivity in a well-differentiated adenocarcinoma, scored as 3+.

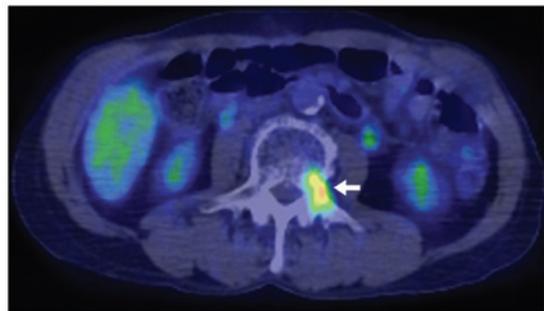


Figure 6. ^{18}F -2-deoxy-2-fluoro-D-glucose positron emission tomography combined with computed tomography imaging (FDG-PET/CT) image showing intense FDG uptake in the third lumbar vertebrae (arrow).

the patient underwent laparoscopy-assisted distal gastrectomy with regional lymph node dissection, resulting in no residual carcinoma and no lymph node metastasis. The post-operative course was uneventful, and the patient was discharged on post-operative day 14.

The patient underwent periodic follow-up physical examinations, and 1 year after the operation, abdominal CT showed a ring-enhanced, well-defined mass measuring 4.8 cm in diameter located in the liver (Fig. 4). Since there was no evidence of further metastatic lesions in other organs, the patient

underwent surgical resection of the liver tumor. Histological examination confirmed the diagnosis of a well-differentiated adenocarcinoma originating from the previous gastric cancer and immunohistochemical analysis of the tumor showed strong reactivity for HER2 (Fig. 5). Therefore, the patient was administered trastuzumab in combination with chemotherapy consisting of capecitabine plus cisplatin.

However, eight months after the second operation, the patient developed metastasis of the third lumbar vertebrae, which was detected using ¹⁸F-2-deoxy-2-fluoro-D-glucose positron emission tomography combined with CT imaging (FDG-PET/CT) (Fig. 6). Therefore, the patient was treated with trastuzumab plus irinotecan/docetaxel and was alive 12 months after the second operation.

Discussion

Solitary liver metastasis from EGC after curative gastrectomy is rare, with a reported incidence of 0.4-0.7%. A significant correlation between liver metastasis from gastric cancer that has invaded the submucosal layer and venous invasion has been reported (2,3,11). This clinical case emphasizes the risk of metachronous distant metastasis even after curative treatment for small EGC infiltrating the submucosa.

In the patient reported in this study, microscopic examination of a resected specimen by gastrectomy showed no residual cancer. Since endoscopic resection is generally performed using a coagulating device, the presence of cancer cells at the margins of the coagulated tissue, within the resected specimen and residual organ site, is unlikely. Therefore, in the present case, it is unlikely that cancer cells were present in the resected stomach following ESD. It has been reported that the rate of the residual tumor was 11.1% among cases where there was incomplete resection due to a positive vertical margin with submucosal invasion (10).

In general, lymph node metastasis is reported to be the most significant risk factor for the recurrence of EGC (2,3,11). Regarding the risk factors for liver metastasis, it has been reported that vascular involvement in the submucosal layer is significantly more important compared with nodal and lymphatic involvement (11,12). Furthermore, lymphatico-portal venous anastomosis due to mesenteric lymphatic occlusion is reportedly an important factor in the occurrence of liver metastasis of gastric cancer (13). Additional factors associated with cancer recurrence include lymphatic invasion, submucosal invasion, large tumor size, and a superficial spreading type (2,5,11). In contrast to these risk factors, the present EGC case was a small tumor of 11 mm in diameter without lymph node metastasis or venous invasion, although lymphatic invasion was positive. Despite the fact that these characteristics likely indicate a good prognosis, the overexpression of HER2 observed in this case may have increased the risk of metastasis, thus contributing to a poor prognosis.

Although HER2 overexpression has been reported to correlate with aggressive biological behavior and poor prognosis, there have been no universal conclusions regarding its significance as a prognostic factor (14-16). While certain studies have reported that HER2 overexpression is associated with a poor prognosis in gastric cancer, the impact of HER2 expression on patient survival is limited, particularly in earlier

stages of the disease (17,18). The present case emphasizes the need for including HER2 status as a risk factor for tumor recurrence even in EGC cases.

The recent development of chemotherapy and administration of novel molecular-targeted drugs for advanced-stage gastric cancer has provided clinical benefits and improved the survival rate of patients (19-21). Trastuzumab is the current standard of care for the treatment of HER2-positive early and advanced breast cancer (22). In a recent international phase III randomized controlled trial, the addition of trastuzumab to chemotherapy significantly improved overall survival compared with chemotherapy alone in patients with advanced gastric cancer (21). Therefore, trastuzumab in combination with chemotherapy could be considered as a novel standard option for patients with HER2-positive advanced or recurrent gastric cancer.

Liver resection for hepatic metastases from gastric carcinoma is, however, not a common procedure due to poor prognosis. Therefore, there is still no widespread agreement regarding surgical resection of synchronous or metachronous liver metastases from gastric cancer (23,24). In the present case, as the first recurrence was limited to the liver, surgical resection was the chosen treatment, followed by a chemotherapy regimen consisting of trastuzumab in combination with capecitabine plus cisplatin. However, in the present case, bone metastasis appeared despite complete removal and disappearance of the liver metastasis. Additional case reports are therefore needed in order for the poor prognosis of EGC recurrence to be improved.

Despite the generally excellent outcome of EGC patients following curative surgery, a strong malignancy potential remains, which is associated with an extremely poor prognosis even in cases of small-sized tumors. Therefore, clinicians should take this possibility into consideration in follow-up management after curative treatment to treat recurrent disease earlier. Determination of the HER2 expression status in addition to conventional pathological diagnoses, such as lymph node metastasis as well as lymphatic and venous involvement may be helpful in predicting the risk of EGC recurrence.

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