Multiple Gastric Metastases after Distal Pancreatectomy for Pancreatic Cancer

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Abstract:
A 67-year-old woman underwent distal pancreatectomy for pancreatic cancer. Recurrence in the form of lung metastasis was discovered eight months after surgery, and chemotherapy was initiated. Two years after the surgery, she was admitted for the evaluation of melena. Esophagogastroduodenoscopy revealed multiple subepithelial lesions with ulceration from the gastric body to the fornix. The histopathology of biopsy specimens was consistent with ductal adenocarcinoma, which appeared similar to the resected pancreatic cancer. The patient was diagnosed with multiple gastric metastases of pancreatic cancer. We herein report a case of pancreatic cancer with multiple gastric metastases that occurred after surgery for pancreatic tail cancer.

Key words: pancreatic cancer, pancreatic ductal adenocarcinoma, gastric metastasis, recurrence

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Introduction
Pancreatic ductal adenocarcinoma is the most lethal of the common human malignancies, with a 5-year overall survival rate of 10%. Surgery is the only curative treatment, but approximately 80-85% of patients have unresectable disease (locally advanced or metastatic) at the diagnosis (1). Furthermore, most patients who are able to undergo surgical resection experience tumor recurrence, even after achieving pathologically margin-free resection (1, 2). Pancreatic ductal adenocarcinoma most commonly metastasizes to the lymph nodes, liver, lung, and peritoneum. While direct tumor invasion to peripheral organs, including the gastrointestinal tract, occasionally occurs (3, 4), metastases to the stomach are rare.

We herein report a case of multiple gastric metastases that occurred after surgery for pancreatic tail cancer.

Case Report
A 67-year-old Japanese woman was referred to our hospital due to a pancreatic mass in August 2018. Laboratory tests were significant for increases in serum amylase (604 U/L; reference range: 44-132 U/mL) and carbohydrate antigen 19-9 (CA19-9; 269 U/mL; reference range: 0.0-37.0 U/mL). Contrast-enhanced computed tomography (CT) showed a 22-mm solid tumor with delayed enhancement in the pancreatic tail (Fig. 1). While the border of the tumor reached the splenic artery and vein, no other major blood vessels were involved. No direct invasion to peripheral organs was observed, and no distant metastases were found on either gadoxetic acid-enhanced magnetic resonance imaging or 18-fluorodeoxyglucose positron emission tomography. Screening esophagogastroduodenoscopy was unremarkable at this time. Endoscopic ultrasonography (EUS) showed a 30-mm hypoechoic, heterogeneous, lobular mass in the pancreatic tail. The patient was clinically diagnosed with resectable...
a 22-mm solid tumor with delayed enhancement in the tail of the pancreas (arrows). (a) Early phase. (b) Late phase.

Figure 2. Representative macroscopic image (a) and histologic images (b, c) of primary pancreatic invasive ductal carcinoma. (a) There was a 35-mm tumor (arrows). (b) Subserosal invasion of the tumor. No tumor exposure to the peritoneal cavity was noted (upper side) [Hematoxylin and Eosin (H&E) staining, objective lens ×2], (c) Poorly differentiated tumor component (H&E staining, objective lens ×4).

Pancreatic tail cancer, cT3N0M0 stage IIA, according to the 7th edition of Japanese Pancreatic Society staging system (5).

Distal pancreatectomy was performed in September 2018 without preoperative EUS-guided fine-needle aspiration (EUS-FNA) due to the risk of needle tract seeding. Histologically, the tumor was determined to be invasive ductal carcinoma of the pancreas, moderately to poorly differentiated, and 35 mm in maximum diameter. The tumor showed lympho-vascular, neural, and splenic arteriovenous invasion with massive subserosal invasion, but no peritoneal exposure was observed (Fig. 2). According to the 7th edition of Japanese Pancreatic Society staging system, the tumor was categorized as pT3pN1aM0, stage IIB. The patient had no postoperative complications and was discharged 12 days after surgery.

The patient received adjuvant chemotherapy with S-1 from October 2018 to February 2019 (6), but recurrence of multiple lung metastases was observed in June 2019. Combination chemotherapy with gemcitabine and nab-paclitaxel was introduced as first-line chemotherapy (7). Due to the progression of her lung metastases, second-line modified FOLFIRINOX therapy was introduced in December 2019 (8). Following central venous port infection that required port removal, 5-fluorouracil and leucovorin were replaced with S-1 in January 2020 (9). In March 2020, follow-up CT revealed an asymptomatic pulmonary embolism and deep vein thromboses, so rivaroxaban was started. In late July 2020, CT showed that pulmonary thrombosis had disappeared, but the progression of lung metastases and peritoneal dissemination in the pelvis were observed. Therefore, fourth-line chemotherapy with gemcitabine and erlotinib combination therapy was started from early September 2020 (10, 11).

In mid-September 2020, the patient presented to the emergency department complaining of melena. While vital signs were normal, laboratory tests revealed a decrease in hemoglobin from 8.9 g/dL one week prior down to 6.9 g/dL (reference range: 11.6-14.8 g/dL). CA19-9 had increased from 1,718.6 U/mL to 19,974.6 U/mL in the period of 1 month, while carcinoembryonic antigen increased slightly to 6.8 ng/mL (reference range: 0.0-5.0 ng/mL). Contrast-enhanced CT showed multiple mildly-enhancing gastric masses in the middle and upper thirds of the stomach (Fig. 3a). Some of the masses protruded into the gastric lumen, with the largest mass observed in the posterior wall of the stomach body.
Figure 3. Computed tomography of multiple gastric metastases. (a) Contrast-enhanced computed tomography showed multiple gastric masses in the middle and upper thirds of the stomach (arrows). (b) A gastric body mass showed ring-like enhancement (arrowhead).

Figure 4. Endoscopic view of multiple gastric metastases. Esophagogastroduodenoscopy revealed subepithelial lesions with apical ulceration in the gastric body and fornix (arrows). (a) White-light imaging. (b) Indigo carmine spraying imaging.
measuring 35 mm. One of the masses with a diameter of 6.5 mm appeared to be limited to the submucosal layer and showed ring-like enhancement (Fig. 3b). None of the tumors protruded from the serosal side into the peritoneum. There was no other obvious source of bleeding. While pulmonary metastases and disseminated nodules in the pelvis had increased in size, no liver metastases, lymph node metastases, or disseminated nodules around the stomach were detected.

Esophagogastroduodenoscopy revealed non-atrophic gastric mucosa with multiple subepithelial lesions accompanied by apical ulcers in the gastric body and fornix (Fig. 4). Gastric biopsy specimens showed irregularly shaped fusing glands with intraluminal necrotic debris, which were consistent with metastasis of pancreatic cancer (Fig. 5). There was no intraepithelial neoplasm of gastric surface epithelium. Immunohistochemistry revealed the same staining patterns as primary pancreatic cancer for MUC5AC, CK19, and CA19-9 (Fig. 6). As a result, the patient was diagnosed with multiple gastric metastases of pancreatic cancer.

Fig. 7 summarizes the clinical course of this patient. Rivaroxaban was discontinued, and palliative radiotherapy was performed to achieve hemostasis (30 Gy/10 Fr). The patient opted for best supportive care and was discharged 40 days after admission, dying at home 1 month later at 26 months after pancreatic surgery.

**Discussion**

According to large autopsy studies, hematogenous metastases to the stomach only occur in 0.2-5.4% of cancer patients. The most common primary tumors are lung cancer, breast cancer, and malignant melanoma (12, 13). While pancreatic ductal adenocarcinoma has come to exhibit various metastatic patterns since recent advances in therapy have improved its prognosis (14-16), the most common metastatic sites of pancreatic cancer are the lymph nodes, liver, lung and peritoneum (3, 4). Hematogenous metastasis of pancreatic cancer to the stomach is extremely rare. Oda et al. found only 2 cases of gastric metastasis in 209 autopsies (0.96%) of pancreatic cancer patients (13).

Possible mechanisms of secondary gastric involvement from pancreatic ductal adenocarcinoma are direct invasion, intraoperative seeding, tumor seeding by EUS-FNA, hematogenous metastasis, lymphatic metastasis, and intraluminal or intramural dissemination (17). It is sometimes difficult to distinguish between direct invasion and hematogenous metastasis when the tumor exists in the stomach wall for pancreatic body or tail cancer (18). In the present case, histology of the surgical specimen confirmed that there was no peritoneal exposure of adenocarcinoma cells. Because serial CT showed no lymph node metastases or dissemination around the stomach, gastric metastasis via the hematogenous route was strongly suggested. Our case also demonstrated the most common endoscopic and contrast-enhanced CT

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**Figure 5.** Histologic image of the gastric biopsy specimen. Cancer cells with round nuclei and eosinophilic cytoplasm formed irregularly shaped and fused glands, more suggestive of metastasis from pancreatic cancer than primary gastric cancer (Hematoxylin and Eosin staining, objective lens ×20).

**Figure 6.** Immunohistochemistry for the gastric metastatic lesion (a-d) and primary pancreatic cancer specimens (e-h). Both specimens were positive for MUC5AC (b and f), CK19 (c and g), and CA19-9 (d and h). Scale bars: 100 μm.
Table. Reports of Gastric Metastasis from Pancreatic Cancer.

| Reference | Year | Age | Sex | Location of PC | Diagnosis of PC | Location of GM | Endoscopic findings | Other metastatic sites | Therapy of GM | Pathological findings | Outcome |
|-----------|------|-----|-----|----------------|----------------|----------------|--------------------|---------------------|--------------|---------------------|---------|
| (20)      | 2005 | 49  | F   | Body           | 1 year after surgery | PW of fornix | SEL (delle-) | Liver (disappeared for chemotherapy) | Partial gastrectomy | Wel | NA |
| (18)      | 2016 | 72  | M   | Tail           | First presentation | Upper body and antrum | SEL (delle-) | Liver, lymph nodes | Chemotherapy | NA | Died 5 months after first presentation. |
| (21)      | 2018 | 58  | M   | Tail           | 4 years after surgery | Antrum | SEL (delle-) | None | Partial gastrectomy | Mod | No recurrence for 13 months after partial gastrectomy |
| (22)      | 2019 | 71  | M   | Body           | 1.4 years after surgery | PW of LC of body and AW of antrum | SEL (delle-) and mucosal irregularity | Gallbladder | Total gastrectomy | Wel | Recurrence 7 months after second surgery |
| (23)      | 2021 | 74  | F   | Head           | First presentation | Antrum | Erosion | None | Chemotherapy | Por | Died 2 months after first presentation. |
| Our case  | 67   | F   | Tail| 2 years after surgery | From middle body to fornix | SEL (delle+) | Lung, peritoneum | Radiation therapy | Mod-por | Died 26 months after surgery |

M: male, F: female, PC: pancreatic cancer, GM: gastric metastasis, PW: posterior wall, LC: lesser curvature, AW: anterior wall, SEL: subepithelial lesion, wel: well-differentiated, mod: moderately-differentiated, por: poorly-differentiated, NA: not available

findings of subepithelial lesions (13) and ring-like enhancement (19) for hematogenous gastric metastasis. We speculated that the basic mechanism of hematogenous metastasis was metastasis via the liver or lung, and indeed, our case had previous lung metastases. However, local hematogenous metastasis might have been possible, since cases without these metastases have been previously reported.

English-language publications were systematically searched in MEDLINE published between 1996 and 2021 using the medical terms of “pancreatic cancer”, “adenocarcinoma”, “gastric metastasis”, and “metastatic gastric tumor”. There are only five full case reports of gastric metastases from pancreatic cancer (Table) (18, 20-23). Unlike hematogenous metastases from other primary cancers, which tend to occur in the upper and middle thirds of the stomach (12, 13), four patients had lesions in the antrum. In general, hematogenous metastases, such as liver and lung metastases, become more common with reduced distance between the primary tumor and caudal pancreas (3). This tendency has also been observed in gastric metastases from
pancreatic cancer. Two patients had liver metastases, of which one experienced complete disappearance of the liver metastasis due to chemotherapy when gastric metastasis was confirmed. No previous reports except for our case had lung metastases. Two other patients had isolated metastases to the stomach, which were difficult to differentiate from primary gastric cancer. Interestingly, one patient had metastatic recurrence in the gallbladder in addition to the stomach. Although two relatively large series of metastatic gastric tumors reported that the most frequent symptom requiring endoscopy was upper gastrointestinal bleeding (12, 13), the present case was the only one in which gastrointestinal bleeding was the presenting symptom after gastric metastasis. The present case was also the only one with ulcerated lesions. This may be due to the fact that the primary pancreatic cancer was a poorly differentiated adenocarcinoma and that the patient had a longer clinical course than patients in previous reports.

Treatment for gastric metastases involved chemotherapy in two cases (18, 23) and surgery in three cases (20-22). While the benefits of surgical resection for recurrent pancreatic cancer remain unclear, it may serve a palliative role when bleeding, obstruction, or perforation is observed. Palliative radiotherapy is another alternative to achieve hemostasis in locally advanced or recurrent inoperable gastrointestinal tumors. Although most published studies are retrospective and involve gastric cancer, radiotherapy appears to be a well-tolerated, effective option (24). However, the optimal dose fractionation has not yet been established, and re-bleeding is known to occur in approximately one-third of patients (25).

Conclusions

We experienced a case of multiple gastric metastases 26 months after distal pancreatectomy for pancreatic cancer. Gastrointestinal metastasis should be considered when signs of gastrointestinal bleeding are observed during follow-up for pancreatic cancer.

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

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