

Pancreatic Metastasis from Gastrointestinal Stromal Tumor of the Stomach: A Case Report

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We report the first documented case of pancreatic metastasis from a gastrointestinal stromal tumor of the stomach. A 42-year-old Japanese man presented with severe abdominal discomfort. Computed tomography of the abdomen showed a huge heterogeneous mass consisting of cystic and solid components in the left upper abdomen. ¹⁸F-Fluorodeoxyglucose positron-emission tomography revealed high tracer uptake in the abdominal mass. After total gastrectomy with lymphodectomy was performed, a hard mass was palpated in the pancreatic tail. The pancreatic tumor was also resected under the therapeutic strategy. Histological examinations of the resected gastric and pancreatic specimens revealed that both tumors consisted of uniform spindle cells with a fascicular growth pattern and were immunohistochemically positive for CD34 and CD117/KIT. Gene sequencing analysis of DNA from each tumor revealed an identical deletion of 21 nucleotides in exon 11 of the gene *KIT*. On the basis of these results, we concluded that the pancreatic tumor was a metastatic tumor from the gastrointestinal stromal tumor of the stomach. (J Nippon Med Sch 2016; 83: 133–138)

Key words: gastrointestinal stromal tumor, stomach, pancreatic metastasis, gene sequencing analysis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract but are rarely malignant tumors of the digestive tract, accounting for 0.1% to 3.0% of all gastrointestinal neoplasms^{1–5}. Gastric GISTs metastasize most often to the liver and peritoneum but rarely to the pancreas, but a solitary pancreatic metastasis is extremely difficult to differentiate from a primary pancreatic GIST. To our knowledge, surgical resection of a solitary pancreatic metastasis from a GIST has not previously been reported. We describe the first documented case of pancreatic metastasis from a GIST of the stomach.

Report of a Case

A 42-year-old Japanese man was admitted to our hospital because of severe abdominal discomfort. His medical and family histories were unremarkable. On physical exami-

nation, a huge, elastic, hard mass was palpable in the left hypochondriac region. The results of laboratory tests were within normal ranges.

Double-contrast barium gastrography showed a well-demarcated filling defect in the greater curvature of the gastric body (**Fig. 1a**). Computed tomography of the abdomen with intravenous contrast material revealed a huge heterogeneous mass, approximately 15 cm in greatest diameter, containing cystic and solid components in the left upper quadrant of the abdomen. The mass compressed the spleen and the pancreas (**Fig. 1b**). Positron emission tomography revealed high uptake of ¹⁸F-fluorodeoxyglucose in the left upper quadrant, with standardized uptake values of 9.0 and 2.9, respectively (**Fig. 1c**). Upper gastrointestinal endoscopy revealed a narrowed gastric lumen with normal gastric mucosa. Endoscopic ultrasonography showed a heterogeneous hypoechoic tumor that had arisen from the muscularis

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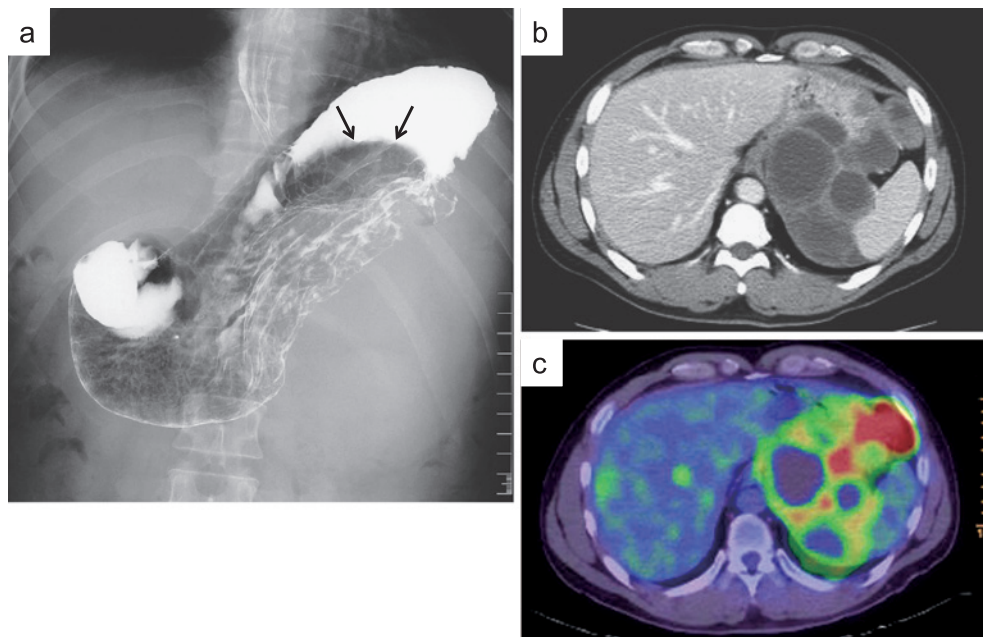


Fig. 1 Gastrography showed a large filling defect on the posterior wall of the gastric body (**black arrows**) (a). A preoperative, postcontrast, computed tomographic scan of the abdomen shows a large heterogeneous lesion occupying most of the left upper quadrant of the abdominal cavity (b). An ^{18}F -fluorodeoxyglucose-positron emission tomographic image shows considerable ^{18}F -fluorodeoxyglucose accumulation in the large heterogeneous lesion at the same level as shown by the computed tomographic scan (c).

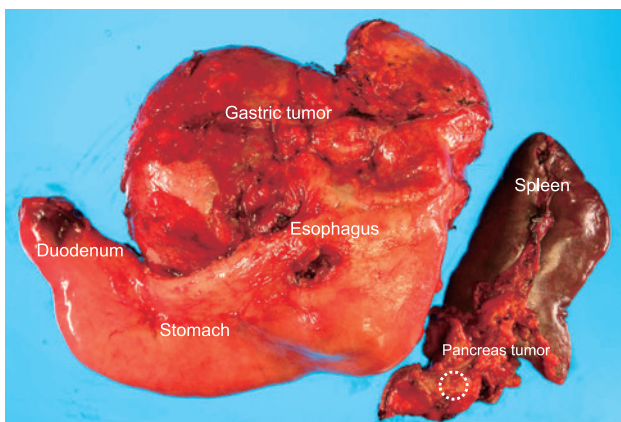


Fig. 2 Macroscopic findings of the resected specimen. A huge submucosal tumor developed on the posterior wall of the stomach as an extrinsic tumor. A solid tumor arising in the pancreatic tail was unexposed on the surface of the pancreas.

propria in the body of the stomach. We strongly suspected that the tumor was a primary GIST of the stomach.

To eliminate the severe symptoms of abdominal fullness, tumor resection was indicated as an emergency oncological treatment. On intraoperative abdominal exploration, the tumor was found to have arisen from the pos-

terior wall of the stomach, with no apparent invasion of adjacent organs. Total gastrectomy with lymphodec-tomy was performed without tumor rupture.

After the huge gastric tumor was removed, a hard, solid mass was palpated in the tail of the pancreas and suspected to be a malignant tumor. Distal pancreatec-tomy with splenectomy was therefore performed. Macro-scopic examination of the resected specimen showed a large, irregular gastric mass, measuring 19×23 cm and extending mainly from the greater curvature to the poste-rior gastric wall of the stomach (**Fig. 2**). The surface of the pancreatic tumor was covered by grossly normal pancreatic parenchyma.

Pathological examination of the resected specimens stained with hematoxylin and eosin revealed that the gastric tumor consisted of uniform spindle cells with a fascicular growth pattern (**Fig. 3a**). The gastric tumor had a high mitotic index (greater than 5 mitoses per 50 high-power fields) and a high proliferation index (Ki-67/MIB-1 > 10%). Immunohistochemical examinations revealed that the tumor cells were positive for CD34 and CD117/KIT (**Fig. 3b, c**) and negative for α -smooth muscle actin and S-100 protein. These pathological features were con-sistent with those of the GIST of the stomach. The pan-

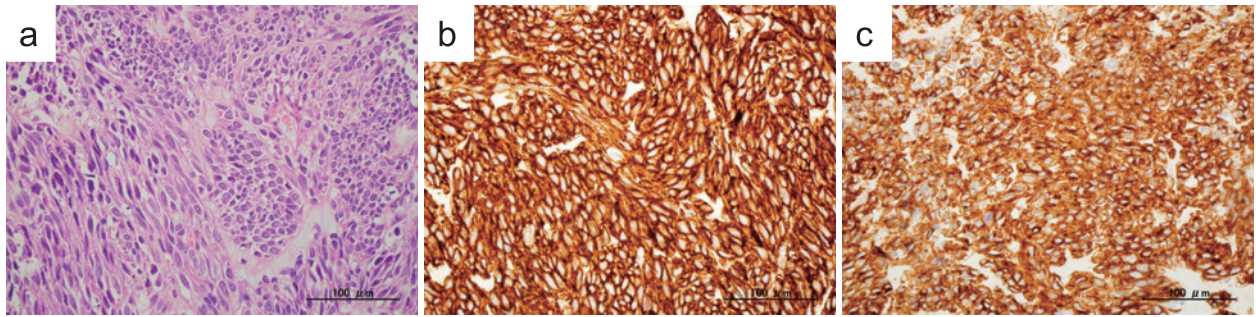


Fig. 3 Histopathological findings of the gastric tumor. The tumor consisted of uniform spindle cells with a fascicular growth pattern (a). (hematoxylin and eosin, $\times 400$) Immunohistochemical examination reveals diffusely positive staining for CD34 (b) and CD117/KIT (c) (CD34, $\times 400$; CD117/KIT, $\times 400$).

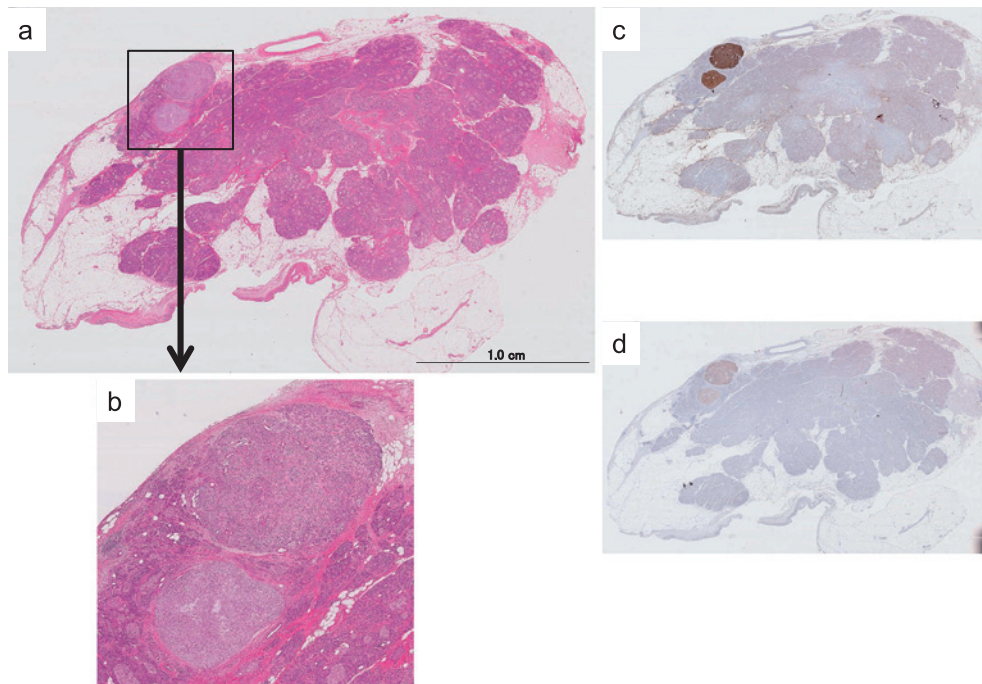


Fig. 4 Histopathological findings of the pancreatic tumor. The tumor was a well-circumscribed round lesion surrounded by normal pancreatic tissue in the pancreatic parenchyma (a, b). The tumor was positive for CD34 and CD117/KIT (c, d).

creatic tumor also showed similar spindle cells after being stained with hematoxylin and eosin and was well circumscribed and surrounded by normal pancreatic parenchyma (Fig. 4a, b). The pancreatic tumor was positive for both CD34 and CD117/KIT (Fig. 4c, d) and was negative for Wilms' tumor 1, cytokeratin, and pancreatic endocrine markers, such as glucagon, insulin, gastrin, and somatostatin.

So that molecular biological examinations could be performed for differential diagnosis, the specific cells positive for CD34 and CD117/KIT were isolated from microscopic regions of both tumor specimens with microdissection techniques. The DNA isolated from each tu-

mor underwent mutational analyses of exons 9, 11, 13, and 17 of the gene *KIT* and exons 12 and 18 of the gene *PDGFRA* (platelet derived growth factor receptor alpha), known as common mutational hotspots for GIST, to identify gene variants. An identical deletion of 21 nucleotides (c. 1656–1675 del21GTATGAAGTACAGTGGAAAGGT) in exon 11 of *KIT* was detected in DNA from both tumors. The mutation was absent from uninvolved tissue of the patient (Fig. 5a, b, c). The gene sequencing analysis revealed that both the gastric and pancreatic tumor cells possessed an identical somatic mutation.

The postoperative course was uneventful. Postoperative adjuvant chemotherapy (imatinib mesylate, 400 mg/

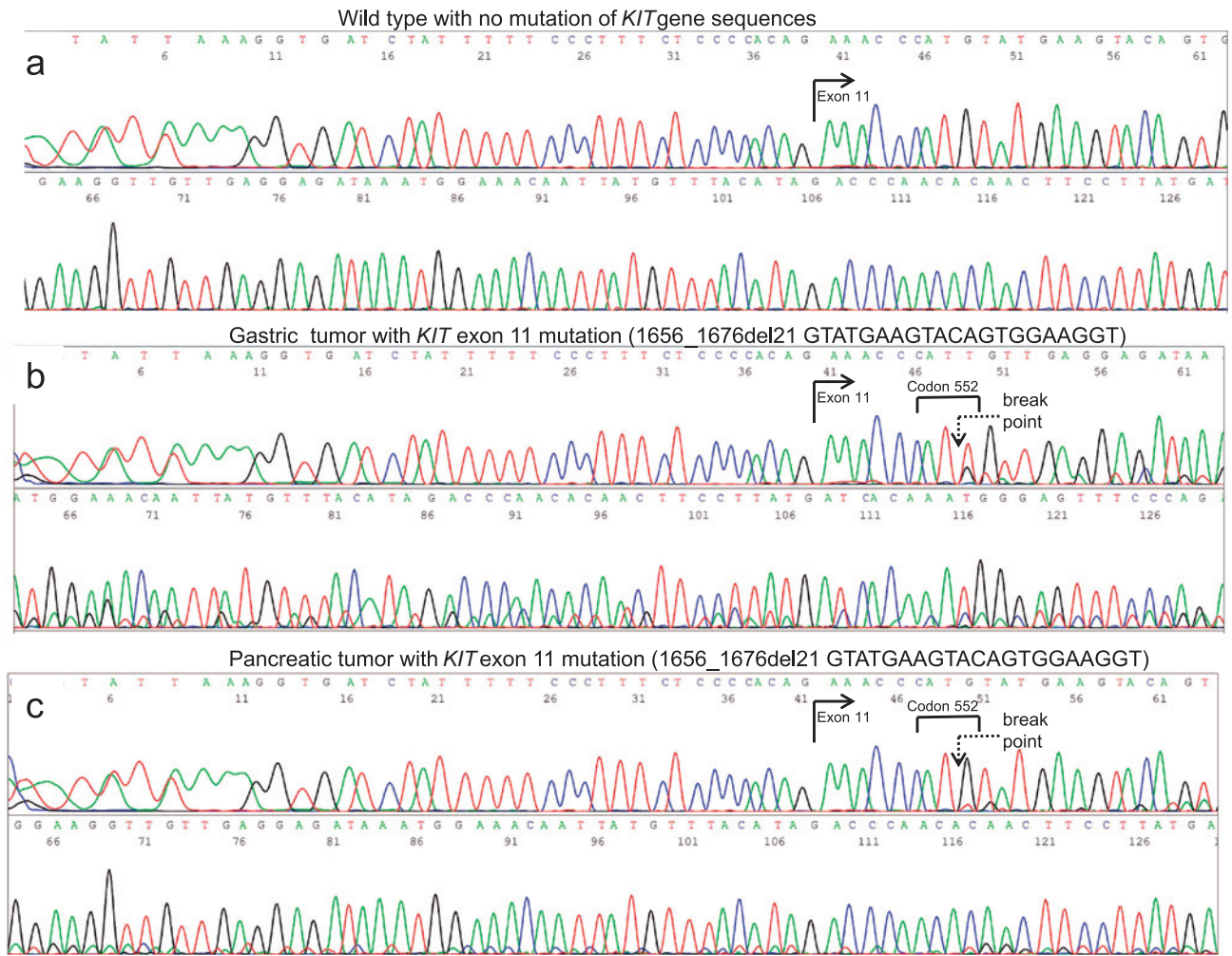


Fig. 5 A DNA sequence of chromosome in exon 11 of *KIT* gene shows wild type DNA sequence (a) and identical deletion of 21 nucleotides (c.1656–1675 del21 GTATGAAGTACAGTGGGAAGGT) in exon 11 in both gastric tumor DNA (b) and pancreatic tumor DNA (c).

day) was started 1 month after surgery. The patient has survived for more than 48 months after surgery without any evidence of recurrence or disease progression and continues to receive imatinib mesylate.

Discussion

The GISTs are known for their tendency to metastasize by way of both intraperitoneal dissemination and hematogenous routes^{6,7}. The most common hematogenous metastatic site of GISTs is the liver⁸. In contrast, the pancreas is not a common site of metastasis from a GIST of the stomach. We found no previously reported case of GIST metastatic to the pancreas in a MEDLINE search with the key words “gastrointestinal stromal tumor,” “pancreatic metastasis,” and “pancreas metastasis.”

Metastatic tumors account for less than 2% of all pancreatic malignancies. The most common primary origins

of metastases to the pancreas are renal cell carcinoma (62.6%); carcinomas of the colon (6.2%), lung (4%), and ovary (4.7%); sarcoma (7.2%); and melanoma of the skin (4%)^{9,10}. However, a previous study has found that at autopsy the most common primary tumor site of metastases to the pancreas is the stomach¹¹. In 2014 a retrospective study of 22 patients found that the malignancy most commonly metastasizing to the pancreas was gastric carcinoma¹². Therefore, gastric malignancies may metastasize to the pancreas more frequently than previously thought.

Histopathological examination of the gastric and pancreatic tumors in our patient revealed similar spindle cells that were diffusely positive for the GIST immunohistochemical markers CD34 and CD117/KIT. A primary GIST arising in the pancreas has been reported as an extragastrointestinal stromal tumor or extra-GIST¹³, and primary pancreatic tumors often cannot be differentiated

from metastatic tumors with currently available histopathological methods. We analyzed DNA sequences to investigate the genetic characteristics of both tumors and found an identical mutational pattern in exon 11 of *KIT* in DNA from both the gastric tumor and the pancreatic tumor. The molecular pathogenesis of GIST has generally been considered to result from expansion of a cell clone that has acquired an activating mutation in the *KIT* proto-oncogene¹⁴. A recent investigation of genetic mutations in primary and metastatic tumor cells has found that paired samples of primary colorectal cancer and metastases show consistent mutation patterns upon the mutational analysis of the gene *KRAS* (Kirsten rat sarcoma viral oncogene homolog)¹⁵. These findings support the notion that the primary GIST tumor and the metastatic pancreatic tumor in our patient had identical origins. On the basis of a comprehensive analysis of these clinical and biological factors, we concluded that the pancreatic tumor was a metastatic tumor from the GIST of the stomach.

Local recurrence and distant metastases have been reported to develop in more than 30% of patients with high-risk GIST despite apparently complete resection¹⁶. Most recurrences or metastases occurring after resection with a R0 margin of a high-risk GIST appear within 3 years after primary surgery. Adjuvant therapy with imatinib mesylate, a specific molecular inhibitor, is beneficial after the primary GIST is resected. Three years of adjuvant treatment with imatinib mesylate has been shown to improve recurrence-free survival and overall survival in patients with high-risk GISTs¹⁷. However, tumor sensitivity to imatinib has been reported to differ according to the location of the mutation¹⁸. The GISTs with exon 11 mutations of *KIT* are more than 10 times as sensitive to imatinib than are GISTs with mutations in other exons¹⁹. Identification of the causative mutation before starting imatinib treatment is thus considered clinically and economically beneficial in patients with GIST²⁰. In our patient, both the gastric and pancreatic GISTs had mutations of exon 11 in the *KIT* gene. The tumors were therefore expected to be sensitive to imatinib treatment. The patient has shown no sign of recurrence or disease progression for more than 4 years after surgery and continues to receive adjuvant treatment with imatinib.

In conclusion, we have reported an extremely rare case of gastric GIST with synchronous pancreatic metastasis that successfully responded to multimodality therapy. Our findings may be helpful for determining a multimodality treatment strategy and for developing new treat-

ment options for a case of GIST with such unusual metastases.

Conflict of Interest: The authors have no conflicts of interest to declare.

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