Author's response to reviews

Title: Neurofibromatosis type 1 (von Recklinghausen's Disease) with duodenal GIST that was difficult to distinguish from pancreatic neuroendocrine tumor: a case report

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A neurofibromatosis type I (von Recklinghausen’s Disease) with duodenal GIST that was difficult to distinguish from a pancreatic neuroendocrine tumor: a case report

Introduction: Gastrointestinal stromal tumor (GIST) is the most frequent nonepithelial tumor of the gastrointestinal tract. One important clinical problem is that GIST, especially the extramural growth-type, can be difficult to distinguish from other organ tumors. In 2005, Uchida reported an extramural GIST of the duodenum that had mimicked a pancreatic head tumor. Here, we report a very rare case of duodenal GIST with extramural growth mimicking a pancreatic neuroendocrine tumor. In this case, the GIST was also associated with neurofibromatosis type 1 (NF1; also known as von Recklinghausen’s Disease). This report is the first description of a duodenal GIST with NF1 in which the radiological findings resembled those of a pancreatic neuroendocrine tumor.

Case presentation: A 60-year-old Japanese woman with a history of NF1 was admitted to our hospital for the treatment of a pancreas tumor. She had no symptoms, but an abdominal ultrasonography screening examination had revealed a hypoechoic mass in the pancreas head. Laboratory data, including tumor markers, were within the normal ranges, and the insulin and glucagon levels were also within the normal range; however, the plasma gastrin level was slightly elevated at 580 pg/mL (30 – 150 pg/mL). A computed tomography examination revealed a hypervascular tumor measuring 14 mm in diameter in the pancreas head. We diagnosed the patient as having a pancreatic neuroendocrine tumor and performed a tumor resection with a duodenal wedge resection. The microscopic findings revealed the presence of spindle cell tumors in a trabecular pattern. Thus, the tumor was finally diagnosed as a duodenal GIST of the uncommitted type.

Conclusion: Extramural growth-type GIST can be very difficult to distinguish from other organ tumors. In this case, a duodenal GIST was very difficult to distinguish from a pancreatic neuroendocrine tumor based on radiological findings. When hypervascular lesions that have adhered to the gastrointestinal tract are identified, the possibility of an extramural growth-type GIST as a differential diagnosis should be considered in patients with NF1.

Introduction

Gastrointestinal stromal tumor (GIST) is the most frequently occurring nonepithelial tumor of the gastrointestinal tract. One important clinical problem is that GIST, especially the extramural growth-type, can be difficult to distinguish from other organ tumors. In particular, duodenal extramural GIST is especially difficult to distinguish
from pancreatic tumor. In 2005, Uchida first reported an extramural gastrointestinal stromal tumor of the duodenum that had mimicked a pancreatic head tumor [1]. Here, we present a rare case of a duodenal extramural growth-type GIST that was also associated with neurofibromatosis type 1 (NF1; also known as von Recklinghausen’s Disease). NF1-associated gastrointestinal lesions include not only GIST, but also hyperplastic lesions of intestinal neural tissue and its supporting structures and endocrine cell tumors of the duodenum and periampullary region [2]. The present case was very rare and was very difficult to distinguish from a pancreatic neuroendocrine tumor based on the radiological findings and etiological features.

Case presentation

A 60-year-old Japanese woman with a history of rheumatoid arthritis and NF1 was admitted to Yokohama City University Hospital for the treatment of a pancreas tumor. She had no symptoms, but an abdominal ultrasonography screening examination had revealed a hypoechoic mass in the pancreas head. Laboratory data, including tumor markers, were within the normal ranges, and the insulin and glucagon levels were also within the normal range; however, the plasma gastrin level was slightly elevated at 580 pg/mL (30 – 150 pg/mL). A computed tomography examination revealed a hypervascular tumor measuring 14 mm in diameter in the pancreas head (Figure 1). Magnetic resonance imaging (MRI) also revealed a massive tumor in the pancreas head. A duodenal endoscopy revealed that the duodenal lumen was not compressed by the extraluminal tumor, and endoscopic retrograde cholangiopancreatography (ERCP) findings showed that the main pancreatic duct was not stenosed or blocked. We diagnosed the patient as having a pancreatic neuroendocrine tumor and planned to perform a tumoral enucleation from the pancreas. A whitish elastic hard nodule was easily removed from the pancreatic parenchyma, but the tumor was connected to the duodenal wall via a stalk. Consequently, we performed a tumor resection with a duodenal wedge resection. As a small whitish nodule was also found in the jejunum during the initial operation, a segmental jejunectomy was also performed. A histological examination of frozen sections of these tumors revealed spindle cells with connective tissues. Thus, we diagnosed the patient as having multiple GISTs and did not perform a more radical resection. Macroscopically, the resected specimens consisted of solid and hard masses that were connected to the duodenal and jejunal walls but not to the pancreas head parenchyma. Microscopically, this neoplasm originated from the muscularis propria of the duodenum wall and consisted of spindle cells in a trabecular pattern without necrosis (Figure. 2). Fewer than five mitoses per 50 high-power fields were observed. Immunohistochemically, both tumors were
diffusely positive for KIT (Dako Cytomation, Copenhagen, Denmark) (Figure 3), while the duodenal tumor was focally positive and the jejunal tumor was diffusely positive for CD34 (Nichirei, Tokyo, Japan). Both tumors were negative for smooth muscle actin (Dako Cytomation) and S-100 (Nichirei). We finally diagnosed the tumors as duodenal and jejunal GISTs of uncommitted type. These GISTs are regarded as being very low risk according to the National Comprehensive Cancer Network (NCCN) guidelines [3]. The patient has remained healthy without any recurrences after surgery for two years.

Discussion

GISTs are the most frequently occurring nonepithelial tumor of the gastrointestinal tract. Based on the recent discovery that GIST and the intestinal cell of Cajal (ICC) express CD34 and the type III receptor tyrosine kinase (TK) named KIT, GISTs are now considered to develop from ICC or to differentiate into ICC. Most GISTs carry mutations in the proto-oncogene \( c\text{-}kit \), which when translated constitutively activates KIT kinase; this gain-of-function mutation in the \( c\text{-}kit \) gene is considered to be the cause of GISTs [4]. The small intestine is the second most common primary site for GISTs after the stomach. Miettenen et al. [5] reported that duodenal GISTs most frequently involve the second portion of the duodenum, followed by the third portion, fourth portion, and first portion. They also reported that many tumors are comprised of a gross ulceration of the mucosa, with a component that bulged underneath the mucosa, forming a partly intramural mass with a centrally ulcerated umbilication. In the present case, the tumor exhibited only extramural growth, and no specific intramural change in the duodenum was present. These clinical features are very rare [5], so it was very difficult to distinguish the GIST from a pancreas tumor. Therefore, we first considered this tumor to be a neuroendocrine tumor in the pancreas head, based on its radiological and duodenal endoscopic findings [6]. CT studies indicated that GISTs are hypervascular and may have cystic and necrotic components combined with intramural and extramural tumor growth and signs of malignancy. Small tumors are depicted as sharply margined smooth masses with moderate contrast enhancement [7]. In this case, these radiological findings were typical of GISTs, but the extramural growth made it very difficult to distinguish the GIST from other types of tumors, especially pancreatic neuroendocrine tumor. Furthermore, the patient’s plasma gastrin level was slightly elevated. Consequently, we misdiagnosed this tumor as a gastrinoma. However, the immunohistochemical features of both tumors (duodenum and jejunum) were diffusely negative for gastrin. Furthermore, almost all gastrinomas are located in the “gastrinoma triangle”. We carefully examined this area, but no other
tumors were observed. After tumor resection, the plasma gastrin level did not change. The plasma gastrin level might have been slightly elevated in this case as a result of atrophic gastritis. In fact, an upper endoscopy and biopsy specimen revealed severe atrophic gastritis. Because of the absence of acid inhibition, the functional G cells were stimulated and gastrin secretion was increased [8].

NF1 is caused by a mutation of the $NF1$ gene, but the mutations are quite heterogeneous and the diagnosis of NF1 is still based largely on clinical criteria. Many patients with NF1 suffer from GIST, as it occurs in approximately 11 – 25% of all NF1 patients [9]. Sporadic GISTs are most commonly found in the stomach and contain mutated kit or PDGER protein; point mutations in the $c$-$kit$ or $PDGFR$ genes have also been identified. On the other hand, NF1 associated with GIST is rarely associated with these mutations, and multiple GISTs are commonly found in the small intestine. Otherwise, the histologic and immunohistochemical differences between GISTs in NF1 patients and non-NF1 patients have not been fully clarified.

According to the NCCN guidelines [3], the GISTs in our case were associated with a very low risk and should be followed up every six months by CT. No obvious evidence exist that adjuvant chemotherapy for resected GISTs might prolong the post-operative survival times. Thus, the present case was not treated with adjuvant imatinib therapy but was followed up every six months using CT for two years. Fortunately, no new tumors have been observed.

The most important issue in surgical strategies for GIST is whether a complete resection can be achieved. A variety of surgical methods can be used to obtain a complete resection, such as duodenopancreatectomy, duodenal wedge resection, and segmental duodenal resection. But in this very low-risk group of completely resectable GISTs, tumor resection with a duodenal wedge resection and segmental jejunectomy might be suitable surgical methods.

NF1-associated gastrointestinal lesions include not only GISTs, but also hyperplastic lesions of intestinal neural tissue and its supporting structures and endocrine cell tumors of the duodenum and periampullary region [2]. In this case, a duodenal GIST was very difficult to distinguish from a periampullary endocrine tumor based on not only the radiological findings, but also the etiological features.

Conclusion

A very rare and difficult case of duodenal extramural GIST associated with NF1 is presented. Duodenal extramural growth GISTs are difficult to distinguish from pancreatic neuroendocrine tumors, especially in patients with NF1.