Hepatopancreatoduodenectomy for metastatic duodenal gastrointestinal stromal tumor

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BACKGROUND: **Duodenal gastrointestinal stromal tumors, which are rare, comprise 3%-5% of all gastrointestinal stromal tumors. We present a case of a metastatic duodenal gastrointestinal stromal tumor that was successfully treated by simultaneous right hemihepatectomy and pancreaticoduodenectomy.**

METHODS: **A 50-year-old woman was admitted to our department for the treatment of a possible metastatic duodenal gastrointestinal stromal tumor (GIST). At laparotomy a large duodenal tumor was found displacing the head of the pancreas. A 3 cm in diameter lesion in the posterior aspect of segment VIII of the liver was also noted. Simultaneous right hepatectomy and pancreaticoduodenectomy were performed.**

RESULTS: **Histological examination revealed a high grade metastatic duodenal GIST strongly positive for c-kit, CD34, and vimentin. The patient had no additional therapy. A follow-up of 21 months showed that the patient is very well and there is no evidence of recurrent diseases.**

CONCLUSIONS: **Malignant stromal tumors of the duodenum are rarely encountered. They are usually slow growing, and may be amenable to curative surgery, even after occurrence of metastases. Resection of localized liver metastasis is still advocated when feasible, since imatinib does not provide a complete or long-term response. Combined surgical resection is an efficacious treatment for patients with metastatic duodenal gastrointestinal stromal tumor.**

(*Hepatobiliary Pancreat Dis Int 2006; 5: 147-150*)

KEY WORDS: **duodenal neoplasms; hepatectomy; pancreaticoduodenectomy; liver metastasis; gastrointestinal stromal tumor**

Introduction

Duodenal gastrointestinal stromal tumors (GISTs) are rarely encountered and comprise 3%-5% of all GISTs.[1] One third of the tumors are malignant, and the liver is the commonest site of metastases, followed by the peritoneum or omentum, while the lungs and bones are rarely involved.[1,2] GISTs are resistant to radiotherapy, and till recently have been chemoresistant. Surgical resection of the tumors remains the only chance of cure. These tumors are relatively slow growing and may be amenable to curative resection, even after they have metastasized. Combined resection of the primary tumor and localised liver metastases should be considered, if feasible.

Combined hepatopancreatoduodenectomy (HPD) is an uncommon operation that is mostly performed for the treatment of cholangiocarcinoma or gallbladder carcinoma.[3] To the best of our knowledge, only two cases of metastatic duodenal GIST have been treated by HPD with favourable outcome and prolonged survival.[3,4] The present case report describes a high grade metastatic duodenal GIST which was successfully treated by HPD.

Case report

A 50-year-old woman was referred to our department for the treatment of a metastatic duodenal GIST. She had had hysterectomy and surgery for varicose veins. Seven months ago she had undergone a local excision of invasive ductal carcinoma in her right breast, followed by adjuvant radiotherapy and administration of tamoxifen. Two months before, she suffered abdominal pain and vomiting. Physical examination and routine laboratory tests showed nothing abnormal, except a low hemoglobin level of 10.6 g/dl. Upper gastrointestinal endoscopy revealed a tumor involving the first and second portions of the duodenum; duodenal biopsy confirmed a GIST. Contrast-enhanced CT showed a well-defined mass 5 cm in diameter in the second part of the duodenum abutting the head of the pancreas (Fig. 1). A 3.5-cm lesion being consistent with a metastatic deposit involved segments VI and VII in the right posterior sector of the liver, but clearly encroached into the

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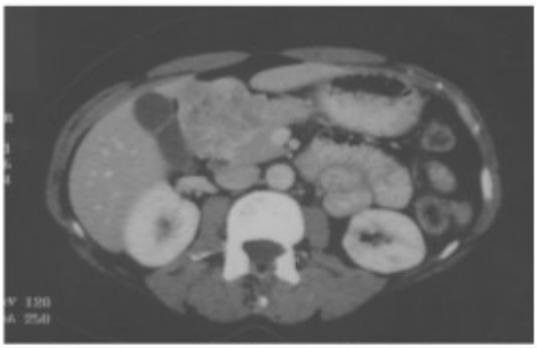

Fig. 1. CT scan image showing a large lobulated mass with well-defined margins, arising from the first and second parts of the duodenum.

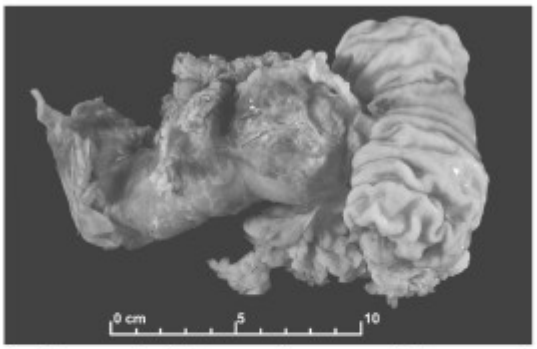

Fig. 3. Photograph of the posterior aspect of the resected specimen showing the relationship of the large tumor to the duodenum and head of the pancreas.

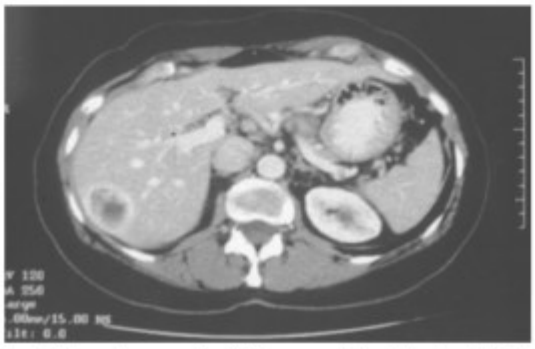

Fig. 2. CT scan image of a 3.5-cm metastasis in the right lobe of the liver.

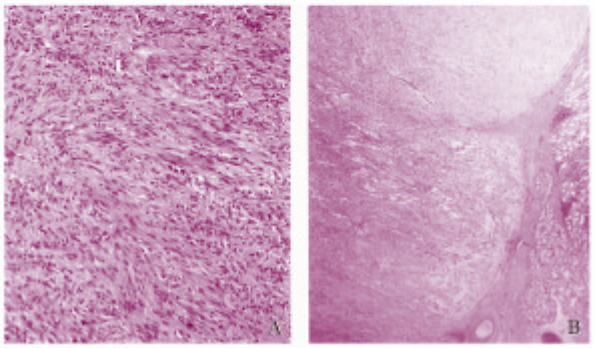

Fig. 4. Photograph of the hematoxylin and eosin stained slide of the specimen; **A**: low power view on the left showing the tumor arising from the muscularis propria of the duodenum, with a well-defined non-invasive margin abutting normal duodenal mucosa (HE, original magnification × 20); **B**: high power view on the right showing sheets of eosinophilic spindle shaped cells arranged in fascicles (HE, original magnification × 40).

right anterior sector (Fig. 2). A CT-guided core biopsy of the liver failed to confirm the suspicion of metastatic disease.

She was referred to Oxford for specialist opinion, and was advised to have an operation. Whipple's pancreaticoduodenectomy and right hepatectomy were performed simultaneously. At laparotomy the metastatic lesion was found to be centrally placed in the right lobe and involved mainly segment VIII. A two-layered end-to-side duct-to-mucosa pancreaticojejunostomy was constructed to an isolated biliopancreatic jejunal Roux limb.

Gross examination of tumor specimens revealed a large lobulated mass measuring 5.6 cm in maximum diameter, protruding through the posterior wall of the duodenum (Fig. 3). The tumor arose from the muscularis propria of the duodenum, and extended outwards and into the lumen, demonstrating a pushing rather than invading margin and displaced pancreatic tissue without infiltration. Histologically, the tumor showed two distinct cytological patterns: some areas of spindle shaped cells arranged in fascicles and whorls, and other areas of large vacuolated cells, often showing intense eosinophilic granular cytoplasm, arranged in a distinct epithelioid pattern. There were extensive areas of necrosis and cystic degeneration. The mitotic rate varied, but was high in some areas with up to 20 mitotic figures per 40 high power fields. None of the 18 lymph nodes recovered from the specimens showed evidence of metastases. Right hepatectomy revealed a single, subcapsular metastatic tumor measuring 3.4 cm. Both primary and metastatic tumors were clear of all resection margins, and perineural or vascular invasion was absent.

Immunohistochemistry showed a staining pattern that was characteristic of GIST. c-kit, CD34 and vimentin were strongly positive (Fig. 4). Markers for neuroendocrine differentiation (chromogranin and synaptophysin) or muscular differentiation (actin, desmin and myoglobin) were negative. Interestingly, many of the tumor cells stained positive for somatostatin.

The patient's postoperative course was complicated by Staphylococcal sepsis and hepatic encephalopathy. She was discharged from the hospital after 65 days, and did not receive adjuvant therapy because there was no evidence for the use of imatinib mesylate in that setting. The patient is doing well 21 months after the operation, with no evidence of recurrence on follow-up CT scans.

Discussion

Gastrointestinal stromal tumors are the most frequent mesenchymal tumors of the digestive tract. As a biologically distinctive tumor type, they are different from smooth muscle and neural tumors of the gastrointestinal tract.[5] A relationship has been proposed to the interstitial cells of Cajal.[6] Being rare, duodenal GISTs comprise 3%-5% of all GISTs.[1] Most of the tumors occur in the second part of the duodenum. They are usually single, but can be multiple, as in Carney's triad or when associated with neurofibromatosis. In order of frequency, the clinical manifestations of duodenal GISTs are occult or overt gastrointestinal bleeding, abdominal pain, a palpable mass, perforation and obstruction.[1]

Histologically, they comprise spindle, epithelioid or mixed cells, and may show a tightly packed architecture resembling a paraganglioma or carcinoid tumor.[1,5] There may be considerable heterogeneity within a tumor.[5] Expression of CD117 (the c-kit receptor present in interstitial cells of Cajal) is seen in almost all GISTs and is therefore considered to be their defining feature. Vimentin expression also seems to be a constant feature.[4,7] They are positive for CD34 and smooth muscle actin in 54% and 39% of cases, respectively.[5] In the present case, immunohistochemistry confirmed a GIST with no smooth muscle or neural differentiation.

GISTs have a wide clinicopathologic spectrum, ranging from small benign tumors to overt sarcomas. The majority of duodenal GISTs are clinically benign, but 35% have recurrence or metastasis.[1] It is difficult to determine their malignant potential and prognosis. It is now accepted that categorizing GISTs into low, intermediate and high-risk ones, based on an estimate of their potential for recurrence and metastases, is more appropriate than dividing them into the benign and malignant.[5] This risk is best estimated by the simultaneous evaluation of several parameters: size, location, invasion of adjacent organs, mucosal invasion, degree of cellularity, cellular architecture, mitotic count, nuclear pleomorphism, necrosis, c-kit mutation, and proliferation rate.[8-11] Large tumors (>5 cm) with a high mitotic index (>50 mitotic figures per 50 high power fields), a common definition of high grade sarcoma, commonly metastasize.

Complete surgical resection is presently the only means of cure.[12] Systematic lymph node dissection is not thought to be necessary, as lymphatic dissemination is rare. The overall survival appears to be in parallel with the completeness of resection.[2,8,13] Every effort should be made to achieve a complete resection with clear margins, sometimes necessitating the removal of adjacent organs.

Metastases are the foremost determinant of a patient's prognosis, with a median survival of 14 months after the appearance of metastases.[4] Patients with isolated hepatic metastases can benefit from liver resection (an overall 3-year survival of 58%).[13] Shima et al[4] demonstrated that resection of liver metastases contributes to a prolonged survival. Repeated hepatectomies for recurrence of hepatic metastasis from a gastric GIST has also been reported.[14] However, HPD is an extensive operation that requires experience and skills; it carries considerable risk of mortality and morbidity. The largest series to date, from the Memorial Sloan-Kettering Cancer Center, gave an operative mortality of 18% for this operation.[3]

Approximately 50% of recurrences occur in the first year after resection.[11] Without evidence of recurrence at 21 months, our patient is well. However, she remains at risk of relapse, and is under close surveillance. The risk of late relapses necessitates a long-term follow-up.[1,12] Miettinen et al[1] noted that nearly all (86%) high-grade duodenal GISTs develop metastases and patients die from the tumor with a median survival of 21 months. Crosby et al[2] reported that 75% of their patients developed metastases and died with a median survival of 17.5 months. Even patients with histologically "benign" lesions and no detectable mitotic figures occasionally develop metastases at a later date.[2]

Imatinib mesylate, a potent inhibitor of c-kit, may have a therapeutic role in patients with advanced or metastatic GISTs. Early reports of this molecular targeted drug suggest good tolerance and appreciable antitumor activity.[15] Imatinib may extend the indications for surgery by downstaging patients with initially unresectable tumor. It may also contribute to the prevention of recurrence after resection.[4] The role of imatinib as adjuvant therapy is presently being evaluated.

In the last few years, research has been conducted into the responsiveness of GISTs to imatinib, showing that the type of c-kit mutation influences response to treatment with imatinib mesylate. Patients whose tumors express exon 11 mutant c-kit protein have a significantly better response rate to imatinib therapy (83%) than those patients whose tumors express either exon 9 mutant c-kit (47%) or contain no detectable mutation of c-kit or platelet-derived growth factor receptor alpha (PDGFRA) (0%). However it is associated with a longer overall survival. Not all GISTs without mutation of the c-kit receptor are resistant to imatinib mesylate. The sensitivity and response to therapy in these cases may be explained by the presence of PDGFRA mutations. A subgroup of GISTs lacks the c-kit mutation but displays a mutation of PDGFRA, which possesses intrinsic tyrosine-kinase activity.[16]

In conclusion, resection of localized liver metastases is still advocated when feasible, since imatinib does not provide a complete or long-term response.[11,17] HPD for

metastatic duodenal GIST is still the treatment of choice, and should be considered in all cases.

Funding: None.
Ethical approval: Not needed.
Contributors: SC proposed the article and wrote the first draft. SC and SZ performed a review of the literature. SZ and FPJ reviewed and revised the manuscript. PJ provided expert guidance and revised the pathological aspects of the manuscript. SC is the guarantor.
Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Received September 9, 2005
Accepted after revision December 10, 2005