Int J Clin Oncol (2009) 14:262–265
DOI 10.1007/s10147-008-0834-7

CASE REPORT

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Gastrointestinal stromal tumor of the stomach with extremely slow-growing hematogenous metastasis

Received: July 2, 2008 / Accepted: August 23, 2008

Abstract A 67-year-old woman underwent resection of a gastric tumor and a synchronous metastatic lesion of the liver in 1991. Histopathologically, both the primary and metastatic tumors were diagnosed as leiomyosarcoma. Four years after the initial resection, another liver metastasis was detected in the caudate lobe, and a partial hepatectomy was performed. Multiple bilateral lung metastases were identified 7 years later and one was resected. Immunohistochemically, tissues from both the primary and metastatic sites were positive for KIT and CD34, and a c-*kit* gene mutation was found in the resected lung lesion. The remaining lung metastases responded to treatment with imatinib mesylate, but the treatment was discontinued because of toxicity. The patient remains under observation and the lung lesions have not progressed. At present she has no symptoms, and she has had no further recurrences in the past 3 years. This case is extremely unusual; a slowly progressing gastrointestinal stromal tumor over the course of 17 years from the initial diagnosis, with hematogenous metastases at multiple sites.

Key words Gastrointestinal stromal tumor (GIST) · Liver metastasis · Lung metastasis ·Imatinib mesylate

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal malignancies of the gastrointestinal tract. Recurrence of a GIST is frequently associated with local recurrence or liver metastasis, but lung metastasis is rare.[1] We describe our experience with a patient with a primary GIST of the stomach who had a synchronous liver metastasis, followed by further liver metastases 4 years after the initial surgery, and metastatic recurrence in the lungs 11 years after the initial resection. It is extremely unusual for GISTs to progress slowly over the course of 17 years from the time of the initial diagnosis.

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Case report

The patient was a 67-year-old woman who noticed an abdominal mass in 1991. A computed tomographic (CT) scan revealed an intraabdominal tumor with liver metastasis (Fig. 1). Distal gastrectomy, transverse colectomy, and right hepatectomy were performed. Macroscopically, there was no residual tumor. The primary lesion arose in the posterior wall of the stomach and had central necrosis. The histological diagnosis for both the gastric tumor and the liver lesion was leiomyosarcoma. Four years after the surgery, an ultrasonographic examination of the abdomen revealed recurrent disease in the caudate lobe of the liver. Magnetic resonance imaging of the abdomen showed low signal intensity on T_1-weighted images in the caudate lobe (Fig. 2) and high signal intensity on T_2-weighted images. Caudate lobectomy was performed. Histopathological examination was consistent with a metastatic lesion from the original tumor.

A CT scan of the chest 11 years after the initial resection revealed multiple lesions in both lungs (Fig. 3). One of the tumors in the left lung was resected by video-assisted thoracoscopic surgery. Histological examination revealed the proliferation of spindle-like (Fig. 4A) or epithelioid mesenchymal tumor cells with low mitotic counts. Based on these findings, the previously resected tumor specimens from the primary site and the liver and lung metastases were reexamined. Immunohistochemically, all tumor specimens were positive for KIT and CD34, and negative for desmin and S100 protein. The MIB-1 labeling index was less than 5%

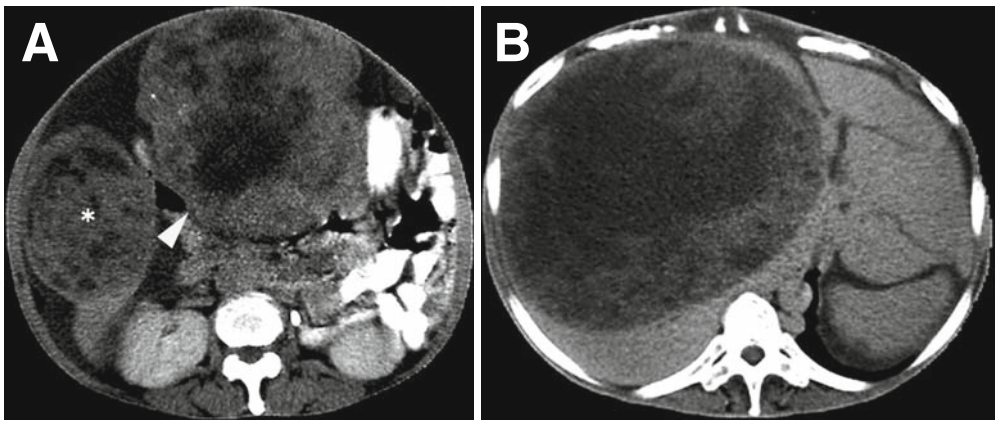

Fig. 1A,B. Computed tomographic (CT) scans of the abdomen. **A** Tumor with central necrosis was contiguous with the gastric wall (*arrowhead*). Liver metastasis was identified (*asterisk*). **B** Metastatic tumors were found in the right lobe of the liver

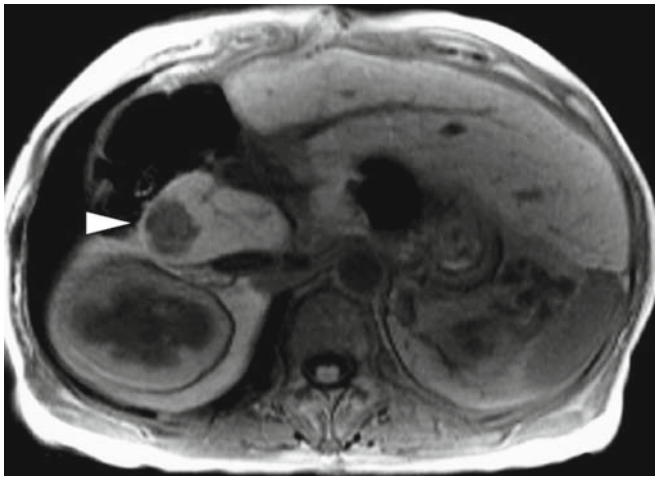

Fig. 2. Magnetic resonance imaging of the liver 4 years after the initial surgery revealed metastatic tumors with low signal intensity on T_1-weighted images in the caudate lobe of the liver (*arrowhead*)

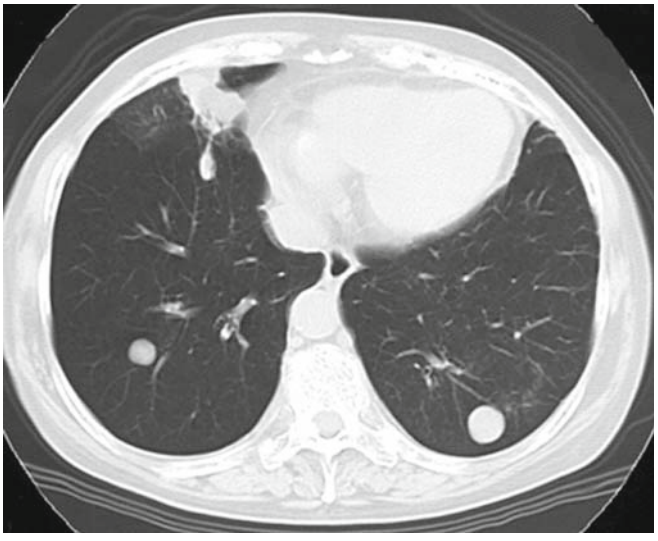

Fig. 3. CT scan of the chest 11 years after the initial surgery shows multiple metastases in both lungs

(Fig. 5B). Mutational analysis of the resected lung lesion revealed an in-frame deletion mutation in exon 11 of the c-*kit* gene (Fig. 6). These findings established a diagnosis of the tumor as GISTs in the stomach with metastases.

The patient was treated with Gleevec (imatinib mesylate, STI571; Novartis, Basel, Switzerland), which has been shown to be efficacious in the therapy of metastatic and unresectable GISTs. After a 3-month course of treatment, CT scan of the chest confirmed that the residual tumor had shrunk by 65%. The patient refused to continue treatment because of drug-related toxicity, and she remains under observation. Seventeen years after the initial diagnosis, there has been no further intraabdominal recurrence, and no change has been seen in the radiographic appearance of the lung metastases on routine follow up during the past 3 years (Fig. 7).

Discussion

Complete resection is the treatment of choice for primary GIST (National Comprehensive Cancer Network: http://www.nccn.org/), and adjuvant imatinib mesylate (IM) therapy is considered acceptable for high-risk patients, but it is not strongly recommended (http://www.cancer.gov/newscenter/pressreleases/GISTtrial). Pulmonary recurrence after radical resection of the primary disease is considerably rare, accounting for just 7% of all recurrences, while other sites of recurrence are more common, including the liver (63%) and local recurrence (52%).[1] The fact that pulmonary recurrence was detected 11 years after the first operation in our patient supports the concept that long-term follow up is needed for patients with GIST (or those previously diagnosed with leiomyosarcoma of the alimentary tract).

In patients with GIST or nonepithelial tumors, histopathological changes can be observed at metastatic sites, reflecting resistance to treatment.[2] The clinical course of the present patient was characterized by extremely slow tumor growth, despite the large tumor at the primary site and the repeated episodes of metastatic recurrence. Tissue from the primary lesion showed deposition of hyalinized collagen fibers and scattered foci of calcification without tumor

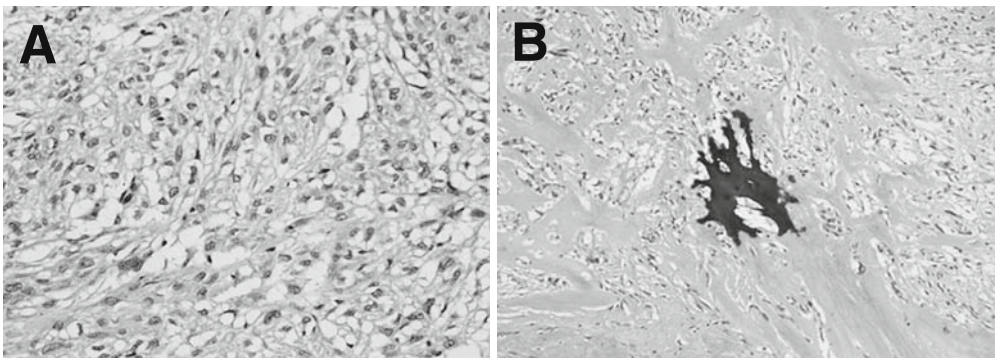

Fig. 4A,B. Histopathological findings of the gastric tumor. **A** Proliferation of spindle-like cells. **B** Hyperplasia and calcification of hyaline-like stroma. **A** H & E, × 400; **B** H & E, × 200

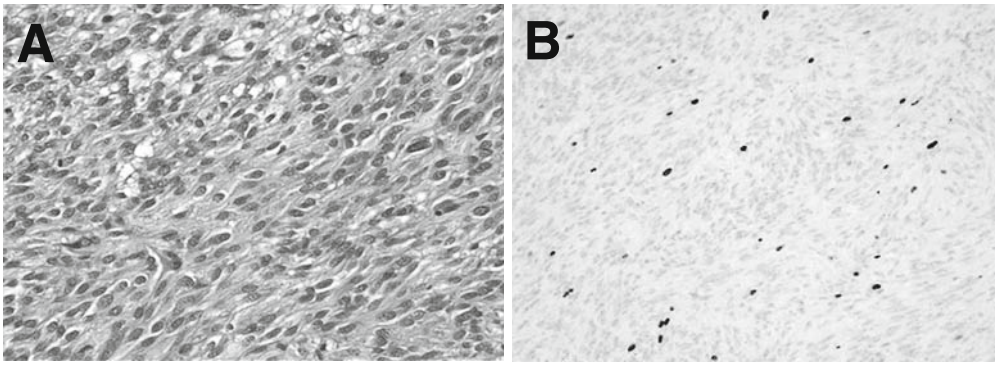

Fig. 5A,B. Immunohistochemical staining of metastatic lung tumor for c-kit and CD34. **A** Proliferation of spindle-like cells. **B** The MIB-1 labeling index was less than 5%. **A** H & E, ×400; **B** ×200

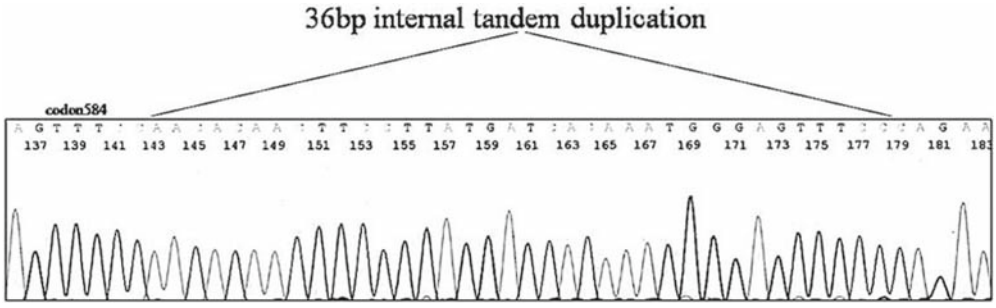

Fig. 6. Mutational analysis revealed a 36-bp internal tandem duplication in exon 11 of the c-*kit* gene

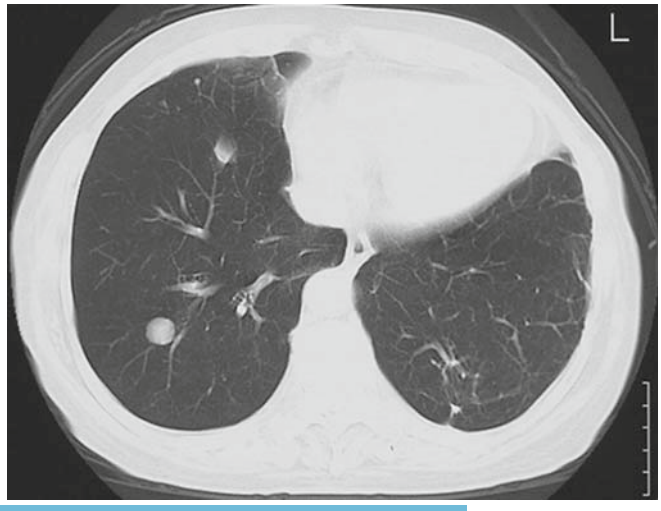

Fig. 7. The lung tumors have not progressed during the past 3 years

necrosis, and the MIB-1 labeling index of the tumor cells was low even at metastatic sites. These histological findings indicate low proliferative activity of the tumors at both the primary and metastatic sites.[3,4]

Guidelines for the treatment of GIST have been published in the United States,[5] and the European Union.[6] At present, IM has become the standard therapy for both tumor recurrence and metastatic disease. Tentative Japanese guidelines for the diagnosis and therapy of GIST indicate that surgical intervention for metastatic lesions is to be considered, if technically possible.[7] Mudan et al.[8] have reported that patients with a disease-free interval of less than 20 months have a poor prognosis and should not be treated surgically. Resection is reserved for those patients with recurrent disease and a prolonged disease-free interval. This suggests that IM, rather than surgery, is indicated for the management of recurrent disease in patients with a short disease-free interval.

Ballarini et al.[9] reported a case of metastatic GIST after a disease-free interval of 11 years. The primary tumor was 4 cm in diameter and had a low mitotic index (1/50 high-power fields). Despite the low malignant potential, a metastatic lesion was found in the liver after a disease-free interval of 11 years. This case emphasizes the variable nature of GISTs and the difficulty in predicting their metastatic risk. Matsuoka et al.[10] reported a case of liver metastasis from GIST almost 17 years after resection of the primary tumor. This is the longest reported disease-free interval between a primary GIST and metastasis;[10] the authors recommended that surgical resection of delayed liver metastasis from GIST should be considered. Inage et al.[11] described the resection of pulmonary metastasis from a GIST arising in the stomach. The operation was performed 10 years after gastrectomy for the primary tumor. As compared with the primary tumor, the metastatic tumor had greater cellular density and more prominent mitotic figures. Brain metastasis developed, and the patient died soon after the surgery, despite the prolonged disease-free interval. The outcome of that patient was considered to be more closely related to the biological malignant potential of the pulmonary metastatic tumor rather than that of the primary tumor. We should bear in mind that, in patients with GIST, even tumors with low mitotic activity can recur, and the metastatic lesions may have a higher malignant potential than the primary lesions. GIST is characterized by diverse sites of metastatic recurrence, variable times to recurrence, and a wide range of metastatic potential associated with the appearance of recurrent lesions.[12,13]

Multiple lung metastases should be treated with IM,[5–7] and our patient did respond to IM induction. According to a prospective randomized phase III study, IM should be continued (even in a patient with complete response) until there is progression of disease.[14] Although our patient refused to continue IM due to toxicity, the tumors have not become larger and she has remained asymptomatic for the past 3 years. Further treatment in this patient awaits the appearance of new agents or respiratory symptoms. In conclusion, we have reported here an extremely unusual case of GIST with slowly progressing multiple hematogenous metastases, and we have noted the treatment guidelines.

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