American Journal of
Experimental and Clinical Research

Am J Exp Clin Res 2014;1(1):11-15

Case Report

Complete response to imatinib mesylate treatment in jejunal leiomyosarcoma subsequently developing gastrointestinal stromal tumor and desmoids tumor

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Abstract. A unique case of a 50-year-old Japanese male with jejunal leiomyosarcoma (LMS) who subsequently developed gastrointestinal stromal tumor (GIST) and desmoid tumor (DT) during five years and six months after the initial surgery is reported. The patient was treated with surgery and oral imatinib mesylate and achieved a complete response. He is still under oral imatinib mesylate therapy. To the best of our knowledge, this is the first case of a LMS subsequently developing GIST and DT in the intestine. As imatinib mesylate targets both c-*KIT* and PDGFR and since LMS, GIST and DT share the expression of c-*KIT* and/or PDGFR, our patient has benefited from the continual treatment with imatinib mesylate. Furthermore, tyrosine kinase inhibitors may be a possible future treatment option for LMS associated with GIST and DT.

Keywords: Jejunal leiomyosarcoma, gastrointestinal stromal tumor, GIST, desmoid tumor

Introduction

Leiomyosarcoma (LMS) involving the jejunum is a very rare tumor and may even rarely occur with different types of malignant tumors, either synchronously or metachronously [1-3]. Furthermore, gastrointestinal stromal tumor (GIST) and desmoid tumor (DT; also known as deep or aggressive fibromatosis) are also two rare mesenchymal tumors. Occasional occurrence of both tumors in individuals has been reported [4-7]. Also, rarely the co-existence of leiomyosarcoma and GIST has been observed [1]. However, the development of GIST and desmoid tumor after gastrointestinal leiomyosacroma has not yet been reported.

The standard treatment for patients with resectable GIST is surgery with the goal of achieving complete resection. However, since the introduction of imatinib mesylate and achievement of complete response (CR), the use of imatinib mesylate has increasingly gained clinical acceptance.

We experienced a unique case of jejunal LMS which subsequently developed GIST and DT during five years and six months after the initial surgery. The patient was treated with imatinib mesylate and achieved CR and is still under oral imatinib mesylate therapy.

Case Report

A 50-year-old Japanese male with a chief complaint of lower abdominal pain visited the emergency room of our hospital in June 2001. Medical and family history was unremarkable. On physical examination, the abdomen was distended and rigid with severe tenderness in the lower or hypogastric area. Blood pressure was 124/98mmHg, pulse was 67/minutes, and body temperature was 38.8 ℃. Laboratory examinations showed an increase in the number of white blood cells (11800/μl) and CRP level (13.85mg/dl) and a SpO_2 of 97%. Other laboratory tests showed no abnormality.

Abdominal CT examination revealed a tumor of 6cm× 6cm large in the jejunum with fluid collection inside (Fig. 1 A). No ascites was present. With the diagnosis of diffuse peritonitis, the patient was hospitalized and underwent emergency surgery. At surgery, a round-shape tumor protruding from the end portion of the jejunum about 150cm from the ligament of Treitz and a jejunal perforation was explored and partial resection of the small intestine was performed. The resected specimen contained a large spherical tumor measuring 6.3 x 7.2 x 7.6 cm which was bisected into two halves and showed central necrosis (Fig. 1 B).

Hematoxylin and eosin stained section of the tumor showed sarcomatoid spindle type cells arranged in a fascicular pattern with atypical nuclei and nuclear polymorphism (Fig. 1 C). There was a high mitotic activity too (5 mitoses per 10 high-power fields). Histopathological and immunohistochemical findings were consistent with a diagnosis of jejunal LMS.

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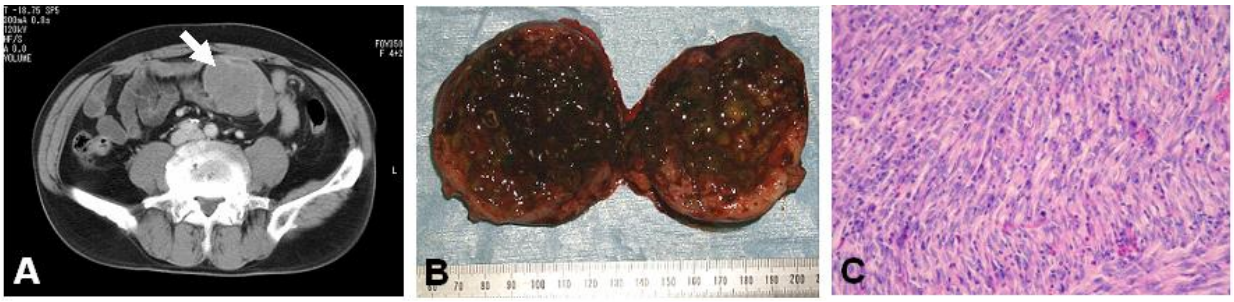

Figure 1 (A) Abdominal CT examination revealed a tumor of 6cm×6cm large in the jejunum with fluid collection inside (arrow). (B) The resected specimen was a large spherical tumor measuring 6.3 x 7.2 x 7.6 cm which was bisected into two halves and showed central necrosis. (C) Histopathological section of the tumor showed sarcomatoid spindle type cells arranged in a fascicular pattern with atypical nuclei and nuclear polymorphism consistent with leiomyosarcoma (Hematoxylin-eosin stain x200).

Postopetrative course was uneventful and the patient was discharged on postoperative day 26 and followed up regularly at outpatient clinic. Four years later on April 2004, a CT scan of abdomen was performed and an abdominal tumor (5cm in diameter) with uneven consistency and central necrosis was identified (Fig. 2 A). With the suspicion of local recurrence, the patient was scheduled for operation. In October 2004, the patient suddenly developed fever and abdominal pain and was underwent emergency surgery. At this second operation, there was purulent ascites and several tumors measuring approximately 5cm in diameter were found spreading in the peritoneal cavity (Fig. 2 B), among them some with different sizes. In addition, tumors of various sizes were found at different locations such as approximately 5cm, 3cm, and 7cm in diameter at about 80cm, 190cm, and 250cm respectively from the ligament of Treitz, and 15cm in diameter at sigmoid colon. Also there were tumors of approximately 1-2cm in diameter spreading in the peritoneum and mesentery. The patient received partial resection of the small intestine and removal of the sigmoid colon. The peritoneal and mesenteric tumors were removed as far as possible however minute-size tumors remained in the mesentery. Histopathological findings showed atypical cells and spindle-shaped atypical hyperplasia with necrosis and hemorrhage (Fig. 2 C). The results of immunostainings revealed positive c-kit (Fig. 2 D) and positive CD34 (Fig. 2 E) and negative α-SMA (Fig. 2 F) and negative S-100 protein (Fig. 2 G). The average mitotic figure was 5 per 10 /HPF. At this stage a diagnosis of GIST was made.

Postoperatively, the patient received oral imatinib mesylate and was regularly followed-up at outpatient clinic. In October 2006, an abdominal CT scan showed a suspected local recurrence which had tended to increase gradually during follow-up. On January 2007 the patient was hospitalized for surgery. On repeated CT scan, a soft tissue nodule measuring 6.3cm in diameter was seen in the mesentery (Fig. 3 A). MRI examination showed a mass of relatively large size (6.3cm in diameter) with low signal intensity in the mesentery at T1 and T2 weighted images (Fig. 3 B). The patient underwent surgery for the third time and laparatomy showed a mass in the mesentery portion of the small intestine at about 80cm from the ligament of Treitz. No intraperitoneal metastasis was found and partial resection of the small intestine was performed. The resected specimen showed a spherical mass of solid nature measuring 6.5cm×5.0cm×7.0cm with a smooth surface (Fig. 3 C). Histopathological findings showed diffuse growth of spindle-shaped fibroblasts and copious fine collagen fibers (Fig. 3 D) consistent with mesenteric DT (fibromatosis). Post-operative course was uneventful and the patient was discharged from the hospital in a satisfactory condition on day 32 after operation. The treatment with oral imatinib mesylate was continued and PET examination on June 2007 showed no evidence of tumor (Fig. 4). Follow-up abdominal CT scan taken at 6 months intervals was also negative for recurrence. Presently, the patient is on oral imatinib mesylate therapy.

Discussion

Leiomyosarcoma (LMS) involving the jejunum is a very rare tumor and may even rarely occur with different types of malignant tumors, either synchronously or metachronously [1-3]. Furthermore, gastrointestinal stromal tumor (GIST) and desmoid tumor (DT; also known as deep or aggressive fibromatosis) are also two rare mesenchymal tumors. Occasional occurrence of both tumors in individuals has been reported [4-6]. Also, rarely the co-existence of leiomyosarcoma and GIST has been observed [1]. However, the development of GIST and desmoid tumor after gastrointestinal LMS has not yet been reported. The standard treatment for patients with resectable GIST is surgery with the goal of achieving complete resection. Since the introduction of imatinib mesylate and achievement of complete response (CR), the use of imatinib mesylate has increasingly gained clinical acceptance.

LMS is the most common sarcoma that can develop in the small intestine, and occurs most frequently in the jejunum, ileum, and duodenum, respectively [7, 8]. The highest incidence of LMS is in the 6th decade, with a small preponderance in males [9]. The presenting symptoms may most likely be anemia and/or recurrent melena. Since small bowel tumors are not very common and rarely cause symptoms, a prolonged period may elapse before they are diagnosed [10]. Therefore, the tumors are frequently accompanied by complications, which LMSs expressed c-*KIT* proto-oncogen [11, 12]. However, they lacked KIT-activating mutation(s) in exon 11 or 17 of c-*KIT* [12].

GISTS are derived from the interstitial cells of Cajal [1]), and mostly occur in the stomach and small intestine

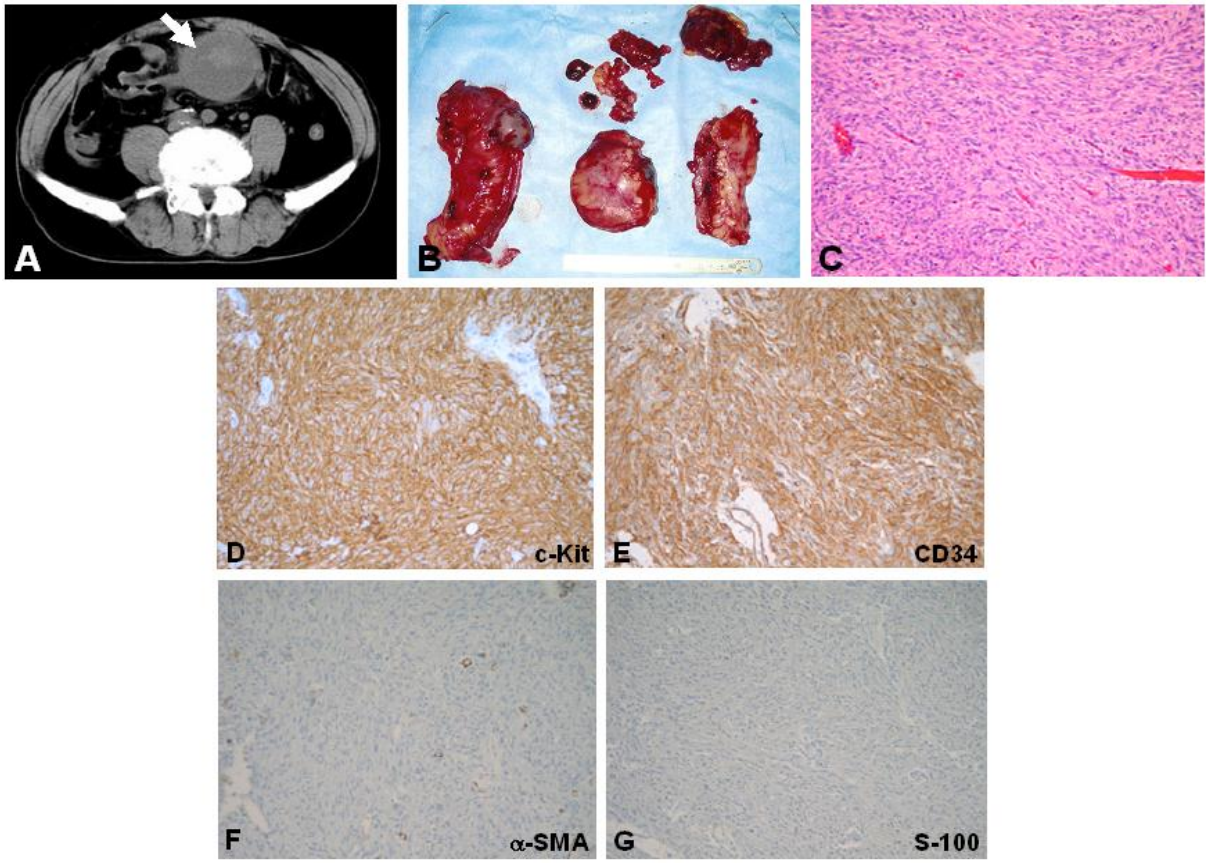

Figure 2 (A) CT scan of abdomen showed an abdominal tumor (5cm in diameter) with uneven consistency and central necrosis (arrow). (B) Resected tumors of various sizes which were found at different locations in the abdominal cavity. (C) Histopathological findings showed atypical cells and spindle-shaped atypical hyperplasia with necrosis and hemorrhage (Hematoxylin-eosin stain x200). Immunohistochemicalstainings revealed diffuse positive CD117 (c-*KIT*) (D) and positive CD34 (F), negative α-SMA (G) and negative S-100 protein (H) consistent with GIST (Original magnification x200).

and rarely involve rectum and esophagus. GISTs invariably show positive immunohistochemical reaction for c-*KIT* proto-oncogene [14] and sensitivity to imatinib mesylate, a receptor tyrosine kinase inhibitor [15, 16]. GISTs may coexist with different types of cancer, either synchronously or metachronously [17]. Recenly, patients with DT and GIST in the same anatomic location were reported [5]. DT is a very rare fibroblastic proliferation with a tendency for slow local infiltrative growth. It occurs sporadically or in association with Gardner's Syndrome and Familial Adenomatous Polyposis [18], and does not metastasize but can cause significant morbidity through their locally destructive effects. The treatment of resectable DT is mainly by complete surgical resection with a wide margin and/ or radiation therapy, however locally advanced DT may be treated by chemotherapy, anti-inflammatory agents and tyrosine kinase inhibitors.

Mutations in the *CTNNB1* gene, which encodes beta-catenin protein, have been found in the majority of DT patients, with most mutations occurring in exon 3 [19]. This finding have implicated an important role for the Wnt/beta-catenin signaling pathway in the development of DT thus the nuclear expression of beta-catenin has increasingly been used in the differential diagnosis of spindle cell neoplasms, particularly in the abdomen [20].

Patients with GIST may be liable to developing DT or patients with DT might be prone to GIST. Although there are no data to support a genetic predisposition for GIST and DT, a germ line mutation might underlie predisposition for these two tumors. The possibility that activated KIT or PDGFR pathway is involved in the development of DT must also be considered. The c-*KIT* expression was rarely found in DTs but both PDGFRs and their ligands were expressed [21]. However, gain-of-function mutations of c-*KIT* have not been found in DT tissues samples [6].

Our present case had undergone abdominal surgery to remove GIST and then developed a DT. Surgical trauma has been shown to induce desmoid growth. Interestingly, several reports investigating the use of imatinib mesylate for treating DT have been published and a series of 19 patients with DT showed a partial response in three patients [22]. Recent clinical data regarding the effectiveness of sorafenib in both GIST and desmoid tumors highlight a possible therapeutic option when medical treatment of both conditions is necessary [23].

Based on immunohistochemical results, GIST shows positive reaction for either c-*KIT* or CD34 and may be classified by additional immunostainings into: 1) smooth muscle type, if positive for alpha-smooth muscle actin; 2) neural type, if positive for S-100 or vimentin proteins; 3)

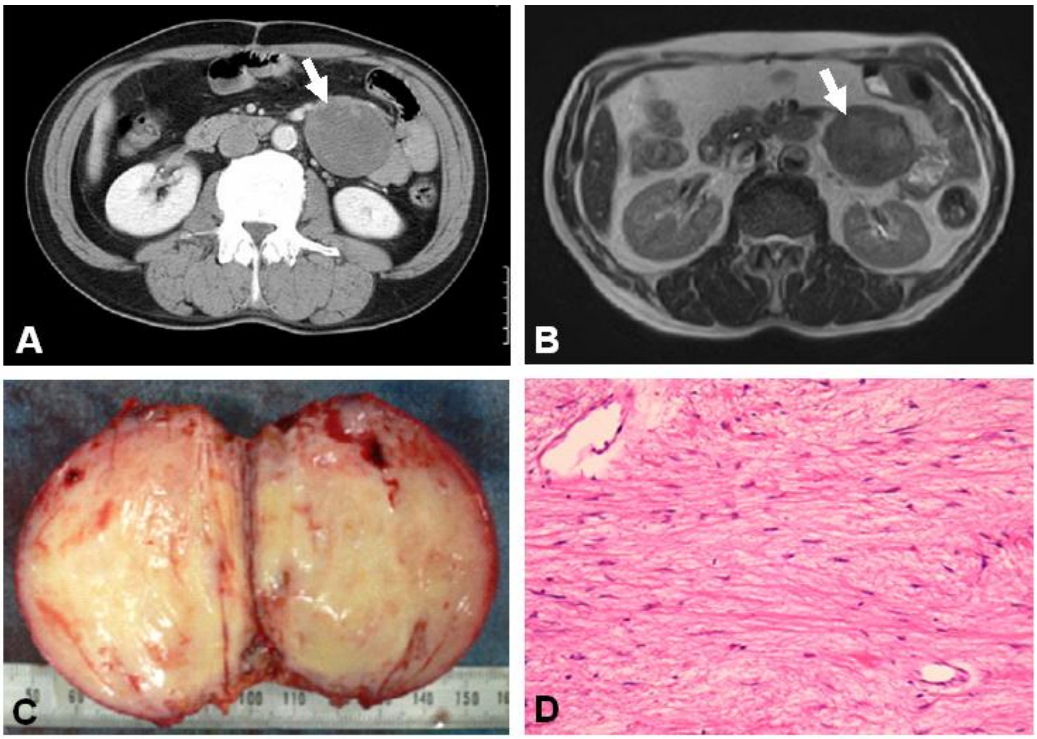

Figure 3 (A) CT scan showed a soft tissue nodule measuring approximately 6.3cm in diameter in the mesentery (arrow). (B) MRI examination showed a tumor of relatively large size (approximately 6.3cm in diameter) with low signal intensity in the mesentery in T1 and T2 weighted images (arrow). (C) The resected specimen showed a spherical mass of solid nature measuring 6.5cm×5.0cm×7.0cm with a smooth surface. (D) Histopathological findings revealed diffuse growth of spindle cells in a massive collagenous tissue consistent with desmoid-type fibromatosis (Hematoxylin-eosin stain x200).

combined smooth muscle-neural type, if positive for alpha smooth muscle actin or desmin and S-100 protein or vimentin; and 4) uncommitted type, if negative for desmin, alpha-smooth muscle actin, S-100 protein and vimentin.

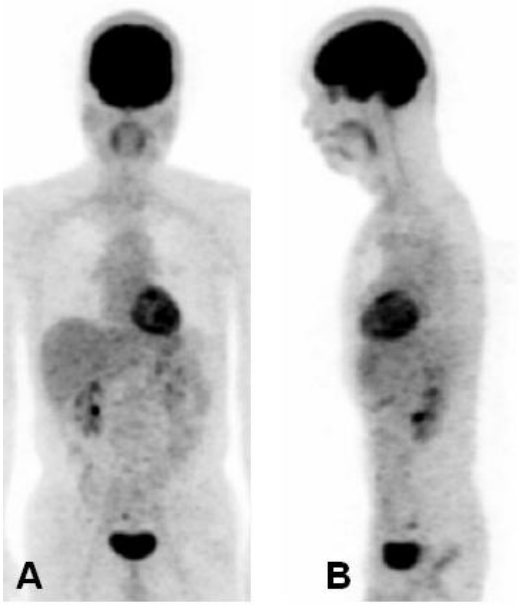

Figure 4 Sagital PET images (A; frontal and B; lateral) showed no evidence of tumor.

The coexistence of LMS with GIST and association of GIST with DT have been described in the literature. However, to the best of our knowledge, this is the first case of a LMS subsequently developing GIST and DT in the intestine. As imatinib mesylate targets both c-*KIT* and PDGFR and since LMS, GIST and DT share the expression of c-*KIT* and/or PDGFR, our patient has benefited from the continual treatment with imatinib mesylate. Further studies are needed to establish the link between LMS, GIST and DT and to elucidate the possible use of tyrosine kinase inhibitors as a treatment option for LMS associated with GIST and DT.

Conflict of Interest

The authors declare no conflicts of interest.

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