Clinical Case Report

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Complete response to sunitinib for more than three years in a patient with a jejunum gastrointestinal stromal tumor

A case report

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Abstract

Rationale: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract and is characterized by KIT mutations. Patientsresistant to 1st-line imatinib therapy are usually given sunitinib assecond-line treatment, which provides a median progression-free survival of 8 to 12 months. We report the 1st case of metastatic jejunum GIST with a KIT exon 11 deletion that showed complete response (CR) to sunitinib for more than 3 years.

Patient concerns: A 34-year-old man with advanced jejunum GIST was surgically treated upon initial diagnosis, and was histologically found to carry a high recurrence risk. Genetic testing revealed a KIT exon 11 deletion, and adjuvant therapy with imatinib was administered. The imatinib dose was escalated following recurrence in the abdomen, but the mass continued to grow.

Diagnosis: He was diagnosed with abdominal recurrence of GIST based on his medical history and histopathological results.

Intervention: Second-line sunitinib therapy was given.

Outcomes: The mass disappeared, and CR was seen following 7 months of sunitinib therapy; this CR was sustained for more than 45 months.

Lessons: In cases of metastatic jejunum GIST with a KIT exon 11 deletion, sunitinib as second-line therapy can be used to achieve CR for more than 3 years.

Abbreviations: CR = complete response, CT = computed tomography, GI = gastrointestinal, GIST = gastrointestinal stromal tumor, ITT= intent to treat, MDT = multi-disciplinary team, ORR = objective response rate, OS = overall survival, PFS progression-free survival, TKI = tyrosine kinase inhibitor.

Keywords: complete response, gastrointestinal stromal tumor, sunitinib

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal (GI) tract, accounting for 0.2% of all GI tumors. The small intestine is the second most common primary site for GISTs, after the stomach.[1] For patients with advanced or metastatic GIST, tyrosine kinase inhibitors (TKIs) such as imatinib or sunitinib are the main drugs of choice.[2] Imatinib is the standard 1st-line treatment for patients with unresectable and/or metastatic GIST. However, while about 4% of the GIST patients are intolerant to imatinib, 50% of them develop resistance within 2 years of imatinib therapy.[3] Sunitinib has been proven to be safe and efficacious in patients with GIST who are resistant or intolerant to imatinib.[2,4,5] The median progression free survival (PFS) for sunitinib treatment is reported to be 8 to 12 months after disease progression or intolerance to imatinib.[4,5] Complete response (CR) to sunitinib for more than 3 years is extremely rare, especially in the case of jejunum GISTs due to their more aggressive nature.[6] Here we describe an extremely rare case of CR to sunitinib as 2nd-line therapy in a patient with metastatic jejunum GIST. To our knowledge, this is the 1st case report to describe such an outcome.

2. Case report

2.1. Patient information

A 34-year-old man who complained of abdominal pain was initially evaluated in January 2011.

Editor: N/A.

Patient Consent Statement: The patient has provided informed consent for publication of the case.

Disclosure Statement: We declare that the paper is being submitted to be considered for publication in the Medicine and that the content has not been published or submitted for publication elsewhere. All the authors have read and approved the manuscript.

Ethics approval and consent to participate: The present study was approved by the Ethics Committee of the Hubei Cancer Hospital (Wuhan, China).

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Abdominopelvic computed tomography (CT) scan revealed a 9-cm mass in the right abdomen, with central necrosis. Following an exploratory laparotomy, he was found to have omental and mesenteric multiple metastases, and all the visible tumors were removed by the surgeon.

Immunohistochemical staining found the tumor to be positive for KIT and CD117, and a diagnosis of high risk jejunum GIST with omental and mesenteric metastases was made. The patient was started on imatinib (400 mg/day) treatment 1 month after the surgery. The treatment was well tolerated, with no grade 3 adverse events. A CT scan 16 months later showed recurrence in the form of a 5 cm mass. Another 5 months later, at the same dose of imatinib, the mass was found to have enlarged. The dose of imatinib was increased to 600 mg/day, following which the tumor showed a decrease in size. However, imatinib had to be discontinued 3 months after the dose escalation because of adverse side effects. Two months after discontinuing imatinib, the mass was found to have again increased in size. He was then referred to our hospital for further treatment in June 2013.

2.2. Clinical findings

The patient's baseline performance status was excellent. A physical examination revealed a right-sided abdominal mass. After an Oncological Committee evaluation, magnetic resonance imaging (MRI) was performed (Fig. 1). The case was discussed again by a multi-disciplinary team (MDT) and a 2nd resective surgery was proposed. The laparotomy this time revealed a $13 \times 7 \times 7$ cm tumor located in the right upper abdomen adjacent to the colon and liver, adhering to the ascending colon and duodenum. Several nodules measuring 0.3–0.7 cm in diameter were seen in the omentum and mesentery. All the visible tumors were resected. Immunohistochemical staining found the tumors to be positive for CD117, Dog-1, and SDHB, but negative for CD34. The Ki-67 labeling index was about 30% (Fig. 2A–D).

Timeline (Table 1)

2.3. Diagnostic focus and assessment

Based on these pathological findings, the tumor was diagnosed as recurrent jejunum GIST. The genetic testing revealed the presence of a KIT exon 11 deletion while there was no mutation in PDGFRα. We recommended treatment with TKIs after the surgery, but the patient did not agree. A CT scan 4 months after the surgery revealed a mass in the left abdomen (Fig. 3A), indicative of a relapse.

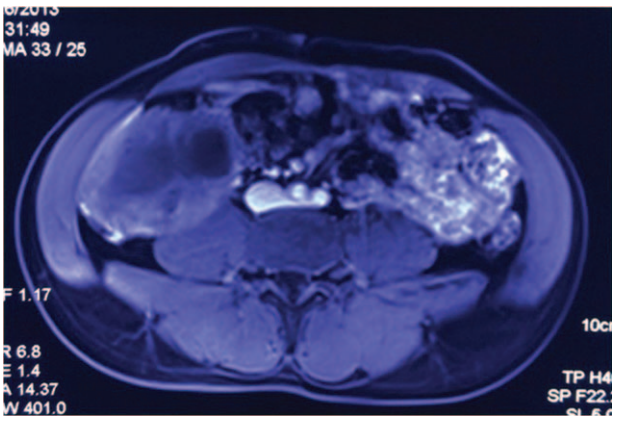

Figure 1. Magnetic resonance imaging (MRI). Shown is the MRI scan of the patient when he 1st visited our hospital. A mass in the right abdomen can be seen. MRI = magnetic resonance imaging

2.4. Therapeutic focus and assessment

Treatment with sunitinib was initiated as a standard regimen (50 mg/day for 4 weeks, every 6 weeks). Three months after sunitinib treatment was started, the tumor showed a significant decrease in size (Fig. 3**B**). Seven months later, the mass showed nearly clinical CR (Fig. 3**C**), which continued until December 2016 (Fig. 3**D**). The treatment was well tolerated, with no grade 3 adverse events. We have followed up the patient for 5 years, and he has been asymptomatic with a good quality of life. The CT showed a recurrence again in August 2017 (Fig. 3**E**), and the tumor further enlarged by September 2017 (Fig. 3**F**).

3. Discussion

The GISTs, specifically those driven by KIT or PDGFR-α signaling are the most common mesenchymal tumors of the GI tract.[7] The small intestine is the 2nd most common primary site for GISTs, after the stomach, which accounts for 20 to 30% of all GISTs. These tumors typically express KIT and have characteristic KIT exon 9 mutations, but lack PDGFRα mutations.[6,8] In our case too, the patient had a deletion in KIT exon 11 but no mutations in PDGFRα. In randomized clinical trials, patients with KIT exon 11 mutations have been associated with better response rates, PFS and OS, compared to those with KIT exon 9 mutations or wild-type KIT.[9–11] Previous studies have demonstrated that deletions are associated with poorer prognosis when compared to other mutation types such as point mutations.[12,13] However, the largest study on small intestinal GISTs showed no significant prognostic differences between point mutations and KIT exon 11 deletions.[6] The patient in this study has survived for more than 5 years, suggesting that the KIT exon 11 deletions in the small intestinal GISTs may be different from those in the gastric GISTs.

About 20 to 30% of the GISTs present metastasis at the initial diagnosis, [14] liver and peritoneum being the most common sites.[15] In this case, the patient had extensive intraperitoneal metastasis at the initial diagnosis. In a metastatic setting, targeted therapy is the main treatment. Previously, for patients with advanced disease, the median survival used to be 10 to 18 months because no effective therapies were available.[16]However, the prognosis of GISTs has dramatically improved following the introduction of imatinib. The current clinical practice guidelines recommend the use of 400 mg of imatinib daily for advanced or metastatic GISTs. However, some patients are intolerant to imatinib or may acquire resistance to it in about 2 years. Sunitinib, a multi-targeted TKI that selectively blocks vascular VEGFRs, PDGFR-α, PDGF R-β, KIT, and FLT3 has been approved by regulatory entities for use after disease progression or intolerance to imatinib. SDH-deficient GIST may have a higher probability of response to sunitinib.

In a randomized phase III placebo-controlled study of patients with imatinib-resistant GISTs, sunitinib was generally well tolerated [4] and resulted in significantly improved, median time to progression (27.3 vs 6.4 weeks); and estimated overall survival (OS). In terms of the best overall objective tumor response for the intent to treat (ITT) population, partial response was the best response in 14 (7%) patients of the sunitinib group, while stable disease was seen in 120 (58%) of them. A recent report from an

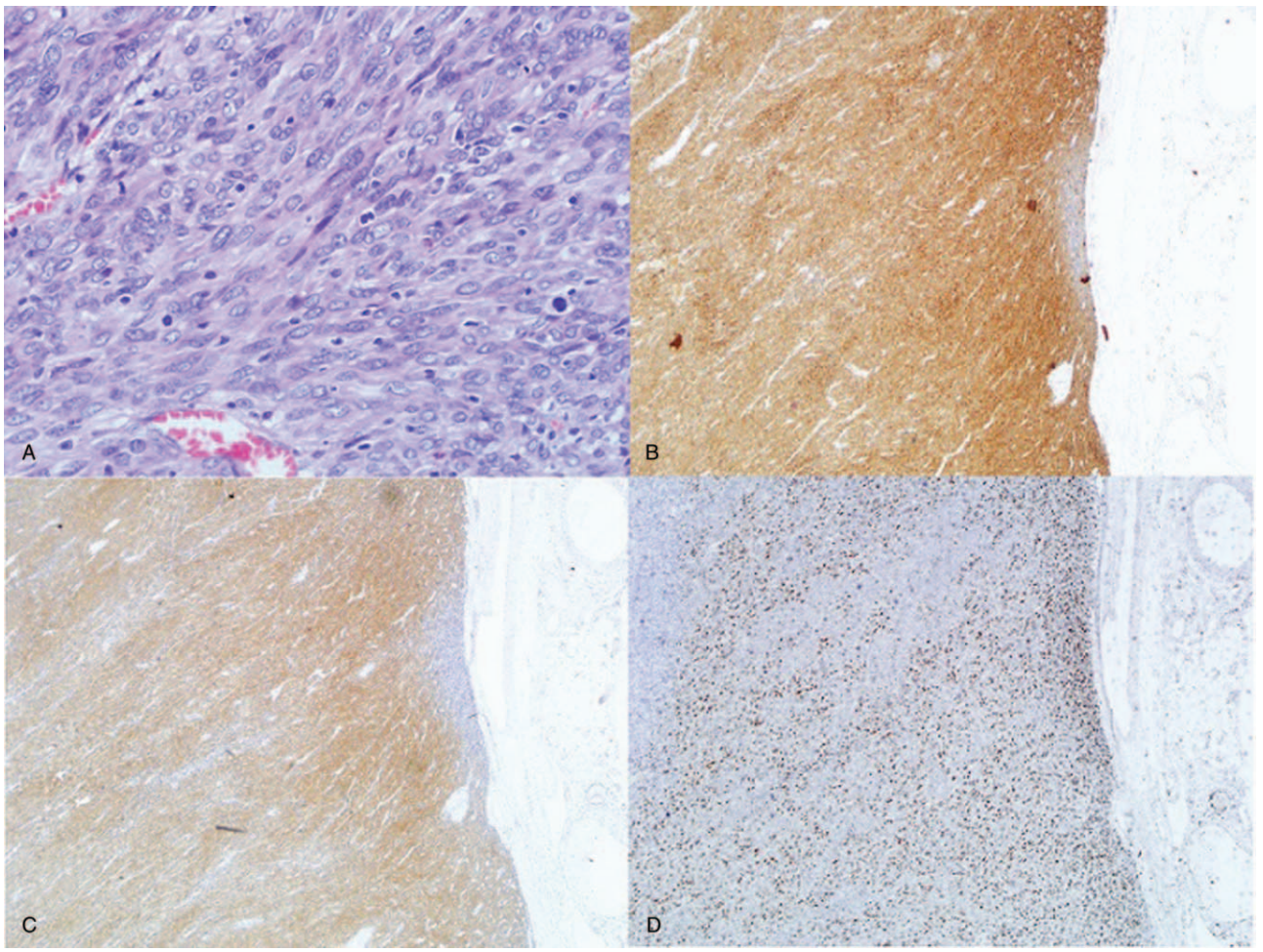

Figure 2. Postoperative pathology after a 2nd surgery in our hospital. (A) Hematoxylin and eosin stainingshow spindle-shaped or polygonal cells with enlarged nuclei. A number of mitoses can be seen in the high-power fields (HPFS) (Original magnification: 40 × 10). (B–D) Immunohistochemistry shows the cells are positive for (B) CD117, (C) Dog-1 and (D) Ki-67 Li is about 30% (Original magnification:4 × 10). HPFS = high-power fields.

international study which enrolled 1124 patients with advanced GISTs and imatinib failure, found that sunitinib treatment resulted in a median PFS and OS of 8.3 months (95%CI, 8.0–9.4 months) and 16.6 months (95%CI, 14.9–18.0 months), respectively.[2]A retrospective analysis of the subgroups of this study (n=230) found that patients with a primary mutation in the KIT exon 9 had significantly better PFS (12.3 months) compared to those with a primary mutation in exon 11 (7.0 months).Similarly, higher objective response rate (ORR) and better OS were observed in patients with a primary KIT mutation in exon 9 versus exon 11.[17] Another study also demonstrated that sunitinib had better clinical benefits (partial response or stable disease for 6 months) in patients with primary KIT exon 9 mutations than in those with KIT exon 11 mutations.[18]Furthermore, a recent study found that patients who have an exon 11 deletion are more likely to benefit from switching to sunitinib directly than from a dose escalation of imatinib.[19]In our case, therefore, the patient who had a KIT exon 11 deletion and showed a CR to sunitinib therapy for 7 months. The disease was controlled for more than 45 months after we switched to sunitinib.

Table 1

Timeline.

January, 2011	First surgery and initial diagnosis of jejunum stromal tumor
April, 2011	Started on imatinib (400 mg/day) treatment
August, 2012	Recurrence, and continued the same imatinib
January, 2013	The mass was found to have enlarged. The dose of imatinib was increased to 600 mg/day
April, 2013	Imatinib had to be discontinued because of adverse side effects
June, 2013	The mass increased in size. He was referred to our hospital for further treatment, and a second resective surgery was proposed
November, 2013	A mass recurrenced in the left abdomen, and sunitinib was initiated as a standard regimen
June, 2014	Nearly clinical CR
August 2017	Recurrence again

CR = complete response.

To the best of our knowledge, there have been only 4 cases showing CR to sunitinib as 2nd-line therapy for GISTs.[20–22]Additionally, there have been no cases of CR to second-line sunitinib therapy for over 3 years in jejunum GISTs. Nevertheless, a limitation of this case study is that fluorodeoxyglucose-positron emission tomography (FDG-PET) was not performed to evaluate the regression of the lesion. However, there are FDG-PET-negative GIST cases, and therefore, FDG-PET is not considered a substitute for CT.[23]

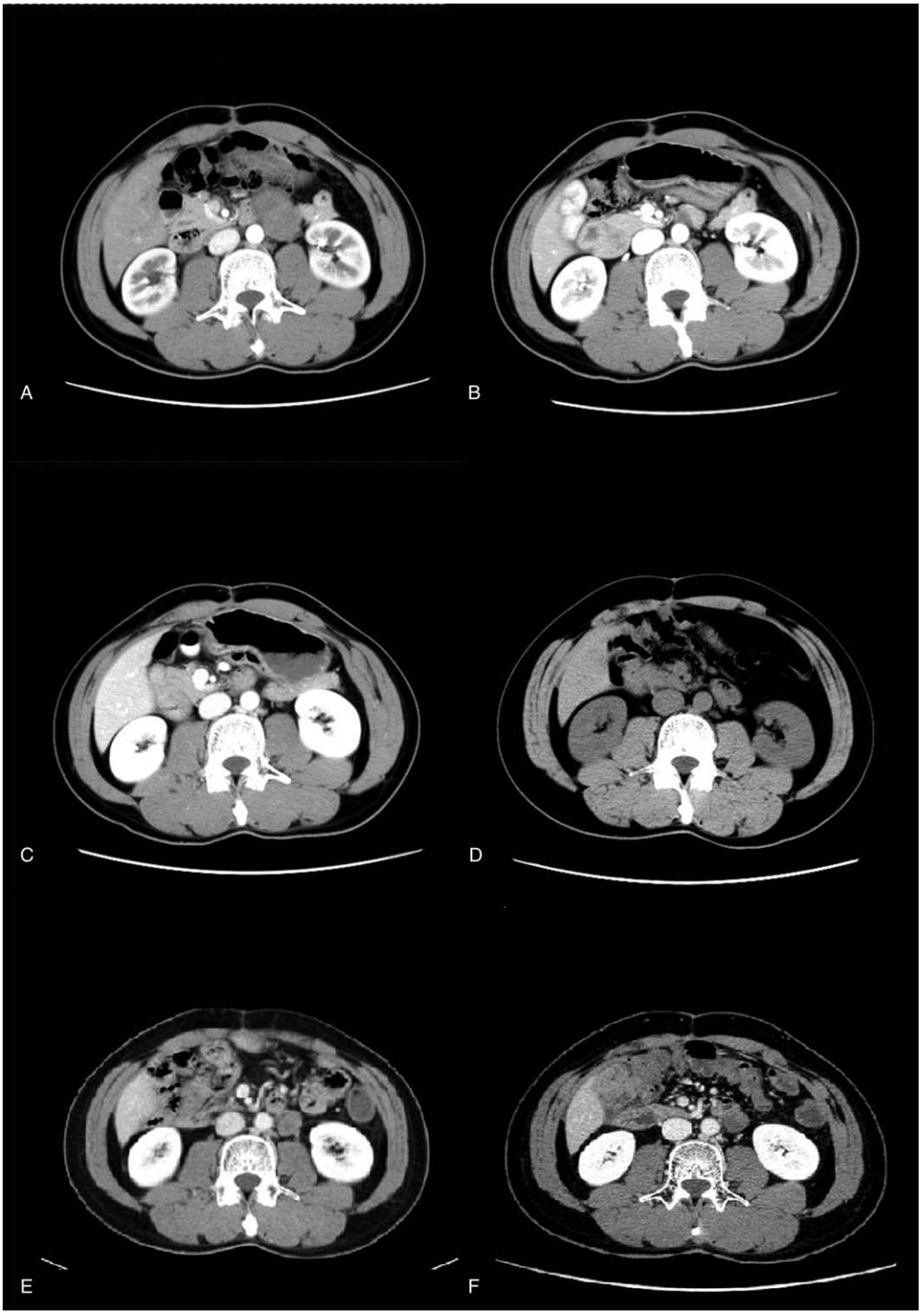

Figure 3. Computed tomography of the abdominal mass. Shown is a CT scan from November 2013. (A) A recurring mass can be seen in the left abdomen, whichshows (B) a significant decreasein size after 3 months of sunitinib therapy, and (C) nearly complete clinical remission after 7 months of the therapy. (D) The complete remission is maintained in December 2016, but (E) the tumor recurs again in August 2017. (F) The most recent view in September 2017. CT = computed tomography.

In conclusion, we have reported an extremely rare case of jejunum GIST with KIT exon 11 deletion wherein the patient showed CR to 2nd-line sunitinib treatment for over 45 months. This report is therefore highly significant for clinical research and the treatment of GISTs.

Author contributions

YN wrote the first draft of the manuscript. SY revised the manuscript substantially and approved its final version. WS and ZX participated in patient care.

Methodology: Wenjia Sun, Zhihua Xiao.

Project administration: Shengwei Ye.
Resources: Yanli Nie, SY.
Review & editing: SY
Writing – original draft: Yanli Nie.
Writing – review & editing: Shengwei Ye.

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