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Case report

Liver transplantation for metastatic non-resectable gastrointestinal stromal tumor after molecular targeted therapies: A case report

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ABSTRACT

Introduction and importance: Metastatic GIST (gastrointestinal stromal tumor) is most commonly seen in the liver. Surgical resection and Imatinib administration are the preferred treatment for localized and potentially resectable GIST. However, it is still a matter of debate about the optimal therapeutic management for unresectable, liver-confined, metastatic GIST even after the administration of imatinib. The present case illustrates the possibility of LT surgery maybe for unresectable GIST.

Case presentation: A 56-year-old man revealed clinical symptoms such as abdominal pain, eating little, fullness of abdomen, and fatigue. A 6.0 cm tumor in the fundus of the stomach was found by gastroscopy, which was confirmed to be GIST by pathological biopsy and molecular testing. Abdominal enhanced CT scanning showed multiple hepatic mass occupying synchronous. Then the patient initiated on targeted drug therapy of Imatinib (400 mg daily). A year later, a follow-up abdominal enhanced CT scanning showed that no tumor was found in the gastric fundus except the thickened gastric wall with poor dilatation, and the liver tumors were significantly smaller than before. When the patient showed symptoms of drug resistance, he was refered to our hospital for LT. The surgery was very successful, and the patient is disease-free and there is no evidence of recurrence until the paper was finished.

Discussion and conclusion: Metastatic GIST to the whole liver is a rare clinical entity requiring unique considerations for treatment. Treatment based on LT might be the last resort therapy for unresectable, liver-confined, metastatic GIST in transplant oncology.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of gastrointestinal (GI) tract characterized by differentiation towards the interstitial cells of Cajal. The tumors can develop anywhere along the GI tract, arising mainly in the stomach (54%) and small bowel (30%), 5% in the colon and rectum, about 1% in the esophagus. Metastatic GIST is most commonly seen in the liver, with an incidence of 15.9%, accounting for 55–72% of distant organ (including liver, lung, bone, peritoneum, etc.) metastases [1–3]. Usually, resection of liver metastases combined with oral tyrosine kinase inhibitor (TKI) is the most effective method for the treatment of GIST liver metastasis, which can significantly prolong the survival time of the patients and improve the quality of life [4]. But it is still a matter of debate

Abbreviations: LT, liver transplantation; CT, computerized tomography; PDGFRA, platelet-derived growth factor receptor A; PET, positron emission tomography; TKI, tyrosine kinase inhibitor; GIST, gastrointestinal stromal tumor; GI, gastrointestinal; MRI, magnetic resonance imaging; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

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about the optimal therapeutic management for unresectable, liver-confined, metastatic GIST even after the administration of Imatinib [5]. LT has emerged recently as an alternative under exceptional circumstances [6]. There are a few literatures on whether LT can prolong the survival time of the unresectable metastatic GIST patients. Herein, we reported a case regarding this rare clinical scenario to explore the comprehensive treatment strategy.

2. Presentation of case

A 56-year-old male patient revealed clinical symptoms such as abdominal pain, eating little, fullness of abdomen, and fatigue in February 2019. Gastroscopic examination of the patient at an outside institution indicated a 6.0 cm GIST in the gastric fundus, which was confirmed by pathology biopsy. Genetic analysis of *C-Kit* mutation revealed KIT exon 11 mutation which resulted in the deletion of codons 1704 to 1727 encoding amino acid p568 to p576. Abdominal enhanced computerized tomography (CT) scanning showed multiple hepatic mass occupying synchronous, the largest being 11.0 cm. The patient initiated on targeted drug therapy of Imatinib (400 mg daily) and hepatic artery lipiodol embolization therapy was performed twice successively at the same time, considering liver metastases originated in the gastric fundus.

In April 2020, a follow-up abdominal enhanced CT scanning showed the liver tumors were significantly smaller than before (the largest was 6.1 cm) and no tumor was found in the gastric fundus except the thickened gastric wall with poor dilatation.

In January 2021, abdominal enhanced CT scanning showed liver masses had gradually increased (the largest was 10.0 cm). Considering Imatinib resistance, Sunitinib (50 mg daily), another TKI and a second-line therapy in patients with metastatic GIST, was used to instead. Subsequently, hepatic artery lipiodol embolization therapy was performed again. But the total bilirubin increased from normal to 112 μ mol/L within 2 weeks, accompanied by yellowing of skin, whites of the eyes, elevated transaminase (ALT: 184 IU/L, AST: 346 IU/L, GGT: 1097 U/L, ALP: 865 U/L). The transaminase was improved after conservation medical treatment, but the bilirubin continued to rise. The abdominal MRI, abdominal enhanced CT, and PET-CT scanning showed further enlargement of liver metastases.

For further diagnosis and treatment, the patient was referred to our hospital for LT. The case was discussed by the ethics committee of our institution, and the feasibility of transplantation with a deceased donor was approved by Health Ministry authorities. The patient was provided good access with the transplant chance due to organ matching through China Organ Transplant Response System. Preoperative examination was completed, including gastroscopy (Fig. 2A), abdominal enhanced CT (Fig. 2B) and PET-CT (Fig. 2C) scanning. The operation was performed on June 16, 2021. The post-operative course was uneventful, with no complications in the perioperative period. He was discharged 59 days after surgery and initiated on Imatinib (400 mg daily). The patient was followed-up regularly, and there is no evidence of recurrence until the paper is submitted. The clinical timeline is displayed in Fig. 1.

The diagnosis of GIST is based on the pathology, including cell morphology and immunohistochemistry. In our case, histopathological evaluation revealed a hypercellular tumor comprised of spindle-shaped cells and epithelioid cells (Fig. 3A-D) which showed a characteristic appearance of GIST with a relatively high mitotic index (30 mitotic figures per 5 mm^2) and an MIB-1 proliferation index of 60% in hot area. Immunohistochemically, the tumor was positive for C-Kit, DOG1 and CD34 (Fig. 3E-G), but negative for S-100, α-SMA, and Desmin.

3. Discussion

The incidence of GIST was approximately 1/100000 to 1.6/100000 per year [7]. Up to 75% of cases present with synchronous or metachronous distant metastases during the course of the disease [8]. Metastatic GIST is most commonly seen in the liver, at an average of 16–38 months after resection of the primary tumor, and multiple metastases occurred in most cases. Most of GIST resulted from a gain-of-function mutation in receptor tyrosine kinases, specifically *C-Kit* proto-oncogene or platelet-derived growth factor receptor A (PDGFRA), and a few cases involve SDHX, BRAF, NF1, K/N-RAS and PIK3CA gene mutations. Genetic analysis of *C-Kit* mutation in our case revealed KIT exon 11 mutation. In addition, GIST is generally radiotherapy resistant, and TKIs were considered the most effective therapy. We hoped they markedly changed the natural history of relapsing or metastatic cases as reported [9].

Because of the success of the pharmacotherapy, our patient benefitted most from Imatinib and no tumor was found in the gastric fundus. Liver metastases were getting smaller. However, resistance to Imatinib treatment eventually occurred soon, consistent with previous report the overall incidence of Imatinib resistance is about 56%, which generally occurs about 2 years after Imatinib treatment [10], especially for patients with KIT exon 11 mutations. Sunitinib was used to instead,

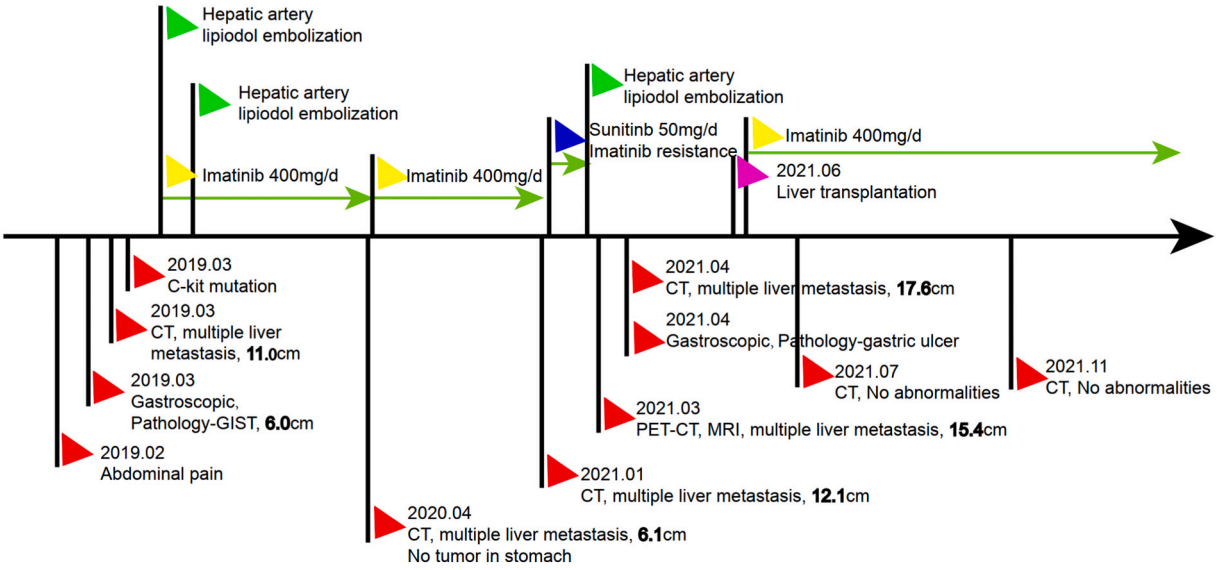

Fig. 1. Clinical timeline.

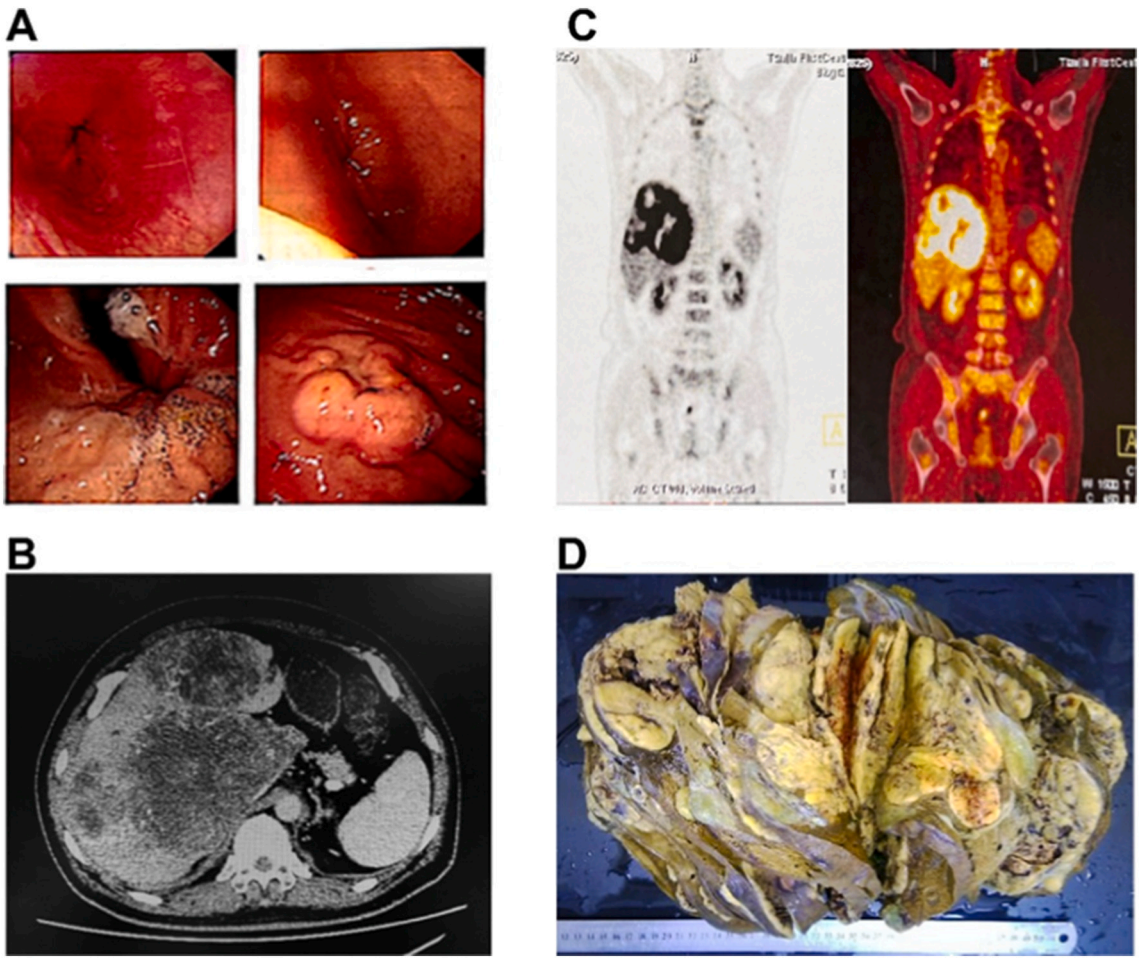

Fig. 2. Imaging data and clinical characteristics.
A, Preoperative gastroscopy revealed only ulcerative lesion, which was confirmed by pathology biopsy. B-C, Abdominal enhanced CT and PET-CT scanning showed multiple hepatic mass occupying synchronous. D, Gross image of metastatic GIST to the liver. The multiple hepatic mass occupying is showing. The biggest lesson is 170 × 110 × 60 mm in size, and the smallest is 13 × 11 × 8 mm. The cut surface features areas of hemorrhage and necrosis.

but the effect was not satisfactory.

Metastatic GIST to the whole liver is a rare clinical entity requiring unique considerations for treatment. According to the Chinese treatment strategy, surgical resection is preferred for localized and potentially resectable GIST [11]. Moreover, some single-center analyses have shown that metastasectomy for recurrent GIST was safe, and could prolonged overall survival [12]. However, when local resection is out of the question, LT, a hard but potentially curative treatment, is a wise choice to some extent, which could cut the risk of oncological progression and give the patient a longer life expectancy. The "1983 National Institutes of Health Consensus Conference" evaluated LT as a promising alternative in the management of the late phase of several forms of serious liver disease [13].

Based on the accumulative therapeutic experience, as well as the better surgical and perioperative care, transplantation for primary and secondary liver malignancies is becoming increasingly common, accounting for 12% of all LTs prior to 1997 with a recent increase to 24% [14]. But due to the lack of donor liver, higher risk and cost of operation, LT cannot be used as a routine treatment. The usage of long-term immunosuppression increases the risk of recurrence of pretransplant malignancies and multiple de novo malignancies [15]. However, as the last resort treatment, it is an alternative, which maybe a new therapeutic option in transplant oncology.

4. Conclusion

LT might be the last resort treatment for unresectable, liver-confined, metastatic GIST, which maybe a new therapeutic option in transplant oncology.

Statement

This work has been reported in line with the SCARE 2020 criteria [16].

Provenance and peer review

Not commissioned, externally peer-reviewed.

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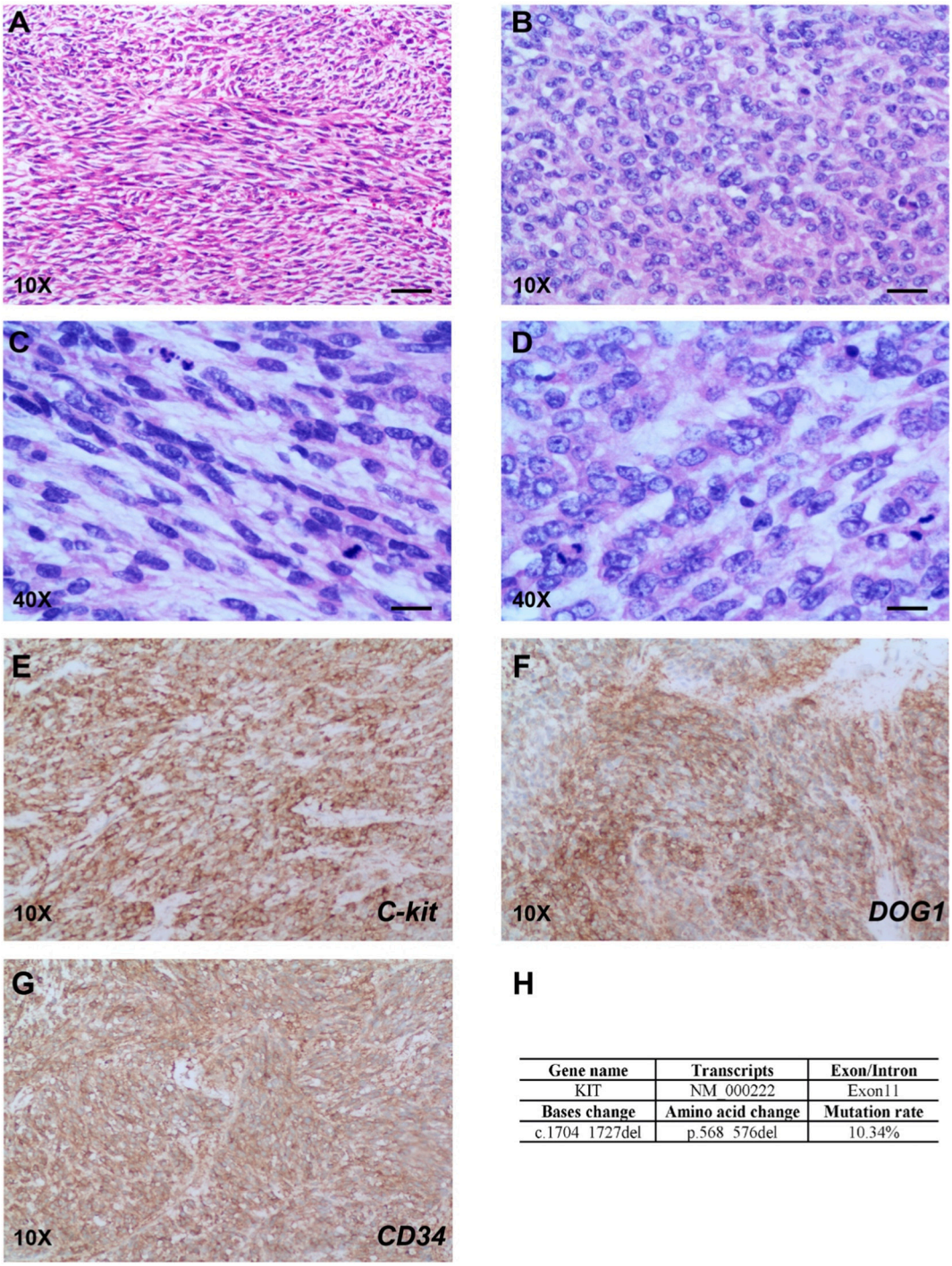
Ethical approval

All procedures used in this study were approved by the ethics committee of our institution.



Gene name	Transcripts	Exon/Intron
KIT	NM_000222	Exon11
Bases change	**Amino acid change**	**Mutation rate**
c.1704_1727del	p.568_576del	10.34%

Fig. 3. H&E, IHC staining and the genetic mutation of the tumor specimen.
A-D, Histopathological evaluation revealed the tumor comprised of spindle-shaped cells (A) and epithelioid cells (B) including 30 mitotic figures per 5 mm^2 (C-D). E-G, Immunohistochemical evaluation indicated that the tumor cells were positive for *C-Kit*, DOG-1, and CD34 expression. H, Genetic analysis of *C-Kit* mutation revealed a KIT exon 11 mutation that resulted in the deletion of codons 1704 to 1727 encoding amino acid p568 to p576. The mutation rate is about 10.34%.

Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Author contribution

Hui Li and Xiaole Meng: diagnosis and clinical management of the case, literature review, write the manuscript.

Kun Zhang and Huamei Tang: diagnosis and clinical management of the case, literature review, manuscript correction and validation.

Registration of research studies

This is not the 'First in Man' study.

Guarantor

Huamei Tang.

Declaration of competing interest

The authors have no conflict of interest to declare.

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None.

Data availability statement

Data available on request due to privacy/ethical restrictions.

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