Case Report
Sequential therapy for liver and bladder metastases of small intestinal stromal tumors after resection: a case report

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Abstract: Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms of the gastrointestinal tract and metastasize outside of the gastrointestinal tract at a very low frequency. The present study reports an extremely rare case of liver and bladder metastases from a small intestinal stromal tumor (SIST). About 32 months later after resection of SIST, liver metastasis was observed by imaging studies and then partial liver was resected. About 19 months later after resection of the liver tumor, bladder metastasis was found by imaging studies, so partial bladder was resected. About 8 months later after resection of the bladder tumor, this patient developed into multiple liver metastases, and was treated with imatinib mesylate. After taking the drug, the hepatic nodules had a decreasing trend. Until now, this patient continues to receive imatinib mesylate. This case suggests that sequential therapy including surgical resection and imatinib mesylate, may be an effective strategy for the treatment of SIST with liver metastasis and bladder metastasis.

Keywords: Gastrointestinal stromal tumor, metastasis, therapy, liver, bladder

Introduction
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. GISTs are most commonly located in the stomach (60%) and followed by the small intestine (30%), and GISTs are rarely originate from the extra-gastrointestinal organs, such as the prostate, pancreas, liver and bladder, and so on [1-5]. All GISTs are currently regarded to be potentially malignant, with different degrees of malignancy. The small intestinal stromal tumor (SIST) has a higher degree of malignancy and poorer prognosis than GISTs of the stomach [6]. The present study reports a case of one woman who even finally developed into multiple liver metastases, was survived 8 years after surgical resection of SIST. During the 8 years, a sequential treatment strategy, including surgery and imatinib mesylate therapy, which were effective in treating liver metastasis and bladder metastasis.

Case report
The first stage (2008.06.20–2011.02.10)
A 52-year-old Chinese woman was admitted to The Second Hospital Affiliated to Jiaxing University (Jiaxing, China) because of severe middle abdominal discomfort on Jun 20, 2008. The patient had a history of chronic liver disease and hepatic cysts. A mass in the pelvic was identified by ultrasound examination and was considered to be malignant. The results of laboratory tests were within normal ranges. To eliminate the severe symptoms of abdominal pain, an exploratory laparotomy was undergone on Jul 7, 2008. Intraoperatively, it was found that the mass was arisen from small intestine, with no apparent invasion of adjacent organs. The whole mass and part of the small intestine was resected. The mass was measured 9×7.5 cm and was located in approximately 50 cm from the ileocecal. Pathologically, the margins of resection were negative. It was demonstrated by hematoxylin and eosin (HE) staining that the tumor was composed of spindle cells. The mitotic activity of the tumor cells was 4 mitoses per 50 high power fields (HPF). Immunohistochemistry of the tumor showed a negativity for S-100, and a positivity for CD117 and CD34 (Figure 1A). These histological and immunohistochemical features led to a final diagnosis as borderline SIST. This patient recovered well and was followed until Feb 10, 2011.
The second stage (2011.02.11–2012.09.19)

The woman was secondly admitted to our hospital on Feb 11, 2011, because of upper abdominal pain. A contrast-enhanced computed tomography (CECT) scan revealed a 6×5 cm solitary tumor within the II segment of the liver, which was the first consideration of interstitial tumor (Figure 2A). A contrast-enhanced magnetic resonance imaging showed a solitary tumor in left external lobe of liver, which could not exclude liver cancer with less blood supply (Figure 2B). Based on a careful preoperative evaluation and found no obvious contraindications of the surgery, the patient was treated with surgical resection of the tumor on Feb 22, 2011. Intraoperatively, the tumor was located in the II segment of the liver. No abnormal lesions were found in other organs of the abdominal cavity. The hepatic tumor was excised. Hematoxylin and eosin staining demonstrated that the tumor was composed of spindle cells with low mitotic activity (3/50 HPF). Immunohistochemical examinations revealed that the tumor was negative for S-100, and positive for CD117 and CD34 (Figure 1B).

On the basis of a comprehensive analysis of these biological and clinical factors, we concluded that the hepatic tumor was a metastatic tumor from the SIST. The follow up was at 3-month intervals during the first year after Hospital Discharge (Figures 2C, 4A).

The third stage (2012.09.20–2013.05.01)

This woman was thirdly admitted to our hospital on Sept 20, 2012, because of pain in the left lower abdomen. A mixed mass and peripheral hypoechoic nodule in the front of bladder were found by the abdominal ultrasound. A CECT scan revealed a nodule in the front of bladder (Figure 3A). After a careful preoperative evaluation, the patient was treated with surgical resection of the nodule on Sept 27, 2012. Intraoperatively, the nodule, which was located in the front of bladder, was measured 3.5×2 cm and invaded serous layer of the bladder. The nodule including adjacent serous layer of the bladder was excised. Pathologically, the margins of resection were negative, and the nodule was composed of spindle cells with low mitotic activity (2/50 HPF) by hematoxylin and eosin staining. Immunohistochemistry of the nodule showed a negativity for S-100, and a
positivity for CD117 and CD34 (Figure 1C). On the basis of a comprehensive analysis of these biological and clinical factors, we concluded that the nodule was a metastatic tumor from the SIST. The follow up was at 3-month intervals during the first year after Hospital Discharge (Figure 3B).

The fourth stage (2013.05.02--now)

Compared with the previous review, a CECT scan revealed a little hypodense mass in liver at this time on May 2, 2013 (Figure 4B). Because the liver tumor could not be excluded, we recommend the review after three months. On Sept 6, 2013, a CECT scan showed multiple liver nodules, which increased significantly when compared with the previous time (Figure 4C). Combined with the previous history, we considered that these nodules were SIST metastasis. Due to the presence of multiple intrahepatic nodules, the hepatic SIST was considered as unresectable. Therefore, adjuvant chemotherapy, which oral imatinib mesylate was administered at a dose of 400 mg per day, was started immediately. The follow up was at
3 months intervals during the first year and at 6 months intervals thereafter. After taking the drug, the hepatic nodules had a decreasing trend (Figure 5A-E). During the course of treatment, the side effect of this drug was lower extremity mild edema of this patient. To improve this symptom, oral administration 20 mg/d of aldosterone was used. This patient, who experienced liver metastasis and bladder metastasis, has survived for more than 8 years after the first surgery. Until now, she continues to receive imatinib mesylate.

Figure 3. The imaging examination revealing a tumor in the bladder (white arrow). A, C, E. Contrast-enhanced computed tomography imaging on Sept 23, 2012. B, D, F. Contrast-enhanced computed tomography imaging on Dec 28, 2012.
Discussion

GISTs are mesenchymal tumors of the gastrointestinal tract, and the incidence of it is low 20 per 100,000 individuals in China [7]. One of the characteristic features of GISTs is the expression of CD117, a receptor tyrosine kinase protein that is encoded by the c-Kit gene [8]. GISTs arising outside of the gastrointestinal tract are defined as extra-gastrointestinal stromal tumors (EGISTs) [9]. EGISTs are rare, with an estimated incidence of 1.5-6.0% worldwide [10] and predominantly occur in the omentum, retroperitoneum or mesentery [11], while multiple organs metastases are extremely rare. In the article, this is the first reported case of SIST, which metastasis to liver and bladder after resection for SIST successively.

The origin of GISTs and EGISTs remain controversial. A previous study has suggested that interstitial cells of Cajal (ICCs) are the likely genesis source of GIST because of the striking immunophenotypic and morphological similarities between GISTs and ICCs [12]. From a molecular genetic perspective, EGISTs are a
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specific type of GIST, so they should be share
the same mesenchymal origin. However, ICCs
are hard to explain the tumorigenesis of EGISTs,
so several hypotheses have been proposed to
explain this. Firstly, some molecular investiga-
tions have confirmed the presence of Cajal-like
interstitial cells in organs outside of the gastro-
intestinal tract, with a similar structure and
function to ICCs [13]. It has been reported that
Cajal-like cells are present in the myometrium
[14]. Secondly, studies have suggested that
EGISTs originate from multipotent mesenchy-
mal stem cells located outside of the gastroin-
testinal tract, and then differentiate into ICCs
[15]. Lastly, GISTs often display an exophytic
growth pattern and lead to tumor cells being
scattered outside of the gastrointestinal tract.
These cells may also result in the generation of
EGISTs in different locations or organs [16].
Until now, the origin of this tumor has not been
elucidated clearly.

Up to 30% of GISTs show high malignant behav-
ior such as metastasis and infiltration of adja-
cent organ [17]. They usually give metastatic
spread into the peritoneal cavity and other
organs. However, no common symptoms spe-
cific to GISTs have been identified until now.
Symptoms may vary greatly and depends on
the size and location of the tumor [18]. Initial
diagnosis of GIST may be delayed due to the
non-specific presentation of the disease. CECT
is currently considered to be the imaging modal-
ity of choice, as it can characterize the lesion,
evaluate the extent and assess the presence or
absence of metastasis. Additionally, it can also
be used for monitoring the response to treat-
ment and for follow-up surveillance of recur-
rence [19].

For resectable patients, the primary treatment
for both GISTs and EGISTs is surgical removal
with a microscopic negative margin. During the
procedure, tumors are considered to be very
fragile, surgeons must be handled with care in
order to avoid tumor rupture and do not cause
implantation metastasis. Lymphadenectomy is
not required, because of a low incidence of
nodal metastasis in GISTs [20, 21]. Additionally,
for unresectable patients, molecularly-targeted
therapies are used. Imatinib mesylate, a tyro-
sine kinase inhibitor of c-Kit, has been the pri-
mary drug available for treatment. It can pre-
vent and slow down tumor progression and
has been shown to improve overall survival
[22-24].

During follow up, more than 30% of patients
with high-risk GIST will develop local recurrence
and distant metastasis following complete sur-
gical resection [25]. The 5-year survival rate is
approximately 50%, while the median time to
recurrence or metastasis after resection with a
R0 margin of primary high-risk GIST appears
within 2 years [19]. Adjuvant therapy with ima-
tinib mesylate is beneficial after the primary
high-risk GIST is resected. At least 3 years
treatment with imatinib mesylate has been
reported to improve recurrence free survival
and overall survival in patients with high-risk
GISTs [26]. According to the modified NIH con-
sensus criteria in 2008, the patient was at high
risk of tumor metastasis, oral administration
400 mg/d of imatinib mesylate was advised as a suitable therapy for at least 3 years after surgery [27, 28]. The side effects of imatinib mesylate are mild and tolerable, such as skin rash, edema, diarrhea, and nausea [29]. Few patients experience serious complications to merit the discontinuation of treatment.

Conclusion

In conclusion, the present study reports a case of stromal tumor diagnosed in the intestine, liver, and bladder. To the best of our knowledge, this is the first case report that patient was treated with a sequential therapy consisting of intestinal surgery, liver surgery, bladder surgery, and imatinib mesylate.

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Disclosure of conflict of interest

None.

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References

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