Int J Clin Exp Med 2017;10(5):8632-8640
www.ijcem.com /ISSN:1940-5901/IJCEM0052570

Case Report

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

Jing Chen, Zhongcheng Zhou, Xujian Chen, Jing Wang, Yiyu Shen, Zhengxiang Zhong

Department of General Surgery, The Second Hospital Affiliated to Jiaxing University, Jiaxing, China

Received March 8, 2017; Accepted April 13, 2017; Epub May 15, 2017; Published May 30, 2017

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.

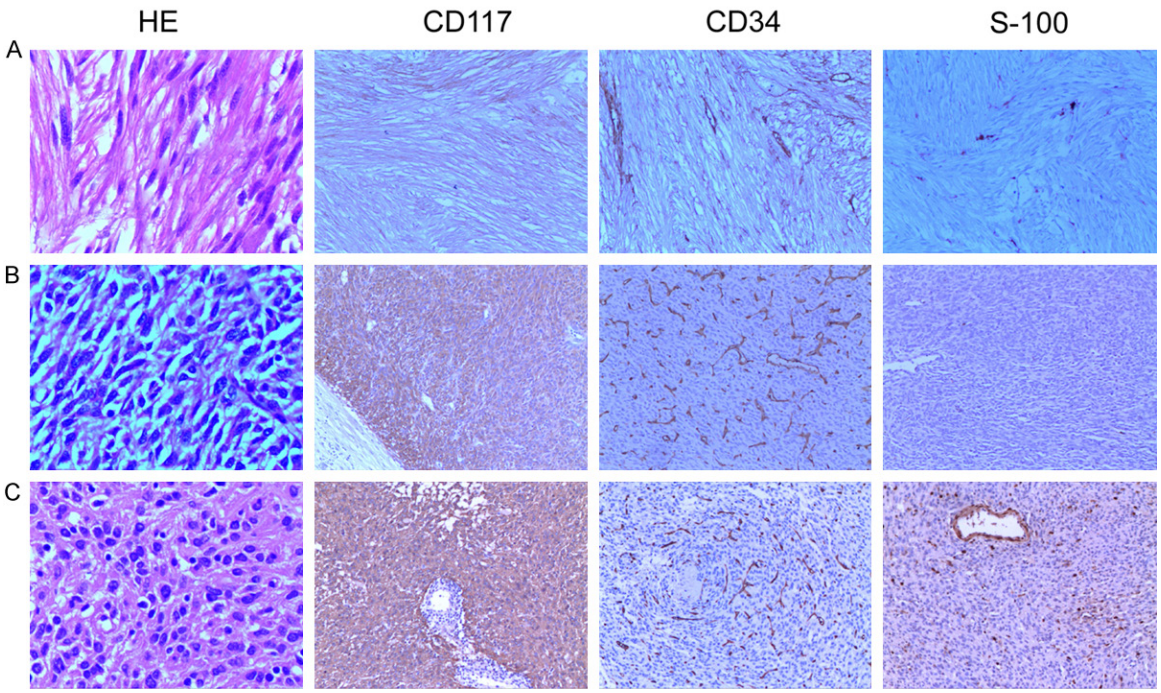


Figure 1. Histopathological findings of the tumors. A. Small intestinal stromal tumor; B. Liver tumor; C. Bladder tumor. Tumors for HE staining (×400). Immunohistochemical examination reveals negative staining for S-100, and positive staining for CD117 and CD34 in tumors (×100).

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

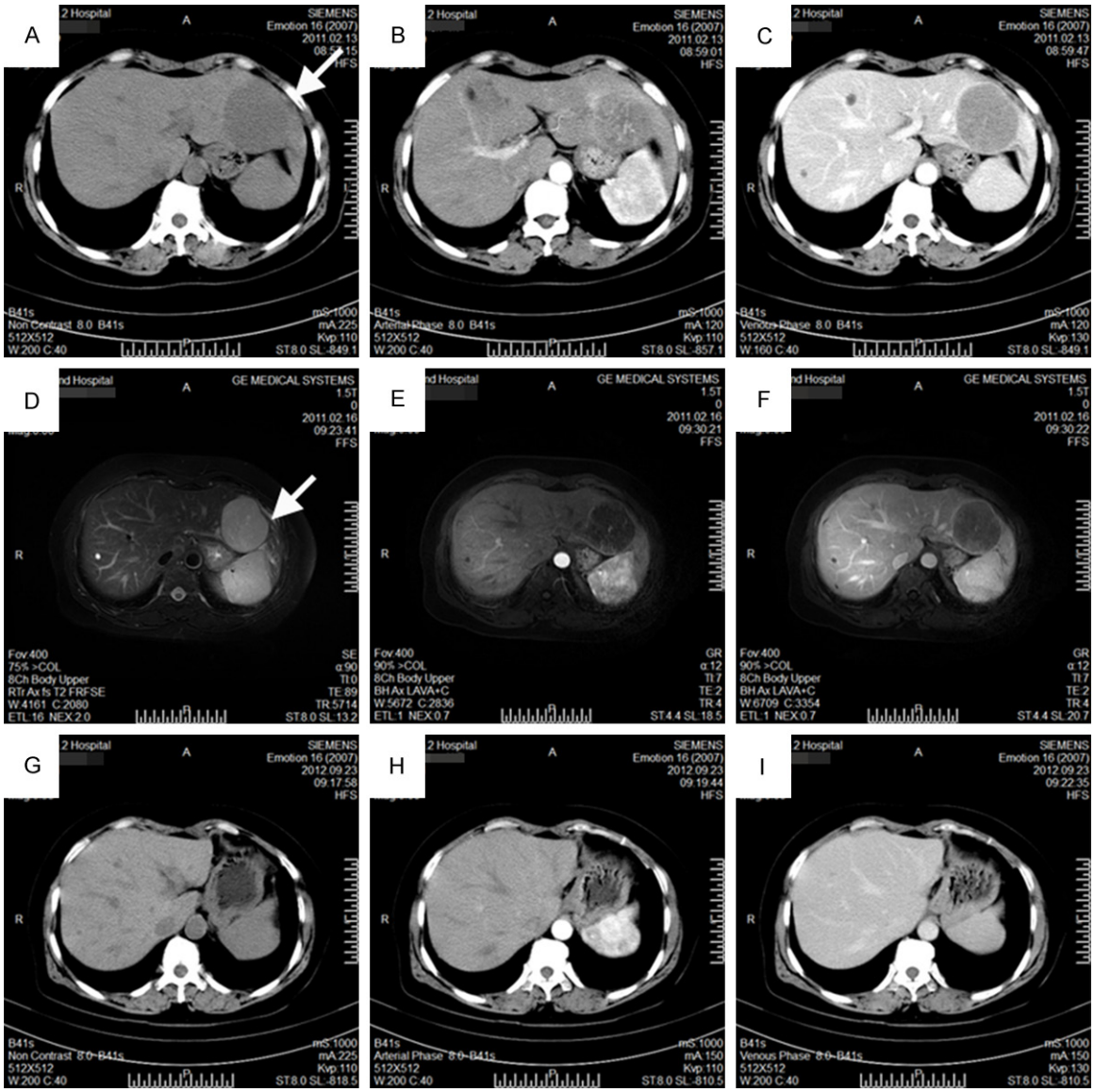


Figure 2. The imaging examination revealing a tumor in the II segment of the liver (white arrow). A-C. Contrast-enhanced computed tomography imaging on Feb 13, 2011. D-F. Contrast-enhanced magnetic resonance imaging on Feb 16, 2011. G-I. Contrast-enhanced computed tomography imaging on Sept 23, 2012.

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

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.

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.

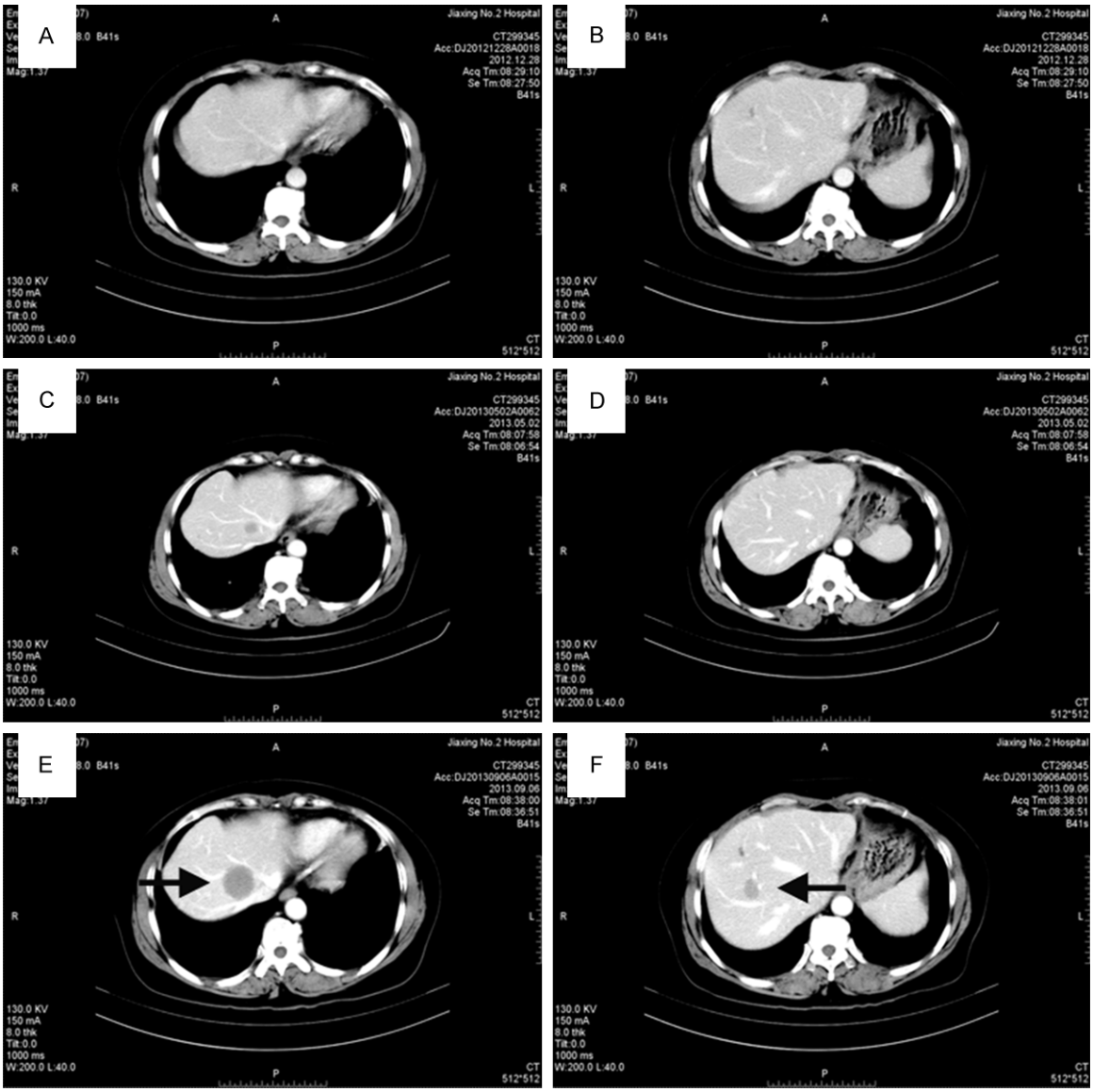
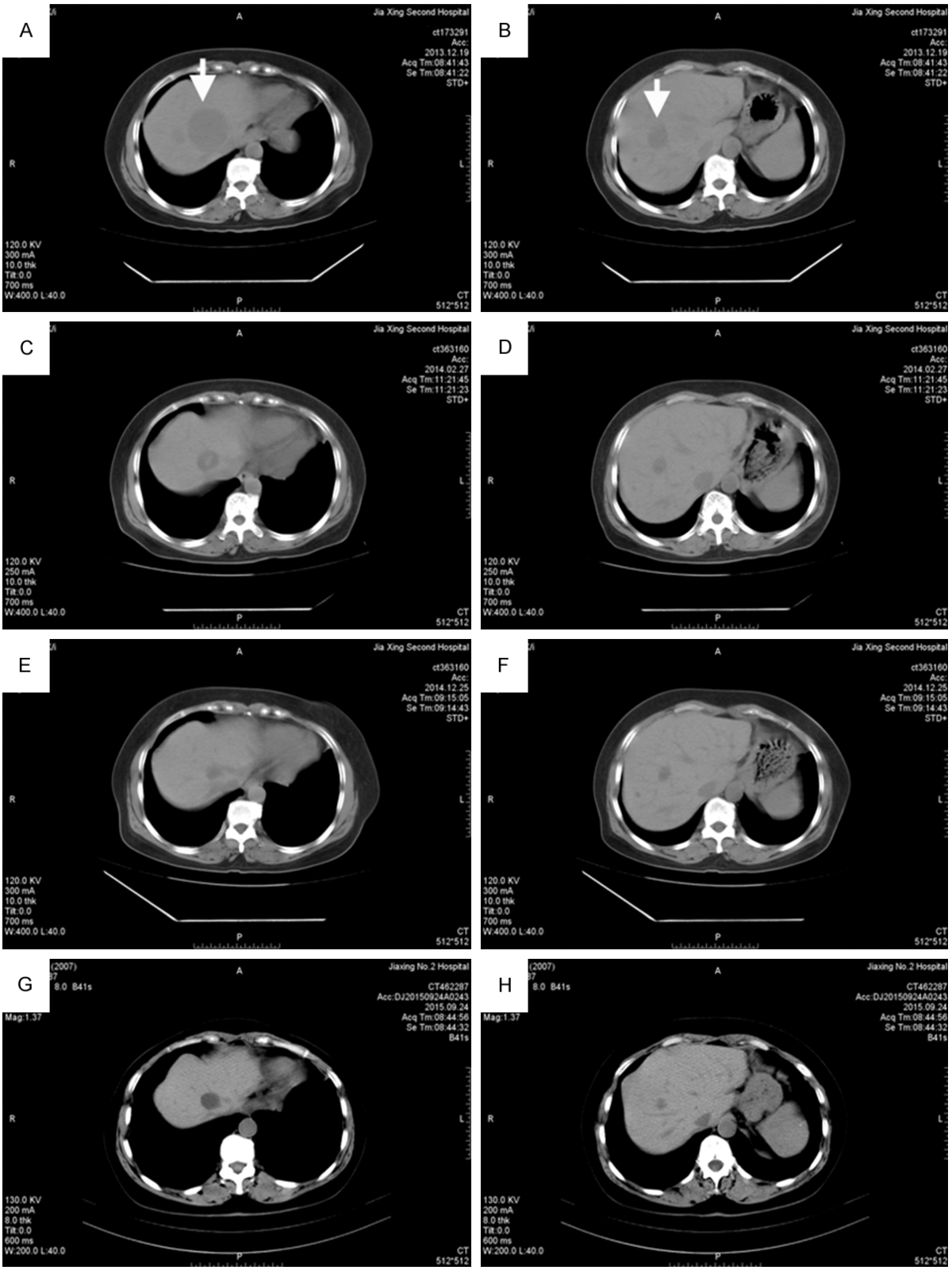


Figure 4. The imaging examination revealing multiple tumors in the liver (black arrow). A, B. Contrast-enhanced computed tomography imaging on Dec 28, 2012. C, D. Contrast-enhanced computed tomography imaging on May 2, 2013. E, F. Contrast-enhanced computed tomography imaging on Sept 6, 2013.

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 track 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


A
Jia Xing Second Hospital
ct173291
Acc:
2013.12.19
Acq Tm:08:41:43
Se Tm:08:41:22
STD+
120.0 KV
300 mA
10.0 thk
Tilt:0.0
700 ms
W:400.0 L:40.0
CT
512*512
B
Jia Xing Second Hospital
ct173291
Acc:
2013.12.19
Acq Tm:08:41:43
Se Tm:08:41:22
STD+
120.0 KV
300 mA
10.0 thk
Tilt:0.0
700 ms
W:400.0 L:40.0
CT
512*512
C
Jia Xing Second Hospital
ct363160
Acc:
2014.02.27
Acq Tm:11:21:45
Se Tm:11:21:23
STD+
120.0 KV
250 mA
10.0 thk
Tilt:0.0
700 ms
W:400.0 L:40.0
CT
512*512
D
Jia Xing Second Hospital
ct363160
Acc:
2014.02.27
Acq Tm:11:21:45
Se Tm:11:21:23
STD+
120.0 KV
250 mA
10.0 thk
Tilt:0.0
700 ms
W:400.0 L:40.0
CT
512*512
E
Jia Xing Second Hospital
ct363160
Acc:
2014.12.25
Acq Tm:09:15:05
Se Tm:09:14:43
STD+
120.0 KV
300 mA
10.0 thk
Tilt:0.0
700 ms
W:400.0 L:40.0
CT
512*512
F
Jia Xing Second Hospital
ct363160
Acc:
2014.12.25
Acq Tm:09:15:05
Se Tm:09:14:43
STD+
120.0 KV
300 mA
10.0 thk
Tilt:0.0
700 ms
W:400.0 L:40.0
CT
512*512
G
Jiaxing No.2 Hospital
CT462287
Acc:DJ20150924A0243
2015.09.24
Acq Tm:08:44:56
Se Tm:08:44:32
B41s
Mag:1.37
130.0 KV
200 mA
8.0 thk
Tilt:0.0
600 ms
W:200.0 L:40.0
CT
512*512
H
Jiaxing No.2 Hospital
CT462287
Acc:DJ20150924A0243
2015.09.24
Acq Tm:08:44:56
Se Tm:08:44:32
B41s
Mag:1.37
130.0 KV
200 mA
8.0 thk
Tilt:0.0
600 ms
W:200.0 L:40.0
CT
512*512

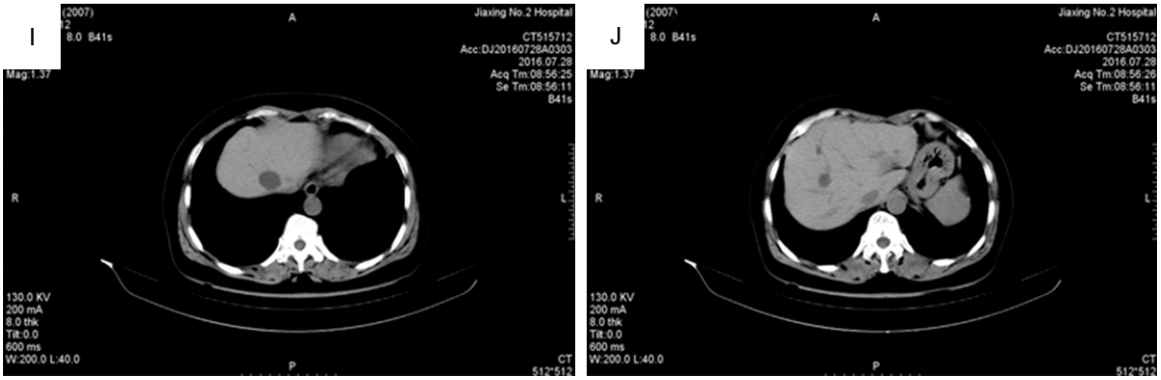


Figure 5. The contrast computed tomography imaging revealing multiple tumors in the liver (white arrow). A, B. Imaging on Dec 19, 2013. C, D. Imaging on Feb 27, 2014. E, F. Imaging on Dec 25, 2014. G, H. Imaging on Sept 24, 2015. I, J. Imaging on Jul 28, 2016.

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 investigations have confirmed the presence of Cajal-like interstitial cells in organs outside of the gastrointestinal 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 mesenchymal stem cells located outside of the gastrointestinal 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 behavior such as metastasis and infiltration of adjacent organ [17]. They usually give metastatic spread into the peritoneal cavity and other organs. However, no common symptoms specific 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 modality 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 treatment and for follow-up surveillance of recurrence [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 tyrosine kinase inhibitor of c-Kit, has been the primary drug available for treatment. It can prevent 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 surgical 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 imatinib 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 consensus 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.

Acknowledgements

We would like to thank Ya-wei Yu (Department of Pathology, the Second Hospital Affiliated to Jiaxing University), for its contribution.

Disclosure of conflict of interest

None.

Address correspondence to: Zhongcheng Zhou, Department of General Surgery, The Second Hospital Affiliated to Jiaxing University, 1518 Huancheng North Road, Jiaxing 314000, China. E-mail: zhouzc0125@163.com

References

[1] Rutkowski P, Hompes D. Combined therapy of gastrointestinal stromal tumors. Surg Oncol Clin N Am 2016; 25: 735-759.

[2] Hechtman JF, DeMatteo R, Nafa K, Chi P, Arcila ME, Dogan S, Oultache A, Chen W, Hameed M. Additional primary malignancies in patients with gastrointestinal stromal tumor (GIST): a clinicopathologic study of 260 patients with molecular analysis and review of the literature. Ann Surg Oncol 2015; 22: 2633-2639.

[3] Aziret M, Cetinkunar S, Aktas E, Irkorucu O, Bali I, Erdem H. Pancreatic gastrointestinal stromal tumor after upper gastrointestinal hemorrhage and performance of whipple procedure: a case report and literature review. Am J Case Rep 2015; 16: 509-513.

[4] Mastoraki A, Toliaki E, Chrisovergi E, Mastoraki S, Papanikolaou IS, Danias N, Smyrniotis V, Arkadopoulos N. Metastatic liver disease associated with gastrointestinal stromal tumors: controversies in diagnostic and therapeutic approach. J Gastrointest Cancer 2015; 46: 237-242.

[5] Zhou J, Teng X. Primary extragastrointestinal stromal tumor of the prostate: a case report. Anal Quant Cytopathol Histpathol 2014; 36: 55-60.

[6] Fu C, Liu N, Deng Q, Tan Y, Ma K, Bie P. Successful treatment of gastrointestinal stromal tumor with multiple liver metastases with radiofrequency ablation and imatinib: a case report. Oncol Lett 2015; 10: 875-878.

[7] Liu L, Zhu Y, Wang D, Yang C, Zhang QI, Li X, Bai Y. Coexisting and possible primary extra-gastrointestinal stromal tumors of the pancreas and liver: a single case report. Oncol Lett 2016; 11: 3303-3307.

[8] Isozaki K, Hirota S. Gain-of-function mutations of receptor tyrosine kinases in gastrointestinal stromal tumors. Curr Genomics 2006; 7: 469-475.

[9] Wang Y, Liu Y, Zhong Y, Ji B. Malignant extragastrointestinal stromal tumor of the liver: a case report. Oncol Lett 2016; 11: 3929-3932.

[10] Agaimy A, Wunsch PH. Gastrointestinal stromal tumours: a regular origin in the muscularis propria, but an extremely diverse gross presentation. A review of 200 cases to critically re-evaluate the concept of so-called extra-gastrointestinal stromal tumours. Langenbecks Arch Surg 2006; 391: 322-329.

[11] Llenas-Garcia J, Guerra-Vales JM, Moreno A, Ibarrola C, Castelbon FJ, Fernandez-Ruiz M, Meneu JC, Ballestin C, Moreno E. Primary extragastrointestinal stromal tumors in the omentum and mesentery: a clinicopathological and immunohistochemical study. Hepatogastroenterology 2008; 55: 1002-1005.

[12] Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152: 1259-1269.

[13] Huizinga JD, Faussone-Pellegrini MS. About the presence of interstitial cells of Cajal outside the musculature of the gastrointestinal tract. J Cell Mol Med 2005; 9: 468-473.

[14] Terada T. Gastrointestinal stromal tumor of the uterus: a case report with genetic analyses of c-kit and PDGFRA genes. Int J Gynecol Pathol 2009; 28: 29-34.

[15] Lin XK, Zhang Q, Yang WL, Shou CH, Liu XS, Sun JY, Yu JR. Primary gastrointestinal stromal tumor of the liver treated with sequential therapy. World J Gastroenterol 2015; 21: 2573-2576.

[16] Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23: 70-83.

[17] Beham AW, Schaefer IM, Schuler P, Cameron S, Ghadimi BM. Gastrointestinal stromal tumors. Int J Colorectal Dis 2012; 27: 689-700.
[18] Yan BM, Kaplan GG, Urbanski S, Nash CL, Beck PL. Epidemiology of gastrointestinal stromal tumors in a defined Canadian health region: a population-based study. Int J Surg Pathol 2008; 16: 241-250.
[19] Sapalidis K, Panteli N, Strati TM, Anastasiadis I, Kanellos I. Surgical management of gastrointestinal stromal tumors: a single centre's experience. Hippokratia 2015; 19: 73-75.
[20] Stamatakos M, Douzinas E, Stefanaki C, Safioleas P, Polyzou E, Levidou G, Safioleas M. Gastrointestinal stromal tumor. World J Surg Oncol 2009; 7: 61.
[21] Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, Sundar HM, Trent JC, Wayne JD. NCCN task force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010; 8 Suppl 2: S1-41; quiz S42-44.
[22] Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, Blay JY, Leyvraz S, Stul M, Casali PG, Zalcberg J, Verweij J, Van Glabbeke M, Hagemeijer A, Judson I. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006; 42: 1093-1103.
[23] Mussi C, Ronellenfitsch U, Jakob J, Tamborini E, Reichardt P, Casali PG, Fiore M, Hohenberger P, Gronchi A. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol 2010; 21: 403-408.
[24] Fiore M, Palassini E, Fumagalli E, Pilotti S, Tamborini E, Stacchiotti S, Pennacchioli E, Casali PG, Gronchi A. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). Eur J Surg Oncol 2009; 35: 739-745.
[25] Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol 2009; 6: 363-371.
[26] Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009; 373: 1097-1104.
[27] Eisenberg BL. The SSG XVIII/AIO trial: results change the current adjuvant treatment recommendations for gastrointestinal stromal tumors. Am J Clin Oncol 2013; 36: 89-90.
[28] Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008; 39: 1411-1419.
[29] Ben Ami E, Demetri GD. A safety evaluation of imatinib mesylate in the treatment of gastrointestinal stromal tumor. Expert Opin Drug Saf 2016; 15: 571-578.