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Primary hepatic gastrointestinal stromal tumor with right adrenal gland invasion

A case report and systematic literature review

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Abstract

Introduction: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors that mainly occur in the gastrointestinal tract. The GISTs that are sporadically reported in extra-gastrointestinal regions are named as extra-gastrointestinal stromal tumors (EGISTs). However, the primary EGISTs that originate from the liver are rare.

Patient Concerns: A 64-year-old female presenting with right upper abdominal pain and thirsty for more than 20 days.

Diagnosis: A diagnosis of a 15 × 14 × 7 cm liver mass located in the posterior right lobe of liver and spread to the right adrenal gland was confirmed. Pathological results showed that the tumor was mainly composed of epithelial cells and tested positive for CD117 and SDHB (succinate dehydrogenase complex iron sulfur subunit B). The gene mutational analyses for c-Kit and platelet-derived growth factor receptor alpha exons revealed negative results. Fluorescence in situ hybridization of murine double minute 2 produced negative fluorescence results which distinguished it from dedifferentiated liposarcomas. The postoperative gastroduodenal and colorectal endoscopy did not find any neoplastic lesions. To this end, the diagnosis of primary hepatic EGIST of wild type nature was confirmed.

Interventions: The patient received right hepatectomy and adrenalectomy, no postoperative chemotherapy was administered.

Outcomes: The patient died 11 months after surgery due to tumor metastasis.

Conclusion: Primary hepatic EGIST is a rare and complicated disease of liver, a multidisciplinary team is necessary in diagnosis and treatment of primary hepatic EGIST.

Abbreviations: EGISTs = extra–gastrointestinal stromal tumors, FISH = fluorescence in situ hybridization, HPF = high-power fields, ICCs = interstitial Cajal cells, MWA = microwave ablation, PDGFRA = platelet-derived growth factor receptor alpha, PET = positron emission tomography, RFA = radiofrequency ablation, sSNP = synonymous single nucleotide polymorphism.

Keywords: chemotherapy, gastrointestinal stromal tumors, gene mutation analysis, pathology

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors and are considered to originate from the interstitial Cajal cells (ICCs) which are pacemakers of the peristaltic activity of the gastrointestinal tract.[1] Genetically, mutations of c-Kit or platelet-derived growth factor receptor alpha (PDGFRA) are known to play important roles in the molecular pathogenesis of GISTs.[2] It is estimated that 5000 patients are newly diagnosed with GIST each year in the United States.[3,4] The classical diagnostic criteria of GISTs is based on morphological and immunohistochemical examinations, because the c-Kit (CD117) protein is positive in approximately 94% to 98% of GISTs patients but rarely detected in other abdominal tumors.[5] GISTs are predominant in the gastrointestinal tract areas such as in the stomach (60–70%), small intestine (20–25%), colon and rectum (5%), and esophagus (<5%).[6] However, because ICCs are also found in organs such as the upper and lower urinary tracts, blood vessels, pancreas, gallbladders and fibrotic liver,[7,8] the number of GISTs cases outside the gastrointestinal (GI) tract are on the rise. These cases are termed as extra-gastrointestinal stromal tumors (EGISTs). Nevertheless, the primary GIST that originates from the liver is extremely rare. The present study will initially describe the procedure of diagnosis and treatment of a rare case of primary hepatic EGIST accompanied with the right adrenal gland invasion. Thereafter, to comprehensively recognize the characteristics of primary hepatic EGIST, a systematic literature review is performed.

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Liang-Liang Xu and Ming Zhang contributed equally to this study.

Written informed consent was obtained from the patient's family member agreeing to publish this case report together with the associated images.

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2. Case information

A 64-year-old female patient was admitted to our hospital in September 23, 2016, with complaints of right upper abdominal pain and feeling thirsty for more than 20 days. She did not present with any other clinical symptoms such as nausea, vomiting, flatulence, constipation, and melena. The patient was diagnosed with hypertension 2 months ago, with the blood pressure (BP) fluctuating between 140 to 160 mm Hg (systolic pressure) and 80 to 100 mm Hg (diastolic pressure), reaching 170/110 mm Hg occasionally. But she did not use any hypotensor or monitor the BP routinely. Two years before, she had undergone a laparoscopic cholecystectomy due to gallstones. There was no history of viral hepatitis or other systemic diseases. No obvious abnormalities were found from the abdominal physical examination. Serum concentration of tumor markers revealed that CA-125 was slightly elevated to 36.15 U/mL (normal range, <35 U/mL), others (alpha fetoprotein, carcinoembryonic antigen, CA-199) were normal. Liver function examination revealed that bilirubin and aminotransferase (alanine aminotransferase and aspartate aminotransferase) were normal, although albumin was decreased to 30.9 g/L (normal range, 40–55 g/L). Renal function was normal. Noradrenaline was obviously increased reaching 548 ng/L (normal range, 174–357 ng/L), while epinephrine was slightly decreased reaching 47 ng/L (normal range, 60–104 ng/L).

The whole abdominal contrast-enhanced computed tomography (CT) scan revealed a 12.3×10.2 cm low-density mass located in the right lobe of liver, enhanced in the arterial phase, and washed-out in the portal phase. The margin of the neoplasm was difficult to distinguish from the right adrenal gland and right

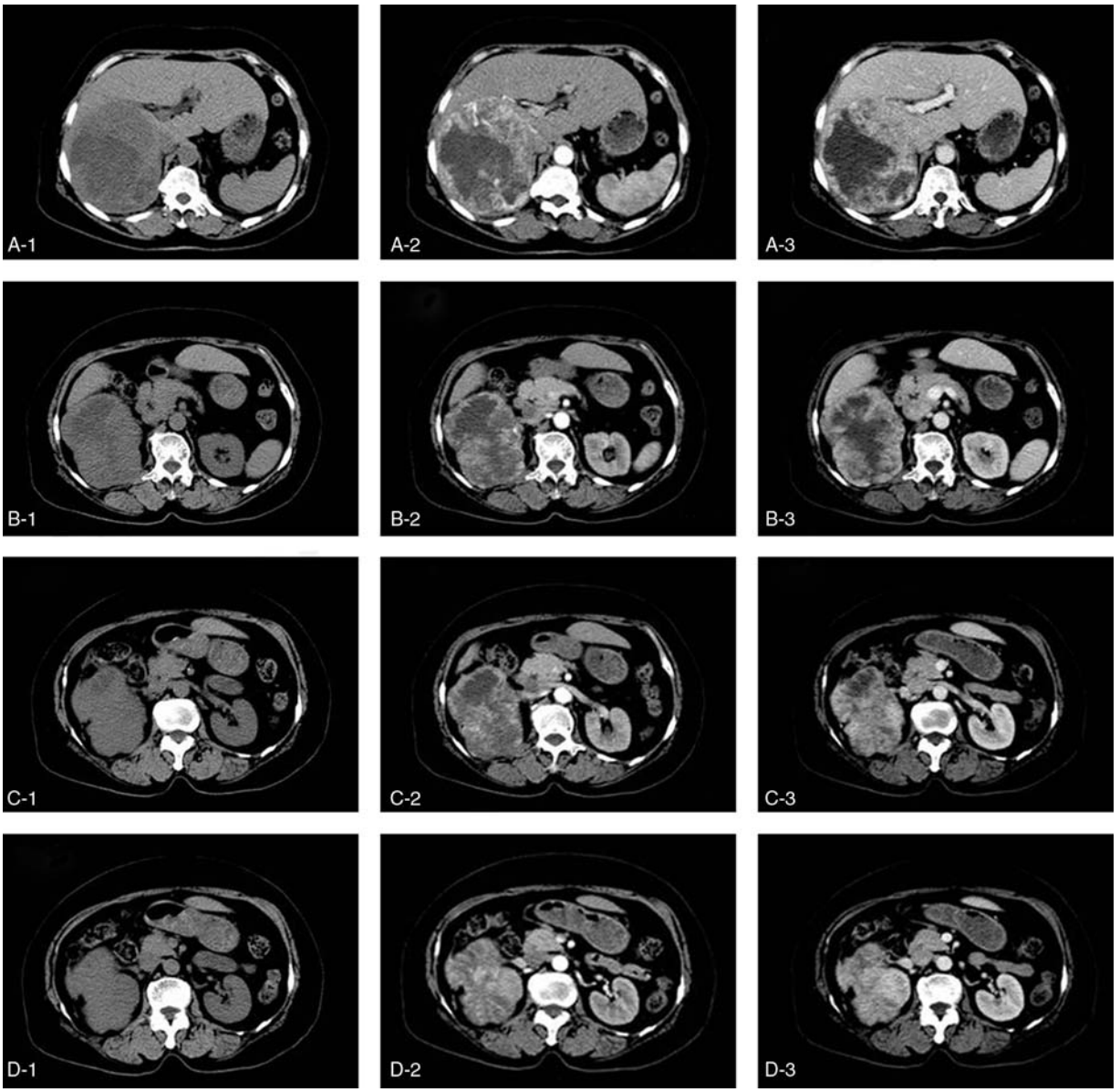

Figure 1. Abdominal contrast-enhanced computed tomography showing a huge low-density mass located in the right lobe of liver, and accompanied with right adrenal gland and right kidney invasion. (A–D) The transverse scan of the first hepatic portal, hepatic-renal space, right adrenal gland, and right kidney level, respectively. (1–3) The presence of contrast-enhanced computed tomography in the plane, arterial, and portal phase.

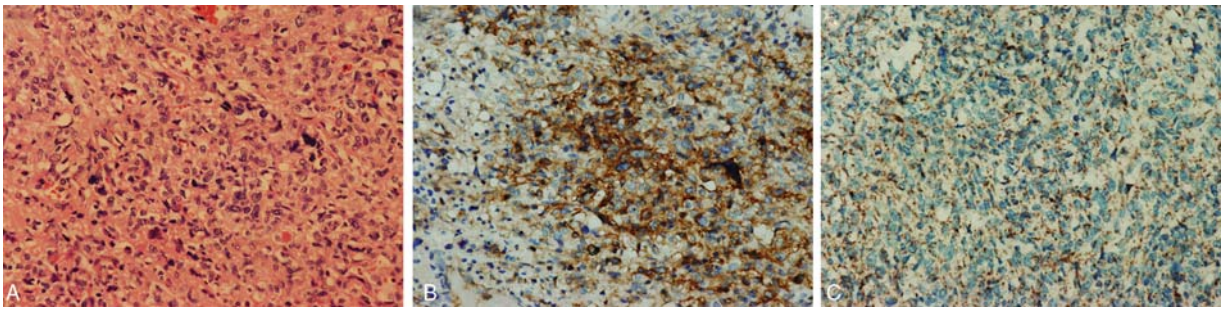

Figure 2. Histological and immunohistochemical findings of hepatic EGIST. (A) The tumor was composed of epithelial cells (hematoxylin–eosin, ×200). (B) The tumor cells were strongly positive for CD117 and slightly positive for SDHB (C). EGISTs = extra–gastrointestinal stromal tumors.

kidney. Initially, hepatocellular carcinoma was suspected because of the typical CT phenomenon (Fig. 1).

According to the location of tumors, the elevated level of noradrenaline and the history of intermittently elevated hypertension, pheochromocytoma with right lobe of liver and kidney invasion was suspected initially. Subsequently, a 20-day preoperative preparation was performed. The detailed protocol was as follows: 1 mg prazosin was given 4 times a day orally, and 2500 mL liquid (colloid: crystal = 3: 2) was transfused daily. In addition, after consulting a cardiologist, 30 mg adalat and 75 mg irbesartan twice a day were given to manage the hypertension.

During the laparotomy, we found that the mass was indeed located in the posterior right lobe had invaded the right adrenal gland. However, the right kidney was not invaded after opening the renal capsule. Additionally, the BP was stable during the surgical process. Moreover, examination of the abdominal cavity did not find any other neoplasm.

On gross observation, the solid mass was found to be $15 \times 14 \times 7$ cm and could be clearly distinguished from the surrounding liver tissues. On cross-section examination, the tumor appeared to be tan-white, medium-texture and focal necrotic and cystic degeneration. Meanwhile, there were no satellite nodules or vascular invasion in the surrounding normal liver tissues.

Microscopically, this hepatic tumor was mainly composed of epithelial cells (Fig. 2A). The immunohistochemical staining specimen showed that CD-117 was strongly positive (Fig. 2B) and SDHB (succinate dehydrogenase complex iron sulfur subunit B) was moderately positive (Fig. 2C). Other parameters including CK, epithelial membrane antigen, glycoprotein hormones, alpha, S-100, CD34, CD31, β-hydroxy-β-methyl butyrate 45, desmin, melanoma antigen recognized by T cells-1, inhibin-α, Syn, murine double minute 2 (MDM2), cyclin-dependent kinase 4, deoxyglucose (DOG)-1 were all negative. Although the pathological results pointed to hepatic GIST, an additional fluorescence in situ hybridization (FISH) examination of MDM2 gene was recommended to further distinguish this condition from the dedifferentiated liposarcoma. However, the FISH result of MDM2 gene showed that MDM2 gene was only expressed in 1% of the cells (positive criteria, ≥10% cells) (Fig. 3). We then screened for the mutation of c-Kit exons 9, 11, 13, 17 and PDGFRA exons 12, 14, 18 using polymerase chain reaction and Sanger sequencing. It was found that there was only 1 synonymous single nucleotide polymorphism (sSNP) in PDGFRA exon 12. Since the liver is the most common metastatic site of GISTs within the gastrointestinal tract, postoperative gastroduodenal and colorectal endoscopy were performed. Interestingly, no neoplastic lesions were observed. To this end, the diagnosis of primary hepatic EGIST of wild type nature was finally confirmed. A previous study showed that adjuvant therapies such as imatinib and sunitinib are not effective for the primary hepatic GIST patients without the mutation of c-Kit and PDGFRA genes.[9] On this basis, postoperative chemotherapy was not administered after communicating with the patient. A clinical follow-up was carried out through outpatient visits at 3 months intervals. Five months after surgery, the patient complained of left hip joint pain, and metastasis at the neck of femur was verified by MRI (Fig. 4AA). However, the liver recurrence was not identified by CT scan (Fig. 4B). The patient died 11 months after surgery due to tumor metastasis.

3. Literature review

Recently, 3 literature reviews have been carried out on the primary hepatic EGIST, which identified 9,[10] 11,[11] and 23[12] cases. To identify more relevant studies and further analyze the characteristics of primary hepatic EGIST, a systematic literature

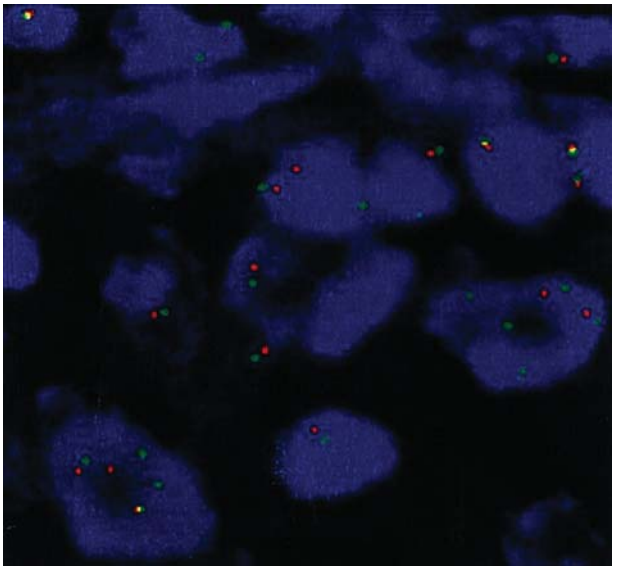

Figure 3. The fluorescence in situ hybridization examination of MDM2 gene. The MDM2 gene amplification was detected in 1% cells. "Green" indicates the CEP12 gene probe, and "Red" indicates MDM2 gene probe.

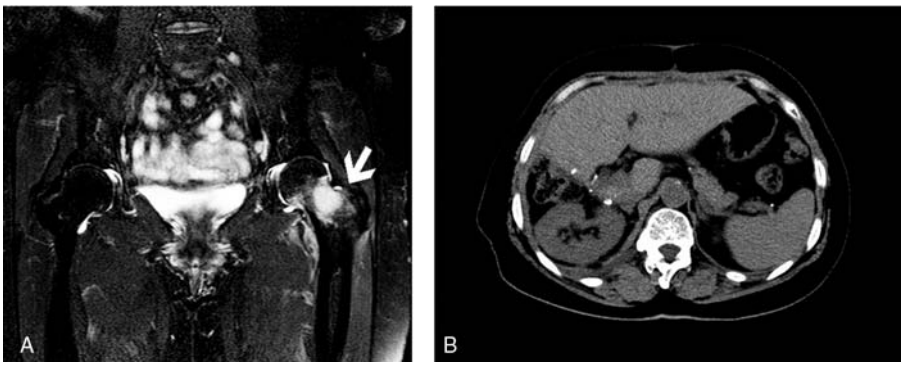

Figure 4. The follow-up results after surgery. (A) The metastasis at the neck of femur was verified by MRI 5 months after surgery. (B) CT scan did not identify liver recurrence.

review was performed via multiple online databases including PubMed (https://www.ncbi.nlm.nih.gov/pubmed), China Hospital Knowledge Database (CNKI) (http://www.chkd.cnki.net), and Wanfang Data (http://www.wanfangdata.com.cn/). The key words including "gastrointestinal stromal tumor and liver," "primary hepatic gastrointestinal stromal tumor," and "extrahepatic gastrointestinal stromal tumor" were used. The references of relevant studies were also carefully scanned to identify more studies. Finally, 30 studies (published between 2003 and 2019) comprising 30 cases (including current case) of primary hepatic EGIST were found. Geographically, most cases were reported in Asia; (China [21, 70.0%],[9,11–30] Japan [3, 10%],[10,31,32] Korea [1, 3.3%]),[33] and other cases were sporadically reported in India (2, 6.67%),[34,35] Italy (2, 6.67%),[36,37] and Chile (1, 3.3%).[38] Among them, 28[9–11,13,14,16–36,38] out of 30 studies provided the basic clinicopathological information and survival outcomes of the patients as shown in the Table 1.

The patients comprised 14 males[9,11,13,17,19,22,23,26,27,29,31–33,36] and 13 females[10,14,16,18,20,21,24,25,28,30,34,35] with the median age of 61 years (range: 17–79). There were no specific symptoms for the patients with primary hepatic EGIST. The main reasons for presentation included up-abdominal pain, shortness of breath, loss of appetite, and physical examination found liver mass or found a palpable epigastric mass. The tumor size ranged from 2.4 to 44 cm with a median size of 15 cm. Among them, 71.4% (20/28) patients[9,11,13,14,17,18,20,21,23,26,27,29–32,34–36,38] had a tumor size of more than 10 cm. Two cases[17,34] presented with multinodular tumors and 1 case[35] had 1 main tumor with 2 small satellite nodules. All other cases had a single separate tumor. With respect to the tumor distribution, 23 out of 28 studies reported that the masses were distributed in 1 lobe of the liver, while the remaining 5 studies[13,17,21,32,34] reported that the masses were distributed in a multilobe pattern in the liver.

The confirmation of primary hepatic EGIST by CT scan was closely associated with the tumor size: the solid mass was commonly observed in the cases where the tumor size was less than 10 cm, while the solid and cystic mixed or even cystic mass was generally observed in the cases where the tumor size more than 10 cm, and the enhancement on the arterial phase was generally presented in the solid parts of the mass due to the abundant feeding arteries.[20,21]

Regarding their treatment, 21 patients[10,11,13–17,19–21,23,25,27,30–36,38] underwent curative hepatectomy, 1 patient[22] underwent laparotomy radiofrequency ablation (RFA) due to a tumor size of 5.1 cm, 1 patient[24] adopted microwave ablation (MWA) for a tumor size of 2.4 cm and 1 patient[29] with multiple huge cystic masses (the smallest 1 was more than 20 cm) underwent repeated drainage, other 4 patients[9,18,26,28] were not treated surgically. For adjuvant therapy, imatinib which is also known as Gleevec, was prescribed for 10 patients[9,11,14,21,24,25,32,34–36] including 1 patient[9] who did not undergo surgery. Morphologically, 23 studies[9–11,13–17,19,21–26,29–36] reported the cell type, of which 19 (82.6%) cases[9–11,13,15–17,19,21–24,26,29,30,33–36] had spindle cells, 2 cases[31] (including current case) had epithelioid cells, and 3 cases[14,25,32] had a mixture of cell types. The mitotic count in the tumor was reported in 19 studies[9–11,13,14,16,21,22,24,25,27,29–34,36] with a range of 0 to 75 mitoses/50 high-power fields (HPF). Five patients[13,22,24,27,31] had a mitotic count of less than 5 mitoses/50 HPF. Similar with the GIST located in GI tract, 27[9–11,13,14,16–31,33–36,38] out of 28 cases were positive for CD117, the remaining case[32] was positive for CD34, protein kinase C θ, vimentin, and smooth muscle actin (SMA). Furthermore, other proteins such as CD34 (57.1% patients), vimentin (35.7% patients), DOG-1 (21.4% patients), and SMA (17.6% patients) were also could be identified in some primary hepatic EGISTs. However, mutation analysis of c-Kit and PDGFRA were only reported in 6 studies[9,21,25,31,32] including the current case. Among these studies, a mutation of exon 11 of c-kit was identified in 2 cases,[21,25] a mutation of exon 12 of PDGFRA was identified in 1 case[31] and no mutation was identified in the remaining 3 cases.[9,32] In the present case, a sSNP was found in exon 12 of PDGFRA. According to the modified National Institutes of Health (NIH) classification system,[39] 26 out of 27 patients (96.3%) were of high-risk grade.

The prognosis outcomes were reported by 17 studies.[9–11,13,14,16,21,22,24,25,27,29,30,32,34–36] During the follow-up, 5 patients[16,25,30,32,36] were diagnosed with recurrent or metastasized tumors. The tissues and organs which primary hepatic EGIST tended to metastasize including hepatic hilar lymph node (1 case),[30] gastric (1 case),[32] lung (1 case),[36] brain (1 case),[16] and bone (present case). And 2 patients[9,16] who were not surgically treated died at 13 months due to primary hepatic EGIST.

4. Discussion

EGISTs have been previously reported in the omentum, mesentery, and retroperitoneum.[40,41] Recently, some studies detected EGISTs in the pericardium,[42] hepatic falciform

Table 1

Clinicopathological characteristics and prognosis outcomes of reported cases suffered from primary hepatic gastrointestinal stromal tumors.

Reference	Year	Country	Age	Sex	Complaint	Location /number	Size (cm)	Mass presentation	Treatment	Cell type	MI (/50 HPFs)	Positive IH items	Mutation analysis	Risk grade	Imatinib	Recurrence (months/ details)	Survival (months/ details)
[30]	2003	China	79	F	Shortness of breath	R/1	15	Solid and cyst	HR	S	20	CD117, CD34, vim	No	High	No	17/Met	21/Alive
[36]	2006	Italy	37	M	No symptom	R/1	18	Solid and cyst	HR	S	20	CD117, vim, CD34	No	High	Yes	14/Met	39/Alive
[17]	2006	China	62	M	Abdominal pain	R+L/2	14.5	Solid and cyst	HR	S	NA	CD117, CD34, CD68	No	High	NA	NA	NA
[29]	2006	China	45	M	Abdominal pain	R/1	20	Cyst	Drainage	S	35	CD117, CD34	No	High	No	NA	3/Alive
[27]	2007	China	67	M	Distention and anhelation	L/1	44	Solid and cyst	HR	NA	3	CD117, CD34	No	High	No	4/DFS	4/Alive
[28]	2008	China	48	F	Physical examination	L/1	4.3	Solid and cyst	No surgery	NA	NA	CD117	No	Unclear	No	NA	NA
[22]	2009	China	17	M	No symptoms	R/1	5.1	Solid	RFA	S	0	CD117, CD34, vim, S100	No	High	No	3/DFS	3/Alive
[32]	2009	Japan	30	M	Abdominal fullness	R+L/1	20	Solid and cyst	HR	M	75	CD117, CD34	Yes, Negative	High	Yes	24/Rec+Met	108/Alive
[31]	2010	Japan	70	M	Loss of appetite	L/1	20	Solid	HR	E	1	CD34, PKCθ, vim, SMA	PDGFRA E12	High	NA	NA	NA
[14]	2010	China	40	F	No symptom	L/1	22	Cyst	HR	M	>5	CD117, vim	No	High	Yes	1/DFS	1/Alive
[26]	2012	China	53	M	Abdominal discomfort	R/1	20	Solid and cyst	No surgery	S	NA	CD117, CD34, DOG1, SMA, vim	No	High	No	NA	NA
[18]	2012	China	65	F	No symptoms	R/1	NA	Solid and cyst	No surgery	NA	NA	CD117, CD34	No	High	No	NA	NA
[16]	2013	China	66	F	Abdominal distention	L/1	8.6	Solid and cyst	HR	S	35	CD117,vim	No	High	No	12/Rec+Met	13/died
[23]	2013	China	71	M	Physical examination	R/1	10	Solid	HR	S	NA	CD117, CD34, DOG1, SMA, vim	No	High	No	NA	NA
[34]	2014	India	55	F	Loss of appetite and pain	R+L/3	18	Solid	HR	S	10	CD117	No	High	Yes	7/DFS	7/Alive
[33]	2014	Korea	71	M	Nausea and indigestion	L/1	7	Solid and cyst	HR	S	32	CD117,DOG1	No	High	No	NA	NA
[13]	2014	China	56	M	No symptoms	R+M/1	10	Solid and cyst	HR	S	<5	CD117, SMA	No	High	No	12/DFS	12/Alive
[35]	2014	India	41	F	Abdominal pain, anorexia	R/2	15	Solid and cyst	HR	S	NA	CD117,SMA	No	High	Yes	5/DFS	5/Alive
[21]	2015	China	60	F	Physical examination	R+C/1	19	Solid and cyst	HR+AT	S	10	CD117,DOG1, vim	E11 of c-kit	High	Yes	12/DFS	12/Alive
[9]	2015	China	65	M	Loss of appetite and pain	L/1	12	Solid and cyst	No surgery	S	25	CD117	Yes, negative	High	Yes	NA	13/Died
[25]	2015	China	67	F	No symptoms	R/1	7.4	Solid and cyst	HR	M	8	CD117, CD34	c-kit E11	High	Yes	25/Rec	50/Alive
[20]	2015	China	48	F	Abdominal pain	L/1	17.6	Solid and cyst	HR	NA	NA	CD117, CD34,DOG1	No	High	No	NA	NA
[24]	2016	China	56	F	Physical examination	L/1	2.4	solid	MWA	S	1–2	CD117,vim	No	Low	Yes	NA	17/Alive
[38]	2016	Chile	61	NA	Palpable mass and pain	L/1	15	Solid and cyst	HR	NA	NA	CD117,CD34	No	High	No	NA	NA
[19]	2016	China	61	M	Physical examination	C/1	7.3	Solid and cyst	HR	S	NA	CD117, CD34, DOG1	No	High	No	NA	NA
[10]	2016	Japan	70	F	Physical examination	L/1	6.8	Solid and cyst	HR	S	35-40	CD117, CD34	No	High	No	6/DFS	6/Alive
[11]	2016	China	63	M	Physical examination	R/1	13	Solid and cyst	HR	S	>5	CD117, CD34	No	High	Yes	60/DFS	60/Alive
Current case	2017	China	64	F	Abdominal pain	R/1	15	Solid and cyst	HR+AL	S	>5	CD117, SDHB	Yes, Negative	High	No	5/DFS	5/Alive

AL = adrenalectomy, AT = autotransplantation, C = caudate lobe of liver, DFS = disease-free survival, DOG = deoxyglucose, E = epithelioid (cell type), and exon (mutation analysis), F = female, HPF = high-power field, HR = hepatic resection, IH = immunohistochemistry, L = left lobe of liver, M = male (sex), and median lobe of liver (location), M = mixed, Met = metastasis, MWA = microwave ablation, NA = not available, PKC = protein kinase C, R = right lobe of liver, Rec = recurrence, S = spindle, SMA = smooth muscle actin, vim = vimentin.

ligament,[43] and diaphragm.[44] Nevertheless, compared with GISTs in the GI tract, EGISTs are rare and reported sporadically. To date, only 30 cases including current one have been reported on primary hepatic EGIST worldwide.

Here, we described a clinical case which was diagnosed as primary hepatic EGIST by morphological and immunochemical examinations. Although the mutational analyses of c-Kit and PDGFRA were negative, the typical epithelial cells, strong positive results for CD117, and the absence of MDM2 gene amplifications supported the diagnosis of GISTs.[45] Moreover, the preoperative whole abdominal enhanced CT scan, intraoperative abdominal examinations, and postoperative endoscopy did not identify any tumors in the abdominal cavity. Based on these evidence, we thought that the GIST was primarily derived from the liver. To the best of our knowledge, this is the first time a primary hepatic EGIST invading the surrounding organs has been reported. This is also the first study to report that a primary hepatic EGIST could metastasize to the bones after surgery. Additionally, we show for the first time that a primary hepatic EGIST may be pathologically positive for SDHB antibody.

Given that there was no specific symptom or typical presence in radiography for primary hepatic EGIST, it is difficult to distinguish primary hepatic EGIST from other liver tumors preoperatively, and thus these types of tumors are often misdiagnosed. Just as current case, the adrenohepatic fusion caused by tumor invasion, not well controlled BP and the increased serum noradrenaline level caused the misdiagnosis before surgery. Fortunately, the delayed operation did not influence the curative resection of the tumor.

Similar to EGISTs, the current diagnosis of primary hepatic EGIST is mainly based on the typical postoperative morphological features (spindle, epithelioid, or mixed cell type) and immunoreactivity of c-Kit (CD117). In addition to these features, mutation analyses for exon 9, 11, 13, and 17 of c-Kit (80% of primary GISTs) and exon 12, 14, and 18 of PDGFRA (10% of primary GISTs) are strongly recommended, because they were useful to verify GISTs which are negative for CD117.[46] Furthermore, it is worthy to note that the exclusion of the hepatic EGIST metastasized from gastrointestinal tract or other organs is also crucial. Therefore, the abdominal cavity should be examined in patients with liver tumors without any underlying liver diseases or elevated serum tumor markers. In these cases, upper and lower gastrointestinal endoscopic examinations or even $_{18}$F-Fluoro-2-deoxyglucose positron emission tomography are recommended once they are diagnosed with hepatic EGIST pathologically.

The en bloc resection of the tumor is regarded as the most effective option for primary hepatic EGIST. Indeed, previous study showed that surgery seems to eliminate the poor prognosis caused by the large tumor size and multiple tumor numbers in GISTs cases.[3,39,47] Noteworthy, deaths due to primary hepatic EGIST were reported in 2 studies for patients who did not undergo surgical treatment. For adjuvant therapy, imatinib which is a KIT/PDGFRA tyrosine kinase inhibitor has been shown to be beneficial to GISTs patients, and is recommended for high-risk patients after surgery.[48–50] However, we found that only 39.3% (11 out of 28) hepatic EGIST patients received the imatinib treatment. Meanwhile, few studies prescribed imatinib guiding by the mutation analyses of c-Kit and PDGFRA, because the higher dose of imatinib (800 mg per day other than normally 400 mg per day) was recommended for patients with c-Kit exon 9 mutation[51,52] and the imatinib was less sensitive or even resistant for the patients with PDGFRA exon 18 mutation.[53]

Taken together, this study showed that primary hepatic EGIST is a rare and complicated disease. As a result, a multidisciplinary team is necessary in diagnosis and treatment of primary hepatic EGIST.

Author contributions

Conceptualization: Mingqing Xu
Data curation: Liangliang Xu
Methodology: Ming Zhang
Project administration: Mingqing Xu
Writing – original draft: Liangliang Xu, Ming Zhang
Writing – review & editing: Mingqing Xu
Conceptualization: Mingqing Xu.
Formal analysis: Liangliang Xu.
Methodology: Liangliang Xu.
Writing – original draft: Liangliang Xu, Ming Zhang.
Writing – review & editing: Mingqing Xu.

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