Incidentally Detected Gastric Gastrointestinal Stromal Tumor during Living Donor Liver Transplant Surgery for Hepatocellular Carcinoma: The First Two Cases

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ABSTRACT

Coexistence of hepatocellular carcinoma and gastrointestinal stromal tumor is rare. In this case series, we aimed to present an unusual coincidence of a gastrointestinal stromal tumor and hepatocellular carcinoma in patients who underwent living donor liver transplantation for hepatocellular carcinoma who had an incidental gastric gastrointestinal tumor which was detected intraoperatively.

KEYWORDS: Gastrointestinal stromal tumor; Hepatocellular carcinoma; Living donor, Incidental discovery; Neoplasms; Stomach

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare but potentially malignant tumors that originate in the wall of gastrointestinal tract. They are responsible for 1% of all gastrointestinal neoplasms and they originate mainly in the stomach and small intestine [1]. GISTs can occur simultaneously with chronic lymphocytic leukemia, lymphoma, renal cell carcinoma or gastric cancer, but the association with hepatocellular carcinoma (HCC) is extremely rare [2].

HCC is the most common form of liver cancer. The global prevalence of HCC is increasing and more than 600 000 people die from HCC each year. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common etiological factors for HCC [3]. Loco-regional, surgical (resection or liver transplantation) and systemic therapies are the main treatment methods for HCC [4].

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It is very rare to encounter an unexpected extrahepatic malignancy during liver transplant surgery and the decision whether to continue the operation can be challenging for surgeons. It is also extremely rare to detect incidental gastric GIST as a second malignancy during a living donor liver transplant operation for a patient with HCC, and we herein report the first two cases in the literature.

CASE 1 PRESENTATION

A 59-year-old woman was admitted to our institute with cirrhosis due to chronic HBV and HDV coinfection. A multi-detector computed tomography (MDCT) scan showed hepatic cirrhosis and a 7 cm diameter mass in the right liver lobe (segment VI) and 2 cm mass in segment IV, with both showing arterial enhancement, compatible with HCC. The alpha-fetoprotein (AFP) level was 11.010 ng/ml preoperatively. One session of trans-arterial chemoembolization (TACE) was performed and three months after this procedure the control AFP level decreased to 383 ng/ml. There was no extrahepatic spread on PET-CT and the 2 viable tumors changed in size to 3.3 cm and 1.4 cm, respectively. The patient then

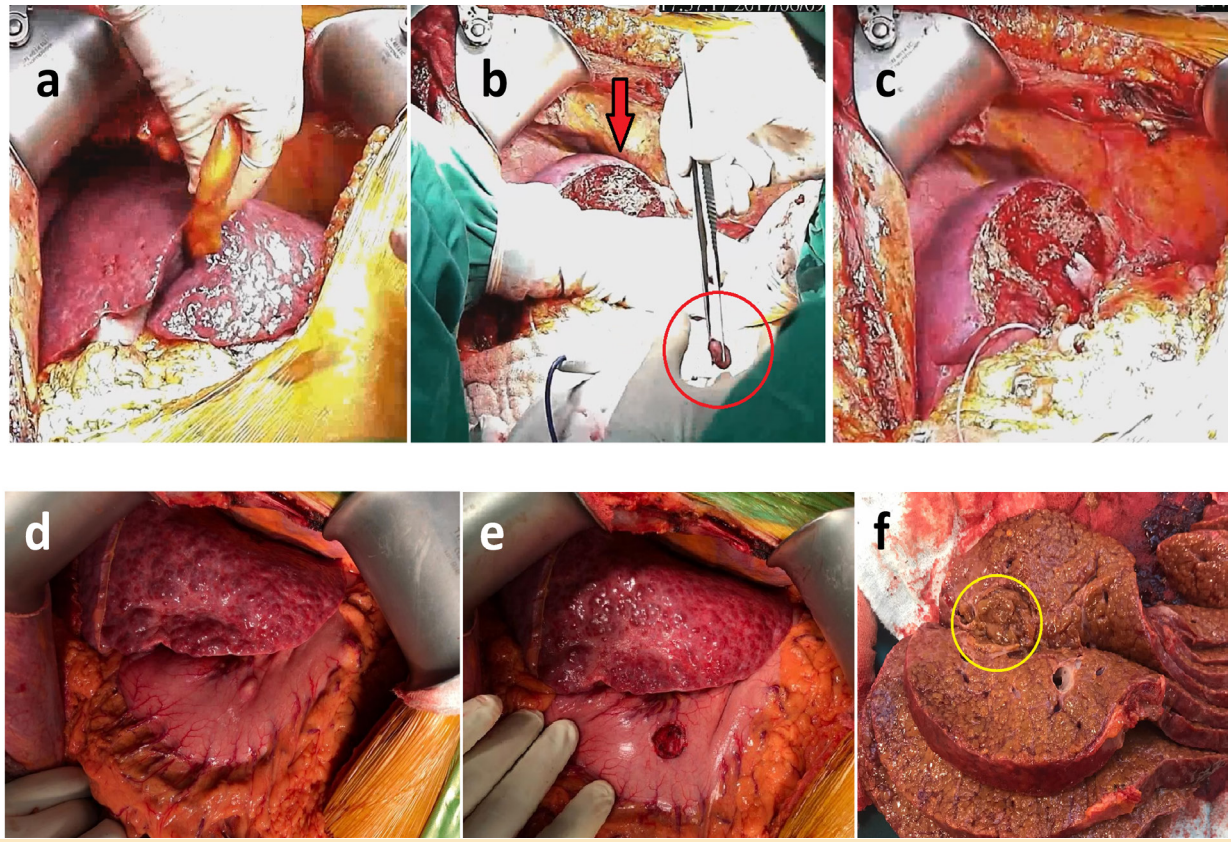

Figure 1: a) Cirrhotic liver of Case 1 b) The view of resected GIST of Case 1, c) The view of at the end of the LDLT operation of Case 1, d) The view of cirrhotic liver and GIST at the corpus of stomach in Case 2, e) The view of resection area of the GIST, f) the view of HCC nodule 3.5 cm diameter in segment 7 of Case 2.

underwent living donor liver transplantation (LDLT) 3 month after the single TACE session. The live liver donor was her 28-year-old son. During abdominal exploration, liver was seen to be cirrhotic (Fig 1a) and a 2x2 cm, exophytic, subserosal mass lesion was detected in the fundus of the stomach intraoperatively, which was resected with clear surgical margins at the same session (Fig 1b) and the planned LDLT procedure was completed (Fig 1c). On histopathologic examination, two HCC nodules (one of them at segment 6 with a 7 cm diameter and centrally necrotic, and the other one at segment 4 with a 2 cm diameter) and a gastric GIST were detected. The histopathological examination results of HCC nodules and gastric GIST are summarized in Table 1. The postoperative period was uneventful, and the patient was discharged home on post-operative day 10. Post-transplant immunosuppression consisted of tacrolimus and everolimus. The patient was monitored on regular follow-up until 38 months after surgery so far. No signs of recurrence for HCC, GIST or HBV were detected and the current AFP level is 1.1 ng/ml.

CASE 2 PRESENTATION

A 56-year-old man was admitted with cirrhosis due to chronic HBV and HDV coinfection. A dynamic magnetic resonance scan image showed hepatic cirrhosis and a 4x3 cm diameter nodule with arterial enhancement in segment 7 of the liver, compatible with HCC. The AFP level was 4.4 ng/ml preoperatively. There was no extrahepatic spread on imaging, and he underwent LDLT. The live liver donor was his 34 years-old son. During abdominal exploration, a 1.5x1 cm, exophytic, subserosal mass lesion was detected in the corpus of stomach intraoperatively and the lesion was resected with clear surgical margins (Fig 1d and 1e), and frozen section revealed low grade

Table 1: Clinical characteristics of the patients and histopathology features of the tumors.

Parameters	Case 1	Case 2
Age	58	56
Gender	F	M
CHILD score, class	A	A
MELD score	8	9
BMI, kg/m2	27.7	22
GRWR, %	1.34	1.33
HBV DNA PCR, IU/mL*	Negative	Negative
HDV RNA PCR*	Negative	479 copy/mL
DELTA (HDV) Antibody*	Positive	Positive
AFP, ng/mL*	384	4.4
AST, IU/mL*	28	57
ALT, IU/mL*	26	52
ALP, IU/mL*	105	82
GGT, IU/mL*	39	71
PLR*	25.7	81.5
NLR*	1.2	1.4
Loco-regional treatment	TACE (1 session)	None
Histopathological features of the hepatocellular carcinoma		
Dominant tumor size, cm	7 (necrotic)	3.5
Number of nodules	2	1
Differentiation	Well	Well
Microscopic venous invasion	Negative	Negative
Macroscopic venous invasion	Negative	Negative
Glisson Capsule invasion	Negative	Negative
Lymph node metastasis	Negative	Negative
Surgical margins	Tumor free	Tumor free
Histopathological features of the gastrointestinal stromal tumor		
Dominant tumor size, cm	2	1,5
Atypia / Necrosis	Negative	Negative
Mitotic index	1/50 HPF	1-2/50 HPF
Ki-67	< 5%	< 5%
CD 117	Positive	Positive
Vimentin	Positive	Positive
Surgical margins	Tumor free	Tumor free
Post-transplant management		
Immunosuppression		
First month	Steroid + Tacrolimus + MMF	
1 – 3 months	Steroid + Tacrolimus low dose + MMF + Everolimus	
Maintenance	Tacrolimus low dose + Everolimus	
HBV prophylaxis	Intraoperative HBV Ig 2000 IU i.v. at the unhepatic phase 500 IU i.v. HBV Ig daily for first week Antiviral, daily for life-long HBV Ig i.v., monthly (the goal anti-HBS ab titer > 50 IU/mL)	
Current status	PO 38th month, alive without any recurrence of HCC, GIST and HBV	PO 6th month, alive without any recurrence of HCC, GIST and HBV

*Parameters are the last lab values before liver transplantation

stromal tumor. LDLT was then completed uneventfully. On histopathologic examination, one HCC nodule, 3.5 cm diameter at segment 7 (Fig 1f) and a gastric GIST were detected. The histopathological features of the HCC nodule and gastric GIST are summarized in Table 1. His HBs Ag was still positive on the 2nd postoperative week and liver transaminases were high. Additional HBV Ig 2000 IU daily was then administered for 4 days and his HBs Ag test became negative and transaminase levels normalized. The patient was discharged on the post-operative day 39. Post-transplant immunosuppression consisted of tacrolimus and everolimus. The patient was monitored in regular follow-up until 6 months after surgery. No signs of recurrence for HCC, GIST or HBV were detected and the current AFP level is 0.6 ng/ml.

DISCUSSION

GISTs can originate from anywhere in the gastrointestinal tract and give rise to metastases predominantly in the liver (more than 60% of metastases) or in the peritoneum [5]. Although GISTs have a high (13-43%) prevalence of synchronous malignant tumors, association with HCC is quite rare [6-7]. To our knowledge, 6 cases have been reported of the association of GIST and a primary liver tumor in the literature. One of them is a perivascular epithelioid cell tumor of the liver [8] and the others are HCC [9-12]. These 2 cases are the first report in the literature that liver transplantation was performed in patients who had coincidental gastric GIST with HCC in a cirrhotic liver.

Liver transplant recipient candidates are screened systematically for the presence of extrahepatic malignancy, since current or prior extrahepatic malignancies that do not meet oncological definition of "cure" are all contraindications to transplantation. Once patients are placed on immunosuppression after transplantation, they are at higher risk for de novo malignancies and may be at increased risk for recurrent malignancy [13]. However, some of them cannot be diagnosed preoperatively and can be detected incidentally during the transplant surgery, like our cases [14]. In our case 1, GIST of stomach could not be detected even by PET-CT. After the operation, we rechecked the MDCT and realized there was a GIST of the stomach but in the second case no imaging could detect the GIST of stomach.

In a recent study from Asan Medical Center, the most common incidentally detected malignancies in 41 liver transplant recipients were colorectal, thyroid and stomach cancer, respectively. Post-transplant tumor recurrence is higher in this group and authors conclude that early-stage extrahepatic malignancy patients may be eligible for upfront LDLT. In this single center study, but with the largest number of patients, there was no gastric GIST co-existence with HCC [14].

All demographic and laboratory parameters were similar in our cases except gender and AFP serum levels. Both of our patients had good prognostic criteria for post-transplant tumor recurrence (summarized in Table 1). We routinely use mTOR inhibitor (Everolimus) due to its anti-tumor effects in our LT patients with HCC. Thus, post-transplant maintenance immunosuppression with low dose Tacrolimus and with Everolimus was used in our patients. We also use hepatitis B Ig in addition to antivirals for HBV prophylaxis in our LT patients with HBV.

The management of this unexpected situation is difficult because LT can treat the HCC but cannot treat the gastric GIST. According to National Comprehensive Cancer Network Guideline Version 6.2019, the predicted metastasis rate is 0 % in GISTs with tumor size ≤ 2 cm and mitotic rate ≤ 5 mitoses/50 HPFs [15]. In case of incidentally detected, exophytic, small gastric GIST during liver transplant surgery, we suggest the resection of the GIST with clear surgical margins, confirming the low risk malignancy of the GIST by frozen section and then completion of the planned liver transplantation. There is no information about GIST prognose is after liver transplantation in the literature, but our 2 patients are still alive without either GIST or HCC recur-

rence. Both patients did not receive any adjuvant therapy for GISTs, and they also have no HBV recurrence.

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