Case Report

De novo Hepatocellular Carcinoma after Liver Transplantation

Sammy Saab*[1,2], Kali Zhou[1], Edward K Chang[1] and Ronald W Busuttil[2]

[1]*Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;* [2]*Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*

Abstract

Liver transplantation is the definitive therapy for patients with advanced liver disease and its complications. Patients who are transplanted with a diagnosis of hepatocellular carcinoma (HCC) are at risk of recurrent cancer, and these patients are monitored on a regular basis for recurrence. In contrast, *de novo* HCC following liver transplantation is a very rare complication, and recipients without HCC at the time of transplantation are not screened. We describe the clinical features of *de novo* HCC over a decade after achieving a sustained viral response with treatment of hepatitis C and two decades after liver transplantation. Our case highlights the necessity of screening for HCC in the post-transplant patient with advanced liver disease even after viral clearance.

Introduction

Hepatocellular carcinoma (HCC) is an important indication for liver transplantation.[1] The risk of recurrent HCC depends on a number of factors, such as tumor burden, grade, and vascular invasion. Recipients transplanted for HCC are frequently surveyed for recurrent cancer.[2,3] Liver transplant recipients are also screened for a number of *de novo* malignancies.[4] *De novo* malignancies in liver transplant recipients are believed to be related to duration and intensity of immunosuppressive therapy.[5] *De novo* HCC in liver transplant recipients and HCC recurrence after liver resection occur predominantly in the liver, whereas recurrent HCC occurs extra-hepatically.[6] *De novo* HCC refers to the development of HCC in a liver transplant recipient without a history of HCC.[7]

De novo HCC is an uncommon complication in liver transplant recipients.[8–15] Although screening guidelines exist for a variety of malignancies in liver transplant recipients, no recommendations exist for screening of *de novo* HCC. We report a woman who developed *de novo* HCC over two decades after her initial liver transplantation.

Case report

The patient is a 47-year-old woman from Kuwait who underwent initial orthotopic liver transplantation (OLT) in the United Kingdom (UK) in 1989 for hepatitis C virus (HCV)-related cirrhosis. Post-OLT, she had a complicated medical course, including prolonged ventilatory failure with development of tracheoesophageal fistula and tracheal stenosis. She also required a colectomy and ileostomy for ulcerative colitis. Her course was also complicated by the need for multiple biliary tract dilatation and stent placement for biliary anastomotic strictures. She achieved a sustained viral response with interferon and ribavirin after a histological diagnosis was made of bridging fibrosis. She was followed regularly with laboratory tests. Because there was no evidence of malignancy on the explant, surveillance imaging was not performed.

While undergoing evaluation for ileostomy takedown, a magnetic resonance cholangiopancreatography (MRCP) in August 2008 revealed a 3 cm lesion in segment 1 of the liver, diagnosed as *de novo* HCC. Upon tissue diagnosis, the patient was treated with chemoembolization, radiofrequency ablation, and sorafenib in the UK. Despite treatment, her alpha fetoprotein (AFP) remained elevated at 1,180 ng/mL, and she was referred to University of California, Los Angeles (UCLA) for consideration of repeat OLT.

At UCLA, she was noted to be a thin woman with no stigmata of chronic liver disease. An ileostomy was present at the right lower quadrant. Computed tomography imaging of the abdomen revealed an ill-defined area of rounded enhancement measuring 4.7 cm × 3.9 cm hypodense lesion, corroborated as a mildly hypervascular lesion on magnetic resonance imaging (Fig. 1). Pathology was consistent with a well to moderately differentiated HCC. The multidisciplinary hepatobiliary tumor board recommended chemoembolization for treatment of the HCC. The patient underwent another two rounds of chemoembolization in 2011 while listed for transplant. Whole body imaging confirmed no evidence of metastatic disease. She received a regional review board model end-stage liver disease (MELD) exception for meeting University of California, San Francisco (UCSF) criteria.[16]

The patient underwent another liver transplant in March of 2012. Three months prior to transplant, she had undergone magnetic resonance imaging that failed to show evidence of recurrent HCC, despite an AFP value greater than 1,000 ng/mL. Systemic chemotherapy was not offered prior to her

Keywords: *De novo* hepatocellular carcinoma; Liver transplantation.
Abbreviations: AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model end-stage liver disease; MRCP, magnetic resonance cholangiopancreatography; OLT, orthotopic liver transplantation; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco; UK, United Kingdom.
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***Correspondence to:** Sammy Saab, 200 Medical Plaza, Suite 214, Los Angeles, CA 90095, USA. Tel: +1-310-206-6705, Fax: +1-310-206-4197, E-mail: SSaab@mednet.ucla.edu

Table 1. Summary of the literature on *de novo* hepatocellular carcinoma in liver transplant recipients

Patient	Ref.	OLT indication	Age	Gender	Treatment	Immunosuppression	Interval (yr)	Outcomes
1	Saxena *et al*[8]	HCV and ALD	63	M	None	CSA and AZA	7	Died 75 d after retransplantation from sepsis
2	Al-Joundi *et al*[9]	HCV and ALD	41	M	IFN	NR	2.2	Died 2 mo after HCC diagnosis
3	Levitsky *et al*[10]	HCV and ALD	48	M	None	CSA, AZA, Pred	5	Died from group G streptococcus
4	Croitoru *et al*[11]	HCV and NAFLD	61	M	IFN/R	CSA & AZA	6	Underwent 2nd OLT, post cirrhosis OLT state unknown
5	Flemming *et al*[12]	HBV	NR	M	HBIG	HBIG	9	Free of disease for 2 yr
6	Flemming *et al*[12]	HBV	NR	M	HBIG & Famciclovir	HBIG and Famciclovir	8	Free of disease for 1 yr
7	Torbenson *et al*[13]	HBV	51	M	IFN	NR	8.5	Died 1 mo after retransplantation because of sepsis
8	Kita *et al*[14]	HBV	43	M	None	NR	8	Retransplanted, free of HBV and HCC 2 yr after 2nd OLT
9	Yu *et al*[15]	HBV	36	M	Antivirals, HBIG	FK, MMF and Pred	8	Died from respiratory failure 4 mo after diagnosis
10	Sotiropoulos *et al*[19]	Budd-Chiari syndrome	61	F	None	NR	22	Died 11 mo after HCC diagnosis
11	Sotiropoulos *et al*[19]	ALD	65	M	None	NR	5	Died due to brain stem ischemia 4 yr after HCC diagnosis
12	Vernadakis *et al*[20]	ALD	59	M	None	CSA, MMF, Pred	3	No signs of HCC recurrence about 12 mo after resection
13	Tamè *et al*[21]	HCV	58	M	Lam, HBIG Two cycle of anti-HCV therapy	FK and Pred taper	16	HCC treated with TACE. Awaiting 2nd transplant.
14	Our case	HCV	47	F	IFN/R	FK, MMF	15	Died due to respiratory distress

ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; IFN, interferon; R, ribavirin; HBIG, hepatitis B immunoglobulin; NR, not reported; TACE, transarterial chemoembolization; AZA, azathioprine; CSA, cyclophosphamide; FK, tacrolimus; MMF, mycophenolate mofetil; OLT, orthotopic liver transplantation; Pred, prednisone.

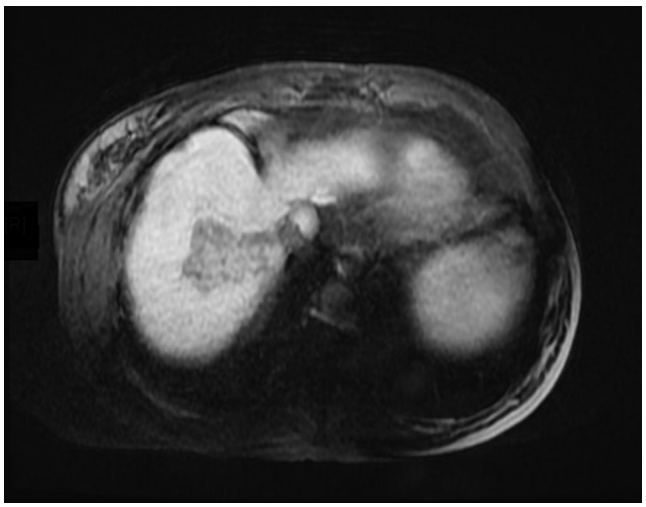

Fig. 1. Hypervascular hepatic mass measuring 4.7 cm × 3.9 cm.

second transplant because there was radiological evidence of tumor.

Findings on explanted liver included a grade 2/4 HCC measuring 6.1 cm in maximal diameter, small and large vessel lymphovascular tumor invasion, and cirrhosis. After transplant, the AFP level decreased to 54.6 ng/mL. On routine chest imaging 9 mo after transplant, a new right lower lobe pleural lesion was noted. Biopsy of one lesion was consistent with recurrent metastatic HCC.

Despite the use of sirolimus, sorafenib, gemcitabine, oxaliplatin, and capecitabine, there was progression of metastatic disease with additional involvement of the skull and dura. The patient expired of respiratory distress in August of 2014.

Discussion

Recommendations exist for the screening of new HCC in the general population and for *de novo* cutaneous malignancies in liver transplant recipients.[4,17] *De novo* HCC is an infrequent complication in liver transplant recipients.[18] Most cases of *de novo* HCC in liver transplant recipients have occurred in men and in the setting of viral hepatitis B or C. However, Budd-Chiari and alcohol liver disease alone have also been associated with *de novo* HCC (Table 1).[19,20] The time interval between liver transplant and diagnosis of *de novo* HCC ranges between 2 and 22 years. The interval between transplant and diagnosis of *de novo* HCC in this case is one of the longest intervals to be reported.

In our review of published cases (including ours), three patients were found to have *de novo* HCC at the time of a second transplant (Table 1).[8,11,13] Of the 13 cases, two were multifocal and in the other 11 cases the mean diameter was 3.2 cm with a range between 0.7 to 7.3 cm.[8,10,12–14] No treatment was rendered to four patients,[9,10,19,20] one underwent radiofrequency ablation,[13] two had surgical resection,[13] and three had transarterial chemoembolization (including our patient).[14,19,21] Two cases of HCC have been described in recipients with a history of HCC in the explants, but evidence of a HCC in the new graft with cells likely originating from the donor.[22,23]

Our case report highlights that despite achieving a sustained viral response, liver transplant recipients may remain at risk of HCC if cirrhosis has developed. Indeed, achieving a sustained viral response may reduce the risk of HCC but does not necessarily eliminate it.[24]

Differentiating between *de novo* and recurrent HCC is important, particularly when considering retransplantation, since recurrent HCC is more likely to be associated with metastatic disease. Retransplanting patients for recurrent HCC is contraindicated because of poor survival.[25–27] Our patient did not have HCC at the time of her first transplantation. All previous cases describing *de novo* HCC occurring in the setting of HCV noted a concomitant cause of liver disease from alcohol or fatty liver. Our patient was neither overweight or had a history of alcohol use. Another possibility is that the tumor arose for from the donor. We do not believe this is likely in our patient, given the long duration between transplantation and diagnosis of *de novo* HCC (approximately two decades). HCC described in two cases occurred less than 7 years from transplant.[22,23]

Conclusions

The review of prior cases also highlights the need for effective therapy for HCC in liver transplant recipients. Patients were treated with a variety of modalities, including systemic therapy, resection, locoregional therapy, and retransplantation. Treatment efficacy is limited for a majority of patients, including our patient, who had expired at the time of case report publication.

Conflict of interest

None.

Author contributions

Designing the research study (SS, KZ), collecting the data (KZ, EKC), writing the manuscript (SS, KZ), critically reviewing and revising the manuscript (SS, KZ, EKC, RWB).

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