Case Report

De novo Hepatocellular Carcinoma after Liver Transplantation

Sammy Saab*1,2, Kali Zhou1, Edward K Chang1 and Ronald W Busuttil2

1Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; 2Department 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.

Keywords: De novo hepatocellular carcinoma; Liver transplantation.

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ref.</th>
<th>OLT indication</th>
<th>Age</th>
<th>Gender</th>
<th>Treatment</th>
<th>Immunosuppression</th>
<th>Interval (yr)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saxena et al⁹</td>
<td>HCV and ALD</td>
<td>63</td>
<td>M</td>
<td>None</td>
<td>CSA and AZA</td>
<td>7</td>
<td>Died 75 d after retransplantation from sepsis</td>
</tr>
<tr>
<td>2</td>
<td>Al-Joundi et al⁹</td>
<td>HCV and ALD</td>
<td>41</td>
<td>M</td>
<td>IFN</td>
<td>NR</td>
<td>2.2</td>
<td>Died 2 mo after HCC diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>Levitsky et al¹⁰</td>
<td>HCV and ALD</td>
<td>48</td>
<td>M</td>
<td>None</td>
<td>CSA, AZA, Pred</td>
<td>5</td>
<td>Died from group G streptococcus</td>
</tr>
<tr>
<td>4</td>
<td>Croitoru et al¹¹</td>
<td>HCV and NAFLD</td>
<td>61</td>
<td>M</td>
<td>IFN/R</td>
<td>CSA &amp; AZA</td>
<td>6</td>
<td>Underwent 2nd OLT, post cirrhosis OLT state unknown</td>
</tr>
<tr>
<td>5</td>
<td>Flemming et al¹²</td>
<td>HBV</td>
<td>NR</td>
<td>M</td>
<td>HBIG</td>
<td>HBIG</td>
<td>9</td>
<td>Free of disease for 2 yr</td>
</tr>
<tr>
<td>6</td>
<td>Flemming et al¹²</td>
<td>HBV</td>
<td>NR</td>
<td>M</td>
<td>HBIG &amp; Famciclovir</td>
<td>HBIG and Famciclovir</td>
<td>8</td>
<td>Free of disease for 1 yr</td>
</tr>
<tr>
<td>7</td>
<td>Torbenson et al¹³</td>
<td>HBV</td>
<td>51</td>
<td>M</td>
<td>IFN</td>
<td>NR</td>
<td>8.5</td>
<td>Died 1 mo after retransplantation because of sepsis</td>
</tr>
<tr>
<td>8</td>
<td>Kita et al¹⁴</td>
<td>HBV</td>
<td>43</td>
<td>M</td>
<td>None</td>
<td>NR</td>
<td>8</td>
<td>Retransplanted, free of HBV and HCC 2 yr after 2nd OLT</td>
</tr>
<tr>
<td>9</td>
<td>Yu et al¹⁵</td>
<td>HBV</td>
<td>36</td>
<td>M</td>
<td>Antivirals, HBIG</td>
<td>FK, MMF and Pred</td>
<td>8</td>
<td>Died from respiratory failure 4 mo after diagnosis</td>
</tr>
<tr>
<td>10</td>
<td>Sotiropoulos et al¹⁹</td>
<td>Budd-Chiari syndrome</td>
<td>61</td>
<td>F</td>
<td>None</td>
<td>NR</td>
<td>22</td>
<td>Died 11 mo after HCC diagnosis</td>
</tr>
<tr>
<td>11</td>
<td>Sotiropoulos et al¹⁹</td>
<td>ALD</td>
<td>65</td>
<td>M</td>
<td>None</td>
<td>NR</td>
<td>5</td>
<td>Died due to brain stem ischemia 4 yr after HCC diagnosis</td>
</tr>
<tr>
<td>12</td>
<td>Vernadakis et al²⁰</td>
<td>ALD</td>
<td>59</td>
<td>M</td>
<td>None</td>
<td>CSA, MMF, Pred</td>
<td>3</td>
<td>No signs of HCC recurrence about 12 mo after resection</td>
</tr>
<tr>
<td>13</td>
<td>Tamè et al²¹</td>
<td>HCV</td>
<td>58</td>
<td>M</td>
<td>Lam, HBIG</td>
<td>FK and Pred taper</td>
<td>16</td>
<td>HCC treated with TACE. Awaiting 2nd transplant.</td>
</tr>
<tr>
<td>14</td>
<td>Our case</td>
<td>HCV</td>
<td>47</td>
<td>F</td>
<td>IFN/R</td>
<td>FK, MMF</td>
<td>15</td>
<td>Died due to respiratory distress</td>
</tr>
</tbody>
</table>

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.
diagnosis of de novo between liver transplant and diagnosis of HCC 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 transplant recipients with a history of HCC in the explants, but evidence of recurrent HCC is more likely to be associated with metastatic disease. Patients with cirrhosis have an increased risk of developing HCC, which is why screening is important. Patients with cirrhosis who are HCV-negative may be at increased risk of HCC if the cirrhosis remains untreated.25 Recent findings have suggested that 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.25,26

**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).

**References**


Saab S. et al: De novo hepatocellular carcinoma after liver transplantation


