Very Late Recurrence of Hepatocellular Carcinoma after Sequential Liver and Kidney Transplant: Is There an Influence of Immunosuppression?


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Abstract

We report a case of a very late recurrence of hepatocellular carcinoma, which occurred after kidney transplantation. Six years earlier, liver transplantation had been performed due to hepatocellular carcinoma. This is the second case reported in the medical literature where a recurrence occurred after a strong immunosuppression regimen. The influence of immunosuppression in the recurrence of hepatocellular carcinoma will be discussed in this case.

Keywords: Liver; Kidney; Transplantation; Immunosuppression; Hepatocellular; Carcinoma; Recurrence; Mycophenolate sodium; Mycophenolate mofetil; Sirolimus and tacrolimus

Introduction

One of the most highly incident cancers in the world is hepatocellular carcinoma (HCC) [1]; it is the fifth most common cancer in males and the cancer second most related to death [2,3]. Usually, the treatment of HCC for patients begins at an early stage of liver disease and with relatively preserved liver function, but this must consider tumor size and number. Curative treatment options include tumor resection, radiofrequency ablation and liver transplantation [4].

The Milan criteria are widely accepted for the indication of liver transplantation, leading to 4- and 5-year survival rates greater than 85% and 70%, respectively. Although several limitations, such as organ shortage and tumor recurrence, other extended criteria have shown similar 5-year survival rates ranging from 71 to 87% [1]. The recurrence ratio (10-60%) is related to factors such as tumor number (especially a tumor size greater than 5 cm), lymphovascular invasion, multifocal tumors, alpha-fetoprotein level greater than 200 ng/dl, poor differentiation, preoperative transparietal biopsy, down-staging of the tumor, and additionally, to the influence of the immunosuppressive drugs [2,3].

Schreibman et al. [1] reported the first case in the literature of a late HCC recurrence after transplantation that could be due to immunosuppression. We report here the second case in the medical literature of a late HCC recurrence after sequential liver and kidney transplantation (Table 1).

Case Presentation

A 48-year-old male patient, with type 2 diabetes mellitus, developed secondary cirrhosis due to alcohol consumption. He was at Child-Pugh B level when he received a non-invasive diagnosis of HCC with an abdominal tomographic scan, which discovered four nodules measuring less than 2 cm in size.
2 cm each, on the right lobe, associated with an Alpha Fetoprotein (AFP) serum level of 350.2 ng/ml.

While waiting for liver transplantation, he underwent two chemoembolization sessions. His liver transplant occurred in May 2003; he had been registered on the waiting list for sixteen months. At that time, in Brazil, patients were submitted to transplantation surgery according to their waiting time on the transplant list; the MELD system was introduced in 2006. By histopathological examination of the explanted liver, we found that he was beyond the Milan criteria, showing multifocal hepatocellular carcinoma spread over all liver segments (I to VIII), with tumor diameters of 1.6 to 1.7 cm, trabecular and pseudo-glandular occurrences, Edmondson-Steiner grade III, and also foci of micro- and macro-vascular invasion (Figure 1A and B). The TNM classification was T4N0Mx, as the two lymph nodes removed from the peripancreatic and portal region were free of malignancy. After liver transplantation, the alpha-fetoprotein serum level fell from 350 ng/ml to 4.4 ng/ml.

On the day after liver transplantation, immunosuppression was started with prednisone 20 mg per day, tacrolimus 2 mg every 12h and mycophenolate mofetil 500 mg daily. After 21 days of immunosuppression, prednisone was decreased by 5 mg every three weeks, until it was stopped at the end of the third month, as required by our pre-stated protocol. The serum level of tacrolimus ranged from 2 to 13 ng/mL (mean of 8.37 ng/ml).

In 2006 April, three years after the liver transplantation, due to severe diabetes complications, tacrolimus had been replaced by sirolimus, with an initial dose of 2 mg per day, adjusted to 1 mg on alternate days. The serum sirolimus level ranged from 2.5 to 6.2 ng/mL (mean of 3.88 ng/mL) throughout the three subsequent years. Mycophenolate mofetil was maintained throughout the period with adjusted doses, according to clinical and laboratorial evaluations.

Six years after the liver transplantation (December 2009), the patient underwent a heterologous kidney transplantation from a cadaveric donor due to chronic kidney failure, as a consequence of diabetic nephropathy. The preoperative evaluation, including bone scintigraphy, thorax and abdominal tomographic scans and serum alpha-fetoprotein, showed no evidence of recurrence of the HCC. After the kidney transplant, the immunosuppressive regimen was

### Table 1: Demographics and clinical characteristics of the two reported patients with very late HCC recurrence after Liver transplantation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>This author</th>
<th>Schreibman et al. [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age at OLTx (y old)</td>
<td>48</td>
<td>69</td>
</tr>
<tr>
<td>Etiology of cirrhosis</td>
<td>ALD</td>
<td>HVC</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>1.6 to 1.7; multifocal</td>
<td>4 and 6</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tumor profile</td>
<td>Edmondson grade III, with multifocal distribution</td>
<td>Edmondson grade I, with focus of clear cells</td>
</tr>
<tr>
<td>Satellite lesions at Transplantation</td>
<td>No; T4N0Mx</td>
<td>No</td>
</tr>
<tr>
<td>Kidney graft time post OLTx</td>
<td>6 years</td>
<td>4 years</td>
</tr>
<tr>
<td>Reason for Kidney graft</td>
<td>diabetic nephropathy</td>
<td>diabetic nephropathy</td>
</tr>
<tr>
<td>Time of HCC recurrence</td>
<td>8 years and 5 month (101 month)</td>
<td>6 years and 7 month (79 month)</td>
</tr>
<tr>
<td>Recurrence site</td>
<td>The lungs, pleura and peritoneal membrane</td>
<td>The abdomen, pelvis, and lungs</td>
</tr>
<tr>
<td>Alpha-fetoprotein at OLTx and recurrence</td>
<td>At OLTx - 232.6; At HCC recurrence - 350 mcg/ml</td>
<td>At OLTx 350 mcg/ml</td>
</tr>
<tr>
<td>Immunosuppression at HCC recurrence</td>
<td>Prednisone, Sodium mycophenolate; and Sirolimus: TAC plus Prednisone</td>
<td></td>
</tr>
<tr>
<td>Surveillance regimen</td>
<td>Yearly</td>
<td>3, 4, and 5 years after OLTx</td>
</tr>
<tr>
<td>Treatment of the HCC recurrence</td>
<td>Sorafenib followed by gemcitabine and oxaliplatin</td>
<td>Surgical resection followed by Arginine deaminize, Adriamycin and thalidomide (study protocol)</td>
</tr>
<tr>
<td>Survival</td>
<td>Eleventh month after HCC recurrence</td>
<td>3 y and 2 m after the kidney grafting and OLTx = orthotropic liver transplantation</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)  
**Figure 1:** Pathological examination of hepatocellular carcinoma. (A) hepatocellular carcinoma (HCC) trabecular, solid and pseudo-glandular in explanted cirrhotic liver (HE, × 40); (B) HCC trabecular and solid adjacent regenerative nodule (HE, × 400).

![Figure 2](image2.png)  
**Figure 2:** Graphic column of immunosuppressive regimens used in function of time.
changed to thymoglobulin (ATG), 4.5 mg/kg divided in three doses and methylprednisolone 500 mg, followed by prednisone 45 mg/day (0.5 mg/kg) and sodium mycophenolate 720 mg every 12 h. Sirolimus was maintained on 1 mg every day. On the eleventh day after the kidney transplant had occurred, acute rejection of the new organ was treated with a methylprednisolone pulse, 1 g for three days. Then, immunosuppression was maintained with prednisone 45 mg/day, sodium mycophenolate 720 mg every 12 h and sirolimus 2 mg/day.

Eighteen months after the renal transplant (June 2011), routine exams showed an increasing alpha-fetoprotein level from 6.7 ng/mL to 232.6 ng/mL. Bone scintigraphy showed no evidence of metastasis. However, a computed tomography chest scan identified nodules with a diameter of 2.5 cm in the right lung (Figure 3). The patient was referred for pulmonary lobectomy, which was not performed once more, immunosuppression was associated with a carcinogenic effect in this group of patients than in the general population and, for 36,000 kidney transplant patients demonstrated a higher incidence of cancer in this group of patients than in the general population and, once more, immunosuppression was associated with a carcinogenic effect [10].

S-adenosyl-L-methionine studies have suggested that sirolimus and everolimus, both inhibitors of the mammalian target of rapamycin (mTOR), are new immunosuppressant drugs with an antitumor effect [13]. Clinical Studies from the Bologna Group have shown that the cumulative dose of CSA in the first year after transplantation is an important factor in tumor recurrence. They also analyzed two patient groups transplanted because of HCC, one treated with cyclosporine and the other with tacrolimus. As a high relapse rate was noted in both groups, they recommend that calcineurin inhibitors should be used with caution in patients transplanted for HCC [11].

Recent studies have demonstrated that elevated levels of calcineurin inhibitors within the first month after transplantation, i.e. tacrolimus > 10 ng/ml or cyclosporine > 300 ng/ml are associated with increased relapse of HCC [12]. Another study with approximately 36,000 kidney transplant patients demonstrated a higher incidence of cancer in this group of patients than in the general population and, once more, immunosuppression was associated with a carcinogenic effect [13].

**Discussion**

Tumor recurrence after liver transplantation is “early” when it occurs within 2 years, “late” when it occurs between 2 and 5 years and those that occur after 5 years of the cancer recovery are considered “very late” tumor recurrences [1,5-7]. Most recurrences usually occur within the first two years after treatment. The literature does not contain many cases of very late recurrences.

Our patient received a liver transplant due to alcoholic cirrhosis and HCC, which was followed by kidney transplantation six years later. He had an HCC recurrence 8.5 years (101 months) after liver transplantation.

During liver transplantation, factors associated with poor survival were discovered: a multifocal tumor, poor differentiation and vascular invasion, known as a predictive factor for tumor reappearance. Although we cannot prove it, we can consider that the balance of these immunosuppressive drugs may have played a role in the long-term survival of HCC in our patient after his liver transplant. On the other hand, we can also postulate that the over-immunosuppression after his kidney transplant, with a triple regimen with ATG, mycophenolic acid and a corticosteroid [8], may have been an important influence on HCC recurrence at a very late time point.

The concept of immunosuppression as an important factor for tumor growth was postulated by Yokoyama [9], who demonstrated that the time for doubling the diameter of a recurrent tumor in a transplanted liver under immunosuppression was only 37 days, whereas the doubling of the tumor recurrence in un transplanted cirrhotic patients without therapeutic immunosuppression occurred in 273 days. Experimental studies also demonstrated that cyclosporine A (CsA) increases the growth and invasiveness of tumor cells by inhibiting DNA repair functions [10].

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S-adenosyl-L-methionine studies have suggested that sirolimus and everolimus, both inhibitors of the mammalian target of rapamycin (mTOR), are new immunosuppressant drugs with an antitumor effect due to their ability to inhibit the proliferation of tumor cells. It has also been demonstrated that sirolimus and everolimus are safe and increase survival in liver transplant patients with HCC [14].

Geisseler et al. [15] showed that sirolimus in liver transplant recipients with HCC do not improve long-term recurrence-free survival beyond 5 years. However, a recurrence-free survival and overall survival benefit was evident in the first 3 to 5 years, especially in low-risk patients. This trial provided the first high-level evidence for selecting an immunosuppression regime in liver transplant recipients with HCC.

Both our patient and Schreibman’s patient had similar high risk
factors for HCC recurrence, such as over-immunosuppression and the timing of disseminated HCC recurrence after sequential liver-kidney transplantation, and both patients had a very low chance of effective treatment. Also, the coincident time of HCC recurrence of these two patients after sequential transplantation may focus attention on using a less powerful immunosuppressive regimen after kidney transplantation. The literature associates longer disease-free survival with a milder immunosuppressive regimen [16]. Additionally, we can also postulate about the benefit of screening the patient more often for HCC recurrence after kidney transplantation, in anticipation to the risk of severe disseminated disease on long-term follow-up.

In conclusion, we present the second case of HCC recurrence after sequential liver and kidney transplantation with a combination of risk factors such as tumor size, vascular invasion, over-immunosuppression and double transplantation. Therefore, we can suggest that patients with HCC who undergo to double sequential transplant, during long-term follow-up, should receive the mildest immunosuppressive regimen possible and more frequent screening for HCC recurrence, i.e. at least every 6 months. We highlight the need for further randomized studies to identify the best protocol for immunosuppression in liver transplant patients with hepatocellular carcinoma to prevent the recurrence of the tumor.

References


