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Very Late Recurrence of Hepatocellular Carcinoma After Orthotopic Liver Transplantation: Presentation and Management

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer and third leading cause of cancer-related deaths worldwide. Although the best available therapies include liver resection and orthotopic liver transplantation (OLT), many patients present with advanced disease and are likely to experience recurrence.¹ This has prompted the development and optimization of methods, such as the Milan Criteria, for anticipating tumor recurrence and transplant eligibility. However, even with these methods of risk stratification, HCC may recur in up to 20% of patients, emphasizing the need for more accurate models that incorporate increasingly sophisticated predictive biomarkers and tumor characteristics.²

In particular, very late recurrence of HCC, >5 years after OLT, is rarely reported in the literature and poorly understood. Here, we present a case of very late recurrence of HCC—>13 years after OLT—in a 54-year-old male. This represents, to our knowledge, the greatest reported time span between OLT and intra-abdominal HCC recurrence to date.²

CASE DESCRIPTION

Our patient was diagnosed with hepatitis C virus (HCV) infection (genotype 1), cirrhosis, and concomitant 4 cm HCC by magnetic resonance imaging and liver biopsy at 40 years of age. The decision was made not to resect the lesion due to his underlying cirrhosis. He underwent bridging therapy immediately with chemoembolization and then OLT ~4 months after initial diagnosis. At this time, the mass was noted to be 2 cm. Explant histology showed

good response to locoregional therapy without evidence of residual malignancy. He recovered uneventfully from the operation and was maintained on cyclosporine-based immunosuppression. One year after transplant, he underwent 3 months of therapy with pegylated interferon and ribavirin which resulted in treatment failure. At this time, the decision was made to hold on further treatment. The patient then transferred from his original transplant center and did not have intensive follow-up for ~7 years until he presented to our center. No imaging was performed at this time due to the patient's stability.

Twelve years after transplant, mild HCV-related liver fibrosis diagnosed by biopsy prompted antiviral therapy with pegylated telaprevir for 12 weeks and pegylated interferon for 1 year. This regimen resulted in sustained viral response.

He remained asymptomatic until 13 years post-OLT, when he presented with vague abdominal fullness. Computerized tomography (CT) imaging demonstrated a 6 × 6 cm heterogeneously enhancing mass in his right iliac fossa (Figure 1). Ultrasound-guided biopsy of this mass revealed well-differentiated HCC, which stained positive for HepPar-1 and negative for PAX8, cytokeratin 7, cytokeratin 20, and inhibin, prompting resection. Alpha fetoprotein (AFP) at this time was 2.5 ng/dL. Although the mass was successfully isolated from most abdominal structures, the ipsilateral vas deferens was intimately involved with the tumor and had to be sacrificed along with a margin of fat. At the time of operation, the mass was thought to be a peritoneal nodule. Of note, the transplanted liver could not be visualized for nodules due to dense adhesive disease. Pathologic analysis confirmed HCC with a negative microscopic margin without lymphoid architecture. None of the 11 excised lymph nodes contained tumor.

He recovered uneventfully and was discharged on postoperative day 2. His postoperative course was complicated only by a wound infection which was managed conservatively. Additionally, he was evaluated for potential adjuvant chemoradiation. A perceived low risk of recurrence led to the decision to defer therapy and surveillance was initiated with measurement of AFP and CT imaging every 6 months.

Cyclosporine-based immunosuppression was used continuously from OLT, although a short trial of conversion to sirolimus was attempted but not tolerated due to oral ulcers. A feeling of fullness in the right lower abdominal quadrant prompted an early CT scan, now 16 years posttransplant. AFP at this time was 1.5 ng/mL, and CT scans showed a nodule in the right lower quadrant (Figure 2) and indeterminate nodules in the right lung.

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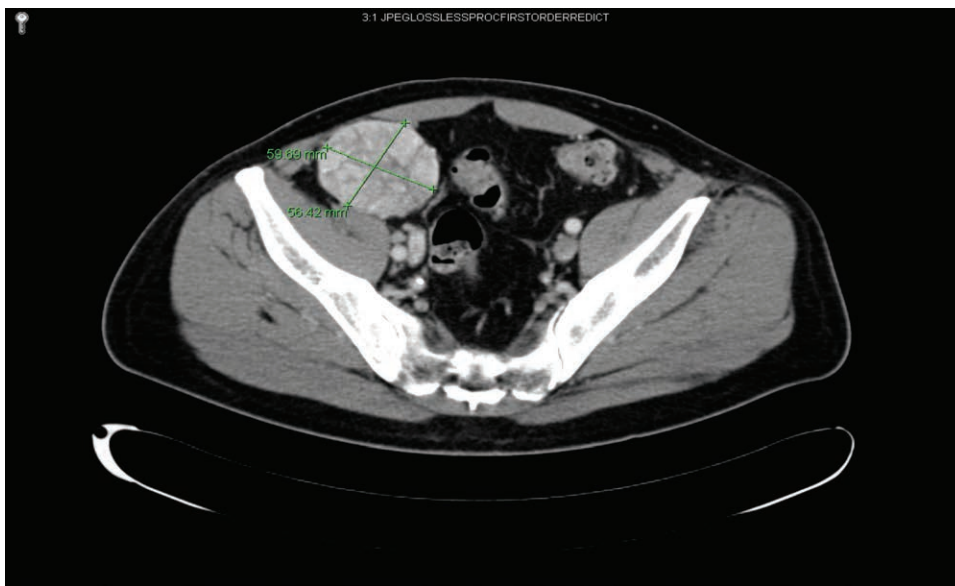


FIGURE 1. CT scan with right lower quadrant mass observed 14 y after transplant. CT, computerized tomography.

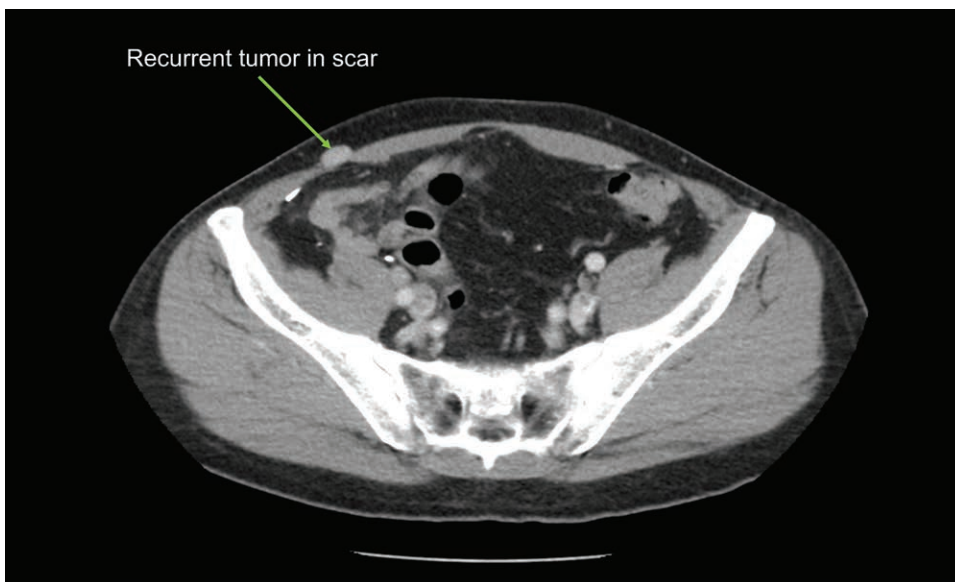


FIGURE 2. Follow-up CT scan demonstrating recurrent tumor at scar 2 y after resection of recurrence and 16 y after OLT. CT, computerized tomography; OLT, orthotopic liver transplantation.

The right lower quadrant mass was biopsied and found to stain for pancytokeratin, CAM 5.2, hepatocyte paraffin 1, and glutamine synthetase but not arginase-1, inhibin, glypican3, PAX8, S100, and carcinoembryonic antigen. Due to the concordance of these results with HCC, treatment with Sorafenib was initiated as the patient deferred operative management. He has been maintained on this now for >1.5 years. Multiple subsequent CT scans have demonstrated stable disease and effectively ruled out the lung nodules as metastases.

DISCUSSION

OLT is currently the best available treatment for nonresectable HCC, improving 5-year survival from 10% in untreated HCC patients to 70%.¹ However, recurrence is common, and poor outcomes are particularly associated with early recurrence within 2 years of transplantation.² A retrospective

cohort analysis found that 16% of recipients experience HCC recurrence, most within 2 years, with an overall survival after recurrence of ~13 months.³ Among patients experiencing recurrence, 5% present with late recurrence 2 years or later after transplantation and have significantly better 3- and 5-year survival than early recurrence patients with similar demographics and disease pathology.⁴ Cases of very late recurrence, >5 years after transplantation, infrequently appear in the literature and may be associated with distinctive clinical and biological characteristics as previously reported instances are restricted to male patients in their 50s and 60s.² Our patient was in this exact demographic category, supporting current literature.

Recent efforts to develop methods superior to the Milan Criteria for predicting the likelihood of tumor recurrence and transplant eligibility have led to the identification and optimization of models incorporating key biomarkers and

tumor characteristics. The Model for Recurrence After Liver Transplantation Score (MORAL), which determines the risk of recurrence based on neutrophil-lymphocyte ratio, AFP level, and tumor size, was demonstrated to predict recurrence more accurately than the Milan Criteria.⁵ The S-LAD score, which considers AFP, *Lens culinaris* agglutinin-reactive AFP, and des-gamma-carboxyprothrombin levels, as well as maximal tumor diameter at the time of transplantation, more accurately predicted recurrence and death for HCC patients than the Milan and University of California, San Francisco criteria.⁶ Additional prognostic markers include microvascular invasion, poor tumor cell differentiation, age, bilobar involvement, absence of necrosis, microsatellitosis, and previous liver resection.^{2,7} In addition to the number, size, and characteristics of tumors, pre- and perioperative factors may impact the likelihood of recurrence. Preoperative biopsies can result in tumor seeding and bleeding, promoting extrahepatic metastasis.⁸ Prolonged cold and warm ischemia times predict recurrence in patients with pathologically proven vascular invasion, perhaps by supporting tumor cell adhesion and the growth of micrometastases in a pro-angiogenic environment.⁹ Reasonably, the development of these markers is focused on preventing early recurrence, which is more devastating than late recurrence. New data on recurrence after resection have identified some risk factors for late recurrence of HCC (>5 y after resection); however, ~90% of this cohort recurred intrahepatically.¹⁰ It seems unlikely that any biomarker would be able to accurately predict an event 13 years in the future.

One current area of intense study is around the effect of HCV treatments on the risk of HCC. There is some literature to suggest that eradication of HCV with direct acting antivirals (DAAs) prior to OLT is associated with an unexpectedly high rate of recurrent HCC after locoregional therapy, potentially due to changes in immune response.^{11,12} However, more recent studies have failed to support this assertion, especially in comparison to interferon-based therapies.^{13,14} For recurrence after transplant, the data are sparse, but one study shows a potential correlation between pretransplant DAA treatment and recurrent HCC.¹⁵ In the current study, it is interesting to note that the patient's recurrence was detected very soon after completion of a treatment course with a DAA (Telepravir). More studies of the clinical outcomes and mechanistic underpinnings of HCC recurrence after HCV eradication are warranted to quantify risk.

Following transplantation, recurrence may be due to re-seeding of the primary tumor or de novo tumor formation. While most primary tumor recurrences occur within 2 years of transplantation, de novo HCCs appear at least 2 years after and are almost always associated with the presence of hepatitis B or C infection.^{16,17} It is possible that instances of late recurrence are attributable to indolent extrahepatic metastases with a less aggressive phenotype. Indeed, this hypothesis corresponds to the improved post-recurrence survival of patients with late recurrence¹⁸ and the stable very late recurrence experienced by our patient. It is also possible that the patient's refractory HCV caused a de novo recurrence, but this seems much less likely given the extrahepatic manifestation. The potential for recurrence >5 years after transplantation highlights the need for long-term follow-up with imaging and the creation of biomarkers for aggressive and nonaggressive

HCC subsets, which may be associated with and predict the time between transplantation and recurrence.¹⁹

A majority (67%) of recipients experiencing recurrence present with extrahepatic lesions.³ Recent advances in management of these lesions has shown that candidates for resection can have favorable long-term outcome.²⁰ For intrahepatic recurrence, standard techniques of noninvasive treatment, including radiofrequency ablation and transarterial chemoembolization, have not been extensively studied.²¹ Recent investigations have demonstrated the efficacy of mammalian target of rapamycin inhibitors, which have direct antitumor effects, for the prevention of HCC recurrence.²² The inability of our patient to tolerate Sirolimus prevented the use of this strategy.

HCC recurrence may occur >10 years after OLT. The biology of these very late recurrences is incompletely understood. Further study is needed to define both risk factors for and management of very late recurrences, especially given the unknown impact of DAAs.

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