A Rare Case of Donor-Origin Intrahepatic Cholangiocarcinoma After Liver Transplantation for Hepatocellular Carcinoma: A Case Report

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ABSTRACT

Background. Tumors may develop in the grafted liver after liver transplantation for hepatocellular carcinoma, most of which are hepatocellular carcinoma recurrences and are rarely of donor origin. We report a rare case of donor-origin intrahepatic cholangiocarcinoma in a liver allograft after liver transplantation for hepatocellular carcinoma.

Methods. A man in his 60s underwent liver transplantation for hepatocellular carcinoma with hepatitis C virus cirrhosis. The donor was a braindead woman in her 60s who had no history of malignancy.

Results. Three years and 5 months after liver transplantation, a tumor developed in the allograft. Computed tomography scans showed a 40-mm tumor that was atypical for hepatocellular carcinoma. Tumor biopsy was most suggestive of intrahepatic cholangiocarcinoma. Fluorescence in situ hybridization of the tumor showed an XX signal pattern, suggesting that it originated from the donor liver. Whole exome sequencing analysis strongly suggested that the tumor was an intrahepatic cholangiocarcinoma derived from the donor.

Conclusions. Although donor-origin cancer after liver transplantation is extremely rare, it should be considered for adequate treatment.

LIVER transplantation (LT) is one of the curative treatments for hepatocellular carcinoma (HCC) [1]. Despite established criteria for LT, recurrence after LT is possible [2,3]. In cases where tumors develop in the transplanted liver after LT for HCC, recurrence of HCC is typically the primary suspicion. Although most of these instances involve recurrent cancer originating from the recipients, it is important to acknowledge the infrequent occurrence of donor-origin cancer (DOC) in transplanted livers [4]. Herein, we report a rare case of donor-origin intrahepatic cholangiocarcinoma (ICC) in a liver allograft after LT for HCC. This study adhered to the Declaration of Helsinki. The ethics committee approved this study and informed written consent was obtained from the patient for using electronic medical record information.

CASE REPORT

A man in his 60s underwent LT for HCC with hepatitis C virus cirrhosis. He had a 5-year history of HCC treatment with transarterial chemoembolization and radiofrequency ablation. Preoperative computed tomography scans revealed a single HCC that was 23 mm in diameter within the Milan criteria. The serum level of α-fetoprotein was within normal limits, whereas the des-gamma-carboxy prothrombin level increased to 437 mAU/mL. His Child-Pugh score was 10, and the model for end-stage liver disease was 18. The donor was a braindead woman in her 60s who had died of a brain hemorrhage. She had no history of malignancy, and preoperative computed tomography scans showed no apparent lesions in the entire body. The interval between the registration on the waiting list and transplantation was 4 years. The operation was uneventful, and he

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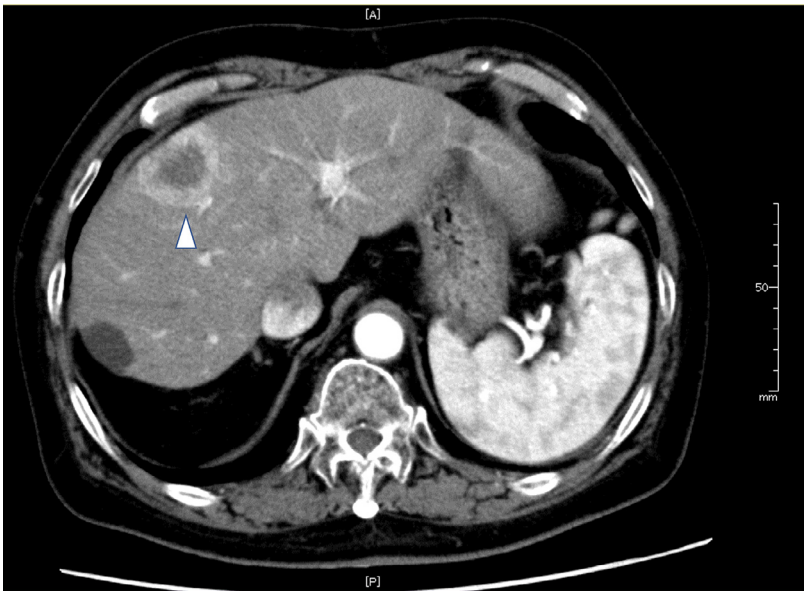

Fig 1. Abdominal enhanced computed tomography scans 3 years and 5 months after liver transplantation. A 40-mm tumor with ring-shaped contrast effect in liver segment 8 in the early phase (white arrowhead).

was discharged on postoperative day 48. Histopathologic examination of the explants revealed 9 lesions with a maximum diameter of 2.2 cm.

He was treated with direct antiviral agents for the hepatitis C virus, and a sustained virologic response was obtained. Imaging studies were performed at least once every 6 months to survey HCC recurrence. Three years and 5 months after LT, a tumor developed in the allograft (Fig 1). Computed tomography scans showed a 40-mm tumor with ring enhancement, which was atypical for HCC. Serum levels of α-fetoprotein and des-gamma-carboxy prothrombin levels were within normal limits.

In contrast, the carcinoembryonic antigen and carbohydrate antigen 19-9 levels increased to 22.2 ng/mL and 71.4 U/mL, respectively. Upper and lower endoscopic examinations revealed no abnormalities. Fluorodeoxyglucose-positron emission tomography revealed a high uptake in the liver tumor, but no other abnormal uptake was noticed. Although these imaging and laboratory findings were sufficient to suspect ICC, a tumor biopsy was performed, given the rarity of ICC in the liver allograft. Hematoxylin and eosin staining suggested ICC rather than HCC. Immunohistochemical staining was negative for hepatocyte-specific antigen (HepPar1) and positive for cytokeratin 19 (CK19), an opposite pattern to the HCCs in the explant. The tumor cells were positive for cytokeratin 7 and negative for cytokeratin 20, suggesting ICC rather than HCC or colorectal liver metastasis (Fig 2). However, positivity for *gata3* was atypical for ICC, indicating the possibility of liver metastasis from breast cancer in the recipient.

Fluorescence in situ hybridization of the tumor showed an XX signal pattern, suggesting that it originated from the donor liver. Whole exome sequencing analysis revealed 166 single nucleotide variants in the tumor when nontumor liver tissue was used as a reference. However, the number increased to 6395 if the reference was changed to the recipient lymphocyte; hence, most variants were considered single nucleotide polymorphisms observed between the genomes of different origins. Taken together, these results strongly suggested that the tumor was an ICC derived from the donor.

We initially intended to resect the tumor, but it grew rapidly, and we lost the chance for resection. The patient underwent systemic chemotherapy with gemcitabine, cisplatin, and tegafur/gimeracil/oteracil. The patient's response was poor; he died 4 months after starting chemotherapy.

DISCUSSION

This report presents a case of DOC arising in a liver allograft. DOCs are divided into donor-transmitted cancer (DTC) and donor-derived cancer (DDC). Donor-transmitted cancer is already present at the time of transplantation, whereas DDC arises in the allograft after transplantation [4]. In 2012, the United Kingdom Transplant Registry and database search at transplantation centers revealed that the DOC after solid organ transplantation was 0.06%, of which the DDC was 0.01%, and the DTC was 0.05%. Donor-derived cancer was 0.02%, and DTC was 0.03% after LT [5]. A review of the French National Database of approximately 13,000 LTs found DDC in 5 cases (0.04%), of which only 1 case was an ICC [6].

Donor-transmitted cancer DTC is clinically diagnosed when tumors are found in the graft within 6 weeks after transplantation with no primary tumors in the recipients [5]. Hence, our patient was diagnosed with DDC. Considering that it took >3 years for the tumors to develop after LT, it is unlikely that tumor cells were present in the graft at the time of LT. However, in a previous report, donor breast cancer recurred in the recipient 73 months after transplantation [7]. Therefore, we cannot completely exclude the possibility that the donor's breast cancer cells in the graft remained latent for 3 years after LT and

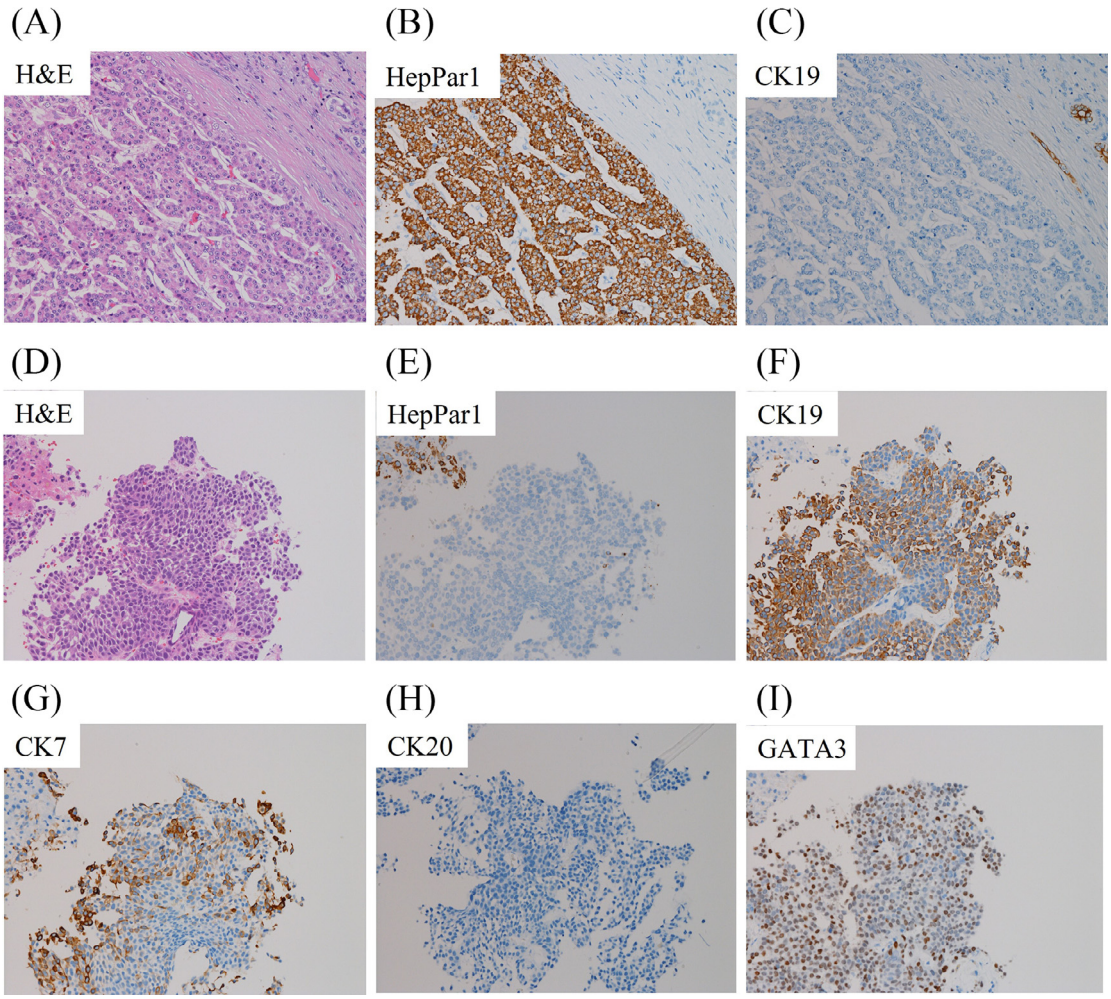

Fig 2. Pathologic examination of liver tumor tissue. **(A–C)** Recipient hepatocellular carcinomas (HCCs). **(D–I)** Donor liver tumor. The recipient HCC was HepPar1 positive and cytokeratin 19 (CK19) negative, whereas the donor liver tumor was HepPar1 negative and CK19 positive; that is, the donor liver tumor was not an HCC. The donor liver tumor was positive for CK7 and negative for CK20. *Gata3* positivity was atypical for intrahepatic cholangiocarcinoma. CK7, cytokeratin 7; H&E, hematoxylin and eosin.

suddenly became overt, although ICC arising from the allograft was much more likely. Whole exome sequencing analysis also indicated ICC (data not shown).

CONCLUSIONS

After LT for HCC, we diagnosed a liver tumor arising in the liver allograft as a donor-derived ICC by careful examination. Although DDC after LT is extremely rare, it should be considered for adequate treatment.

DATA AVAILABILITY

The data that has been used is confidential.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

[1] Mehta N, Bhangui P, Yao FY, et al. Liver transplantation for hepatocellular carcinoma. Working group report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104:1136–42.

[2] Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.

[3] Kaido T, Ogawa K, Mori A, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery 2013;154:1053–60.

[4] Chapman JR, Lynch SV. Donor-transmitted, donor-derived, and de novo cancer after liver transplant. Exp Clin Transplant 2014;12 (suppl 1):50–4.

[5] Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer transmission from organ donors-unavoidable but low risk. Transplantation 2012;94:1200–7.

[6] Allaire M, Sérée O, Coilly A, et al. De novo primary liver cancer after liver transplantation: a French national study on 15803 patients. Exp Clin Transplant 2018;16:779–80.

[7] Matser YAH, Terpstra ML, Nadalin S, et al. Transmission of breast cancer by a single multiorgan donor to 4 transplant recipients. Am J Transplant 2018;18:1810–4.