

Donor-Transmitted Malignancy in a Liver Transplant Recipient: A Case Report and Review of Literature

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Abstract Donor-transmitted malignancy is a rare complication of organ transplantation. This case illustrates a donor-transmitted adenocarcinoma in a patient 11 months after an orthotopic liver transplant for cryptogenic cirrhosis and hepatocellular carcinoma (HCC). Diagnosis of donor-transmitted malignancy may be challenging and can be confused with HCC recurrence. A timely diagnosis is crucial as a delay may limit treatment options. Biopsy of newly found liver lesions and the use of karyotypic and microsatellite analysis may be essential for diagnosis. Protocols should be in place to help recognize and limit the incidence of donor-transmitted malignancy.

Keywords Liver transplant · Donor-transmitted malignancy · Microsatellite analysis · Hepatocellular carcinoma

Introduction

Donor-transmitted malignancy is a neoplasm that has been transferred from the donor to the recipient via micrometastases within the donor parenchyma or from circulating tumor cells contained within the donated organ. It was first reported in 1965 by McPhaul and McIntosh [1], who described the development of wide-spread carcinomatosis

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in a young woman after she received a kidney from a donor with squamous-cell carcinoma of the pyriform sinus. From 1994 to 2000, UNOS recorded 108,062 cadaveric organ transplants and found 13 cases of malignancy transmission for a transmission rate of 0.012 % [2]. We report a case of donor-transmitted adenocarcinoma in a patient who underwent deceased-donor, orthotopic liver transplantation (OLT) for cryptogenic cirrhosis and hepatocellular carcinoma (HCC). We also review the current literature on donor-transmitted malignancy in liver transplantation.

Case Presentation

A 66-year-old man with history of cryptogenic cirrhosis and HCC underwent OLT but developed liver enzyme abnormalities 11 months after his transplant.

Five years prior to his OLT, the patient was diagnosed with cirrhosis when he presented for medical care after fracture of his right proximal humerus in the setting of a fall, while working on his roof. During the hospitalization, he developed lower extremity edema with ascites, and ultrasonography of his abdomen revealed a small and echogenic liver, an enlarged spleen, and a significant amount of ascites. Extensive work-up for his new diagnosis of liver disease was negative including viral, autoimmune serologies, and metabolic markers (Table 1). The patient had history of hypertension and hyperlipidemia. The patient's family history revealed no liver disease. He denied tobacco and alcohol use as well as intravenous drug

use. The patient was started on furosemide and spironolactone for diuresis.

The patient's pre-OLT course was complicated by upper gastrointestinal bleeding from gastroesophageal varices despite multiple sessions of endoscopic band ligation (EBL). One year prior to OLT, he eventually underwent transjugular intrahepatic portosystemic shunt (TIPS) procedure for recurrent variceal hemorrhage. Post-TIPS, the patient had no further episodes of bleeding.

The patient was placed on the waiting-list for liver transplant. On routine imaging 1 month prior to his transplant, a magnetic resonance imaging (MRI) of his liver revealed a new 2.0 × 1.6-cm peripherally enhancing lesion in the inferior aspect of segments V/VI of the liver, concerning for HCC. The patient received 22 exception points for presumed HCC. He was not pretreated with transarterial chemoembolization (TACE). Soon after, he received a full-sized allograft from a 79-year-old female brain-dead donor. The donor was initially admitted with altered mental status and noted to have a large intracerebral hemorrhage. She had a prior history of diabetes mellitus, hypertension, hyperthyroidism, depression, and deep vein thrombosis of her lower extremity for which she was on warfarin. She had no prior history of malignancy, with no known screening for cervical, breast and colorectal cancer. Over the course of her admission, she had progressive deterioration in her mental status with eventual loss of all reflexes. She was pronounced brain dead and her liver was harvested. No suspicious lesions were reported during donor examination of the intrathoracic and intraabdominal cavity. The donor had positive hepatitis B viral (HBV) core antibody and negative surface antigen. She was also cytomegalovirus (CMV) antibody positive and Epstein–Barr virus (EBV) antibody positive.

Liver transplantation was unremarkable. Post-transplant, the recipient patient received 6 days of IV hepatitis B immune globulin (HBIG) and was maintained on entecavir. His initial post-transplant course was complicated by high arterial resistive index of the hepatic artery, for which he was started on warfarin. Postoperatively, the patient received triple immunosuppressive therapy consisting of sirolimus, prednisone and mycophenolic acid (MMF), but was eventually maintained on sirolimus alone at levels between 8 and 10 ng/mL.

Three months after the liver transplant, the patient had normal liver chemistry tests. His abdominal CT scan with contrast showed no signs of recurrent HCC. A 1.0-cm simple cyst was seen in the left hepatic lobe. Thoracic CT showed no evidence of metastatic disease to the chest.

Eleven months after the liver transplant, the patient was noted to have an asymptomatic elevation in his liver enzymes. His AST was elevated to 48 U/L, ALT to 106 U/L, and AP to 199 U/L. The patient underwent a right upper

Table 1 Laboratory data

Variables	Reference range, adult male	Results
HCV Ab	Negative	Negative
HBS Ag	Negative	Negative
HBS Ab	Negative	Negative
HBC Ab	Negative	Negative
HIV Ab	Negative	Negative
ANA	Negative	Negative
ASMA	Negative	1:20 titer
AMA	Negative	Negative
ALKM-1	Negative	Negative
Ferritin	10–300 ng/mL	297 ng/mL
Ceruloplasmin	18–36 mg/dL	28 mg/dL
Alpha-1-antitrypsin genotype		PI × M/PI × M

HCV Ab hepatic C virus antibody, *HBS Ag* hepatitis B virus surface antigen, *HBS Ab* hepatitis B virus surface antibody, *HBC Ab* hepatitis B virus core antibody, *HIV Ab* human immunodeficiency virus antibody, *ANA* anti-nuclear antibody, *ASMA* anti-smooth muscle antibody, *ALKM-1* anti-liver/kidney microsomes

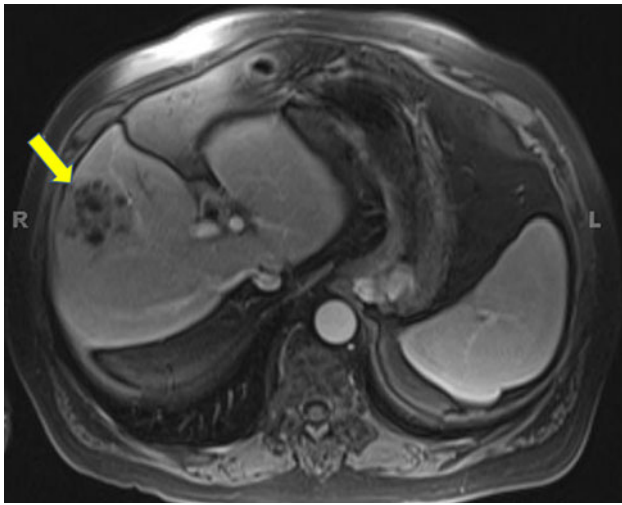


Fig. 1 T1-weighted MRI of abdomen during portal venous phase demonstrating a 4.4 × 5.5-cm mass in segment V/VI of the liver (arrow)

quadrant ultrasound which showed a new ill-defined 5.0 × 3.8 × 4.1 cm heterogeneous area in the inferior right lobe of the liver of unclear etiology. MRI of the abdomen showed a heterogeneous 4.4 × 5.5-cm mass in segment V of the liver. The lesion was predominantly hypointense on T1 and hyperintense on T2 (Fig. 1).

Ultrasound-guided needle biopsy of the mass as well as a core biopsy of the hepatic parenchyma was performed. The transplanted liver parenchyma had no significant signs of portal or lobular inflammation. Neither steatosis nor significant fibrosis was seen. The mass was found to be adenocarcinoma with tumor cells diffusely positive for CK20 and CDX2. It was negative for CK7, TTF, synaptophysin, and chromogranin (Fig. 2). It had focal, weak positivity for CD56. The immunoprofile was suggestive of a colonic primary. Serum CEA level was elevated at 1,597 ng/mL.

The patient had an esophagogastroduodenoscopy (EGD) and colonoscopy performed prior to his transplantation

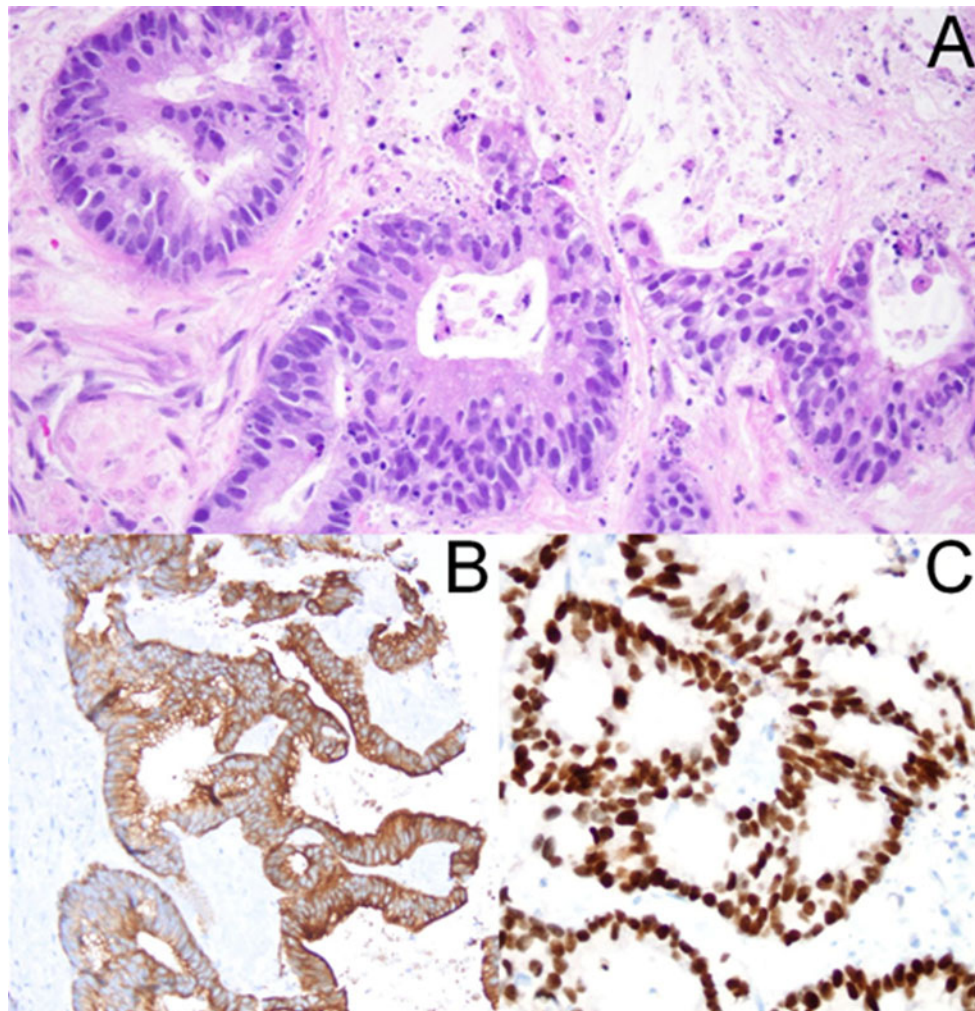


Fig. 2 Liver allograft biopsy demonstrating adenocarcinoma with immunostain consistent with colonic primary. **a** H&E stain. **b** CK20 immunostain. **c** CDX2 immunostain

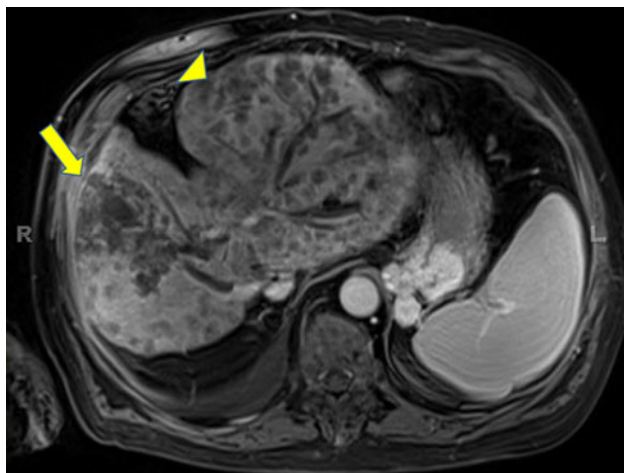


Fig. 3 T1-weighted MRI of abdomen during portal venous phase demonstrating increase in size of the index lesion in segment V/VI to 9.4×8.0 cm (arrow), as well as innumerable new nodules throughout both lobes of the liver (arrow head)

which were both unremarkable. Repeat EGD and colonoscopy again showed no suspicious lesions.

Microsatellite analysis comparing the patient's gastric biopsy, liver adenocarcinoma, and uninvolved area of the transplanted liver tissue was performed. The assay was performed using a forensics kit employing nine polymorphic microsatellites and the amelogenin locus (AmpFISTR Profiler, Applied Biosystems, Foster City, CA, USA). The result was most consistent with the adenocarcinoma being of donor origin.

Tumor resection and relisting for liver transplantation were discussed, but given the rapid development and size of his adenocarcinoma, surgical intervention was felt to be a poor option. Locoregional therapy was started, and the patient underwent Yttrium⁹⁰-based selective internal radiation therapy (SIRT) of the right lobe of the liver. However, despite SIRT, there was rapid growth of the tumor to 9.4×8.0 cm, as well as development of innumerable new hypoenhancing masses in both lobes of the liver (Fig. 3).

In light of this, no further treatment regimen was recommended. After a thorough discussion with the patient and family, the patient was transferred to hospice care where he passed away 8 months after his initial diagnosis of adenocarcinoma and 17 months after his OLT.

Discussion

Diagnosing Donor-Transmitted Malignancy

Donor-transmitted malignancy is rare, and determining the origin of a newly diagnosed malignancy in a liver transplant recipient can be challenging, especially when the

original indication for transplant was HCC, as in our patient. When a new mass developed post-OLT, initial suspicion was HCC recurrence. However, the presentation appeared to be inconsistent with recurrent HCC. The patient's original cancer was within the Milan criteria [3] and no vascular or lymphatic invasion was seen in the patient's explanted liver. A biopsy of the new lesion showed adenocarcinoma. In cases where donor and recipient genders differ, the presence or absence of a Y chromosome by fluorescence in situ hybridization may verify recipient origin of a malignancy [4]. This technique however is not helpful if the donor and recipient are of the same gender. Prior case reports have shown the utility of microsatellite allelic analysis to confirm or refute a diagnosis of donor-transmitted malignancy in same-sex donor-recipient transplants [5–7]. In our case, the result of the nine polymorphic microsatellites, as well as the locus for the amelogenin gene, which helps determine the presence of X and Y chromosomes, was important in revealing that the tumor was of donor origin.

Managing Donor-Transmitted Malignancy

Although rare, donor-transmitted malignancy carries significant morbidity and mortality. From 2005 to 2009, 20 cases of confirmed malignancy transmissions were reported to the organ procurement and transplant network (OPTN). Of these cases, ten deaths were attributed to the malignancy [8]. Cessation of immunosuppression with emergent retransplantation has been successful in treating patients with early diagnosis of tumor transmission after organ transplantation [4, 9, 10]. For kidney transplants, this is a viable option as transplanted kidneys can be explanted and patients maintained on renal replacement therapy indefinitely until another organ becomes available for retransplantation. In the case of liver transplants, no extracorporeal hepatic replacement exists. It is essential that the original replaced liver, despite harboring malignant cells, be kept in place and immunosuppression continued to prevent rejection until another organ is made available for retransplantation. Waiting for another organ may prolong the time the recipient may be exposed to circulating malignant cells. Furthermore, immediate recognition of tumor transmission can be difficult in cases where no discernible mass is noted in the donor at the time of organ harvesting. In a series of donor transmitted malignancies reported to the OPTN, the mean time to diagnosis was 14.2 months after organ transplant [2]. Diagnosis may only be made after significant, detectable growth of the tumor has occurred in the recipient. An optimal treatment strategy in cases of delayed diagnosis has yet to be determined. The tumor in our patient developed rapidly. Surgical resection and retransplantation were discussed. Ultimately, given the size of the tumor and rapidity

of its growth, surgical intervention was felt to be too invasive with high-risk for subsequent hepatic decompensation and tumor recurrence. Treatment options were limited, and the decision was made for palliative therapy. Locoregional therapy with Yttrium⁹⁰-SIRT had been shown to induce tumor regression in patients with unresectable liver metastases from primary colonic adenocarcinoma [11]. The patient received one dose of SIRT without clinical response, ultimately passing away from his disease.

Reducing the Risk of Donor-Transmitted Malignancy

Donor-transmitted malignancy is an increasingly recognized complication among organ transplant institutions. As our population ages and use of organs from older donors rise, the incidence of donor-transmitted malignancy may also rise. Mandatory routine donor autopsy may help in early detection of donor malignancy to facilitate early cessation of immunosuppression and retransplantation of the organ. However, permission for an autopsy is not always granted by the surrogate, and a full autopsy often occurs only after transplantation of the organ has taken place [12]. Furthermore, in donors with known malignancies, the transmission of the neoplasm to the organ recipient is variable, depending on the tumor pathology [13]. Donor choriocarcinoma, melanoma, breast, colon and lung cancers appear to carry high risk of recurrence in recipients while low-grade CNS tumors and skin cancers appear to be at lower risk [14]. If a donor autopsy does reveal an occult malignancy and the patient has no gross signs of tumor transmission, a difficult decision will need to be made regarding watchful waiting versus cessation of immunosuppression and emergent retransplantation. Undoubtedly, many prophylactic retransplantations would occur in patients that may never have developed a donor-transmitted malignancy. Conversely, despite early retransplantation, undetected metastasis may have already occurred and malignancy may develop even after a second transplantation [15].

A strategy to avoid transplanting organs from patients with malignancies in the first place is obviously ideal, and protocols should be in place to screen for potential donor malignancies. Careful donor selection is crucial. Although the availability of donor cancer history can be variable, every attempt should be made to obtain a history to avoid donors with past and current malignancies. Organs from donors with high risk malignancies, such as melanoma and choriocarcinoma should not be used as they carry high malignancy transmission rates [13, 14]. Careful examination of abdominal organs and thoracic cavity should be performed at the time of organ procurement to evaluate for potential malignancies. Despite a thorough examination, occult malignancies may still be missed, as in this case.

This may occur due to small or non-palpable primary tumors at the time of organ harvesting. An optimal method for palpation of the abdominal and thoracic cavity has not been systematically studied. Brain death secondary to nontraumatic cerebral hemorrhage should prompt a thorough investigation as it may be a result of metastatic disease. Misdiagnosed brain death has been associated with an increased incidence of donor-transmitted malignancy [13].

From 2002 to 2005, a donor cancer screening protocol consisting of pre-surgical and surgical phases was implemented in Italy. The presurgical phase included collecting patient history, external examination, laboratory data, and instrumental examination including chest X-ray and total body ultrasound. CT scans were performed in the presence of any suspicious ultrasound findings. The surgical phase included sampling of any internal effusions and careful evaluation of all internal organs with biopsy of suspicious lesions [16]. Of the 7,608 potential donors screened, 98 potential donors (2.6 %) were excluded from donation secondary to discovery of a tumor felt to be at high risk of tumor transmission. However, 14 donors (0.2 %) without tumor suspicion after screening eventually were found to have potentially transmissible malignant tumors. Twenty-three patients received organs from these 14 donors, and after a median follow-up of 23 ± 14 months, no documented tumor transmission has been reported in these patients [17]. This illustrates that a large-scale donor screening protocol is feasible, but it is yet unclear if this increased vigilance will result in decreased malignancy transmission rates.

Advanced age undoubtedly increases the presence of occult malignancies. An age limit for donors may help to decrease donor-transmitted malignancy incidence, but this must be considered with great caution. In 2009, 8.6 % of all organ donors were above 65 years old, and any limitation on donor age will likely have a significant impact on the potential donor pool [18]. Whereas ten deaths related to donor-transmitted malignancy were reported from 2004 to 2009, there were 7,127 deaths among patients on the organ transplant waiting lists in 2009 alone [8, 18]. Although donor-transmitted malignancy carries significant morbidity and mortality, it should be taken in context of organ transplantation as a whole. An ideal protocol will reduce the rates of tumor transmission without significant, adverse impact on donor availability.

Conclusion

Donor-transmitted malignancy has been increasingly reported as a complication of organ transplantation. Provider recognition and diligence are crucial for early diagnosis for potential treatment. Certain mandatory procedures

at the time of organ harvesting may limit the incidence of tumor transmission during organ transplantation. However, any strategy that attempts to decrease rates of donor-transmitted malignancy should be weighed against its potential impact on an already constrained organ donor pool.

Conflict of interest None.

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