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Donor-Derived Hepatic Neuroendocrine Tumor: Pause Before Proceeding With Liver Retransplantation

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ABSTRACT: Gastrointestinal neuroendocrine tumors (NET) are rare but the age-adjusted incidence in the United States has increased, possibly due to improved radiographic and endoscopic detection. In advanced NET, hepatic metastases are common. Orthotopic liver transplant (OLT) is currently considered an acceptable therapy for selected patients with limited hepatic disease or liver metastases where complete resection is thought to have curative intent. The development of NET of donor origin is very uncommon after organ transplant, and it is unclear if the same treatment strategies applied to hepatic NET would also be efficacious after OLT. Here, we describe a unique case of an OLT recipient with a donor-derived NET that was treated with redo OLT as the primary therapy. The donor-derived NET recurred in the recipient's second liver allograft suggesting an extrahepatic reservoir. This case describes the natural history of such a rare event. Here, we highlight the treatment options for hepatic NET and challenge the role of OLT for a donor-derived hepatic NET.

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Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from neuroendocrine cells located throughout the body. The NETs have a variable biologic behavior. The NET confined to the liver is a rare event. However, hepatic metastases from gastrointestinal NETs are common in advanced disease. Liver transplantation for nonresectable hepatic metastases is an acceptable practice in selected patients.[1]

Cancer in a transplant recipient can be classified into 4 types: (I) donor transmitted, which is present within the allograft at the time of transplantation; (II) donor-derived, which develops within the donor cells after transplantation; (III) de novo, which develops from the recipient cells; and (IV) recurrent cancer, which is the recurrence of cancer after transplantation that the recipient had before transplantation.[2] Donor-derived cancers after liver transplantation were predicted by Professor Thomas Starzl and coworkers,[3] and the first report of an "allometastasis" was in a kidney transplant recipient documented with a metastatic bronchial carcinoma of donor origin.[4] It remains unclear whether the classification of donor-transmitted versus donor-derived affects prognosis or therapy choices.

Donor-derived NETs are very rare with an unknown incidence.[5-8] As a result, there are no evidence-based guidelines for treatment. Numerous treatment options including pharmacotherapy, surgical resection, locoregional therapies, and liver transplantation exist. Here, we report the first case with long-term follow-up of a donor-derived hepatic NET that was treated only with liver retransplantation.

CASE REPORT

A 59-year-old woman with a history of hepatitis C and hepatocellular carcinoma (HCC) within Milan criteria underwent orthotopic liver transplant (OLT) in 2006. The recipient had routine health screening including colonoscopy, Papanicolaou smear, mammogram, and chest computed tomography (CT). Her HCC was treated preoperatively with transarterial chemoembolization. At transplantation, she was critically ill with a Model for End-Stage Liver Disease score of 40. The deceased donor was a 77-year-old man without known malignancy who had died of a hemorrhagic stroke. The

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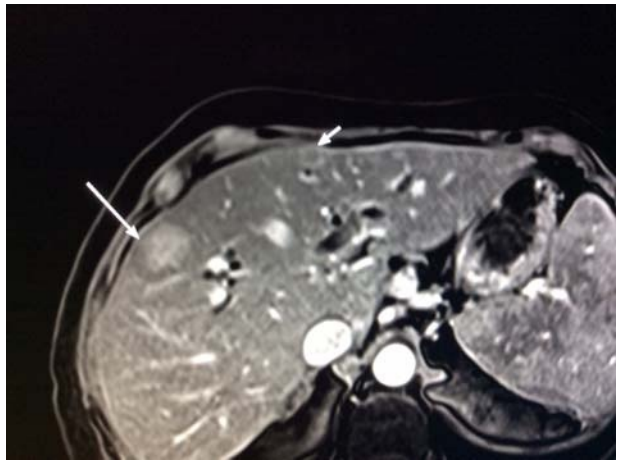

FIGURE 1. A, contrast-enhanced MRI five years after first OLT demonstrating new masses (white arrows).

native liver explant revealed a single 2.2-cm necrotic HCC without lymphovascular invasion. No other recipients received organs from this donor.

The postoperative course was uneventful. Immunosuppression was managed with tacrolimus, mycophenolate mofetil, and a prednisone taper. Conversion from tacrolimus to sirolimus occurred within 1 year, and she remained on sirolimus monotherapy (mean dose, 4 mg daily; goal level, 4-6 ng/mL). Follow-up annual abdominal magnetic resonance imagings (MRIs) revealed no lesions for 4 years. At year 5, abdominal MRI revealed 3 new hepatic lesions, the largest in segment II measuring 2 cm. The arterially enhancing lesions did not meet Liver Imaging Reporting and Data System's criteria for HCC (Figure 1). Three months later, MRI revealed growth of the largest lesion to 2.4 cm. A CT-guided biopsy was performed. The histology revealed closely packed nests of poorly differentiated neuroendocrine cells, strongly positive for synaptophysin, chromogranin, TTF-1, CK7, and Ki-67 and negative for CK20, CDX2, HepPar1, Glypican 3, and ER. Ki67 index was 4%.

Chest CT, positron emission tomography CT, upper endoscopy, colonoscopy with terminal ileum intubation, mammogram, and octreotide scan did not reveal a primary extrahepatic source. Chromogranin A level was 28 ng/mL (normal, 1.9-15 ng/mL), and neuron-specific enolase was less than 10 ng/mL. Genetic analysis of the NET tissue was performed. The DNA was polymerase chain reaction-amplified for 15 short tandem repeats (STRs) (ARUP Laboratories, Salt Lake City, UT). The results from the donor liver and the tumor were identical for all 15 STRs and for amelogenin, consistent with donor-derived NET.

As the donor-derived NET appeared to be confined to the liver, the multidisciplinary team decided that retransplantation was the best curative option. The patient was relisted and received a United Network for Organ Sharing Regional Review Board Model for End-Stage Liver Disease exception of 22 points. No other NET treatments were performed before the second transplantation. A second liver transplantation occurred approximately 1 year after appearance of the donor-derived hepatic NET. The deceased donor was a 54-year-old woman who had died of a hemorrhagic stroke. The postoperative course was uneventful. Immunosuppression was managed with tacrolimus, mycophenolate mofetil, and a prednisone taper. Tacrolimus-based immunosuppression was changed to sirolimus within 6 months. She remained on mycophenolate mofetil 250 mg twice daily until 12 months after OLT, then sirolimus monotherapy (mean dose, 3 mg daily; target level, 4-6 ng/mL). Although negative at 6 and 12 months, abdominal MRI 24 months after transplantation showed a single 1.4 × 1.4 cm mass in segment VI of the liver (Figure 2). The CT-guided liver biopsy revealed a poorly differentiated neuroendocrine tumor that was histologically similar to the first biopsy. Analysis again demonstrated identical alleles at all 15 STR loci and amelogenin, consistent with origin from the original liver donor.

Chest CT, bone scan, and octreotide scan showed no metastatic disease. Chromogranin A level was 112 ng/mL. Radioembolization of a selective segment VI artery was performed with 41.9 mCi of Y-90–labeled Sirspheres (Sirtex, Woburn, MA). Immunosuppression with sirolimus monotherapy was dose reduced. A 3-month follow-up MRI showed a necrotic lesion, but also revealed a new 5-mm liver lesion and a mass in head of the pancreas. Needle biopsy of the pancreatic lesion confirmed NET. Despite systemic sunitinib and octreotide therapy, repeat imaging showed progression of disease. She died several months later, 9 years after the first liver transplant and 3 years after retransplantation. No autopsy was performed.

DISCUSSION

The shortage of donor organs for liver transplantation has led many centers to accept older donors, steatotic livers, non–heart-beating donors, donors with viral hepatitis, and donors with malignancies.[9] These extended criteria have played an important role in increasing access to liver transplantation. However, 1 possible consequence of this practice may be a rise in the incidence of donor transmitted and donor-derived malignancies.

In our case, the decision to pursue retransplantation for donor-derived NET was based on the patient's excellent performance status and health, unique donor-derived circumstances, and the absence of extrahepatic NET. Based on the available literature, it was felt that her best chance at cancer-free survival was with resection of all known donor-derived malignancy at time of OLT. Retrospectively, it is not known

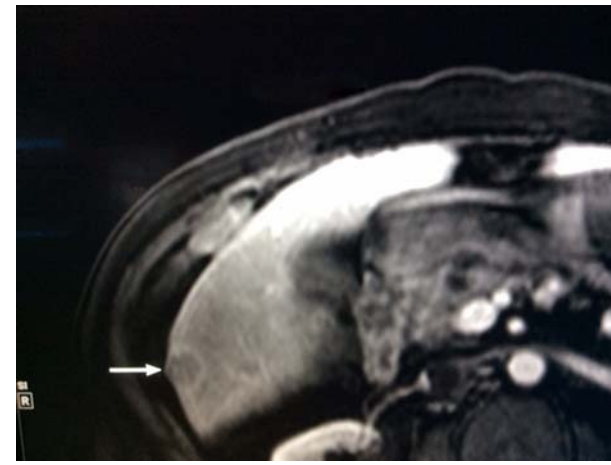

FIGURE 2. Contrast-enhanced MRI demonstrating segment VI lesion in the second OLT (white arrows).

whether systemic octreotide or sunatinib would have impacted the clinical course.

As the population ages, the incidence of NET has also increased.[10] Donor transmitted and derived NETs are extremely rare and often difficult to distinguish. In addition to our case, there are only 3 other donor transmitted or derived NETs published in the last 15 years.[7,8,11] In 1 case, both kidneys were procured from the same donor, and 1 recipient required nephrectomy due to development of NET in the donor kidney.[7] In another case, a liver transplant recipient with donor transmitted NET died 7 months after OLT despite systemic chemotherapy.[8] There is a single case of a donor-derived hepatic NET that underwent liver retransplantation for multiple hepatic lesions.[11] However, this case is different from ours in that this patient developed NET a brief 8 months after OLT, raising the likelihood that this was donor transmitted and likely present in allograft at the time of OLT. This patient underwent locoregional therapy, then systemic chemotherapy, then retransplantation. The recipient died within 3 months after retransplantation from complications of metastatic NET to the brain.[11]

The rate of donor-derived cancers has been estimated among transplanted cadaveric organs to be 0.017% (18 of 108 062), but the incidence appears to be increasing, possibly due to aging of the donor pool.[6,10,12] Of the 6 donor-derived malignancies, 3 occurred in liver recipients.[5] Although donor-derived NETs are rare, other donor-derived malignancies may become more common as donor criteria are extended and more living related transplants are performed.

Hepatic NET was the indication for 184 of 108 924 liver transplantations performed in the United States from 1988 to March.[1,13] The 5-year patient survival is 10% to 15% lower than for recipients transplanted for other etiologies, and death from NET recurrence is observed in about 50%.[1,13-15] Prognostic factors associated with increased survival for patients with NET who underwent liver transplantation included limited hepatic disease, nonduodenopancreatic tumors, timing of resection of primary disease, and age younger than 50 years.[1,15-17] Low tumor expression of Ki67 and E-cadherin may identify patients with potentially favorable outcomes.[18,19] It is unclear if these prognostic factors apply to donor-derived NET.

Our case is the first to describe late-onset (>4 years) donor-derived NET. It also is the first to highlight redo OLT as a potential first line therapy for donor-derived hepatic NET. This case outlines the systemic nature of advanced NET. Single-organ targeted therapy with OLT may not lead to eradication. It is hypothesized that clinically occult NET must have existed outside the liver at time of the second transplantation and served as the source for the recurrent tumor. The recurrence in the second liver allograft was much more rapid, metastasizing outside the liver to the pancreas within 27 months. The impact of sirolimus immunosuppression, locoregional therapy, or sunatinib on the natural history of her disease is unknown. The negative outcome seen in this case and others[11] needs to be considered when considering organ directed therapies. Even with favorable prognostic markers, as in this case, therapies other than OLT should be considered first-line. Redo OLT may not have a role in the treatment of donor-derived or donor-transmitted hepatic NET.

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