Transmission of Lung Adenocarcinoma From a Single Donor in 2 Transplant Recipients: A Case Report With Literature Review

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ABSTRACT

Malignancies transmitted to recipients during solid organ transplants carry significant morbidity and mortality. We present 2 cases of adenocarcinoma of donor lung origin transmitted via liver and kidney transplant from a single donor. Both recipients developed metastatic adenocarcinoma of lung origin with p.L858R mutation in the epidermal growth factor receptor gene and a microsatellite signature of donor origin. Osimertinib was trialed in the liver recipient; however, it was discontinued because of hepatotoxicity and disease progression. Standard donor screening protocols limit malignancy transmission but do not include multicancer detection assays. As these technologies evolve, they may be implemented in donor screening.

DONOR-TRANSMITTED malignancy (DTM) is a tumor or tumors transmitted to the recipient during transplant. The United Network for Organ Sharing suggests the incidence is 2 per 10 000 [1,2]. Most originate from kidney and liver allografts [3] and carry significant morbidity and mortality. Preventive strategies include donor history and, in living donors, using screening guidelines from the American Cancer Society and the United States Preventive Services Task Force [4]. Malignancy is not a contraindication to donation, but the transmission risk varies concerning the type and stage of cancer [5]. We present 2 cases of DTM from a single donor and discuss implications for new cancer screening and surveillance technologies.

CASE 1

Consent for participation was obtained from 1 of the recipients and from the family of the deceased recipient. A 66-year-old woman received a liver transplant due to nonalcoholic steatohepatitis and hepatocellular carcinoma. Nine months posttransplant, she presented with fatigue, diarrhea, acute kidney injury, and liver dysfunction. Multiple liver lesions were seen on magnetic resonance imaging (Fig 1), and increased fluorodeoxyglucose-avidity was observed on positron emission tomography/computed tomography. Biopsy demonstrated adenocarcinoma positive for cytokeratin 7, thyroid transcription factor 1, and Napsin-A, suggesting lung origin (Fig 2). Her carcinoembryonic antigen level was elevated as well. Microsatellite instability (MSI) analysis (Fig 3) matched donor tissue, and molecular profiling revealed epidermal growth factor receptor p.L858R mutation. Osimertinib was initiated, but within 2 weeks, she progressed and transitioned to hospice.

CASE 2

A 54-year-old woman received a deceased donor kidney transplant because of diabetes mellitus. She was hospitalized twice within the following 18 months, once for *Escherichia coli* bacteremia and the second for COVID-19. At 21 months posttransplant, she presented with shortness of breath, fatigue, edema, elevated urine protein, and acute kidney injury with a creatinine level of 1.7 mg/dL. Renal ultrasound of the transplanted kidney did not demonstrate any abnormalities. Allograft biopsy showed active chronic T cell-mediated rejection and adenocarcinoma. The serum carcinoembryonic antigen level was significantly elevated, and computed tomography of the abdomen and pelvis revealed

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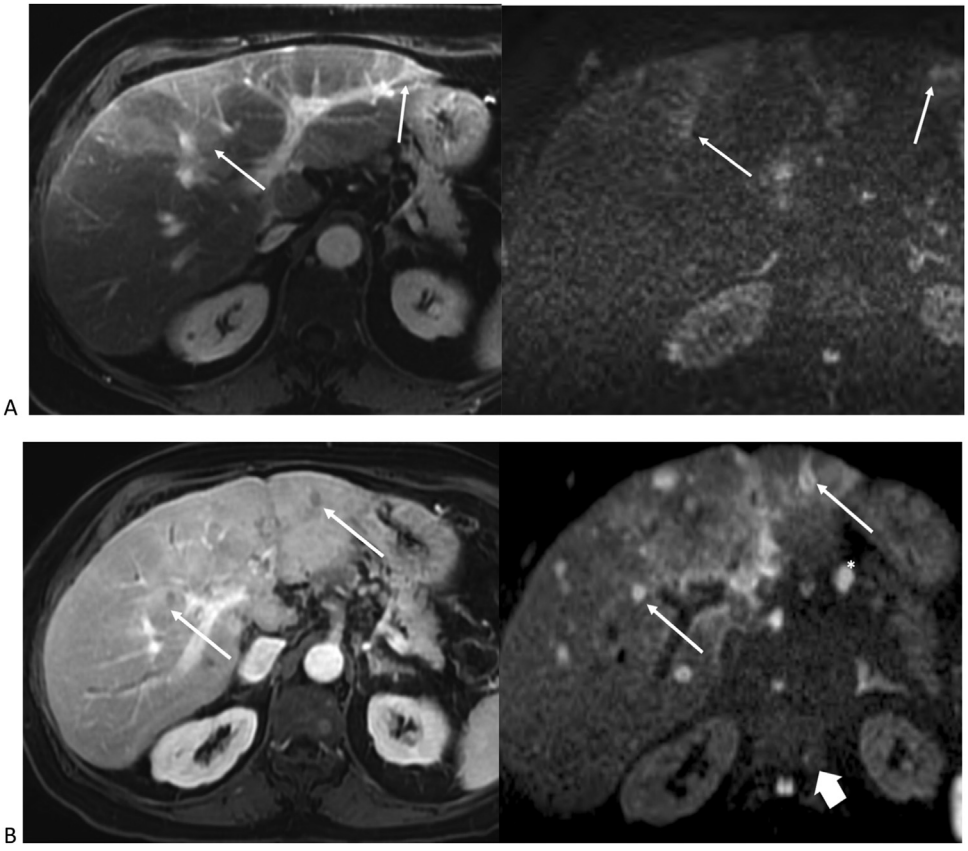

Fig 1. (A) Contrast magnetic resonance T1-weighted imaging (left) performed shortly after biopsy shows geographic areas of altered enhancement but no focal mass. Diffusion-weighted imaging (right) from the same examination reveals subtle foci of restricted diffusion concealed in these areas of fatty infiltration consistent with micro-tumor deposits too small to be detected by computed tomography or ultrasound because of superimposed steatohepatitis. **(B)** Contrast-enhanced T1-weighted (left) and diffusion weighted (right) magnetic resonance images from examination 2 months after initial diagnosis shows findings of significant disease progression including numerous hypoenhancing and diffusion restricted liver lesions (thin arrows) as well as enhancing vertebral body metastasis (wide arrow) and upper abdominal lymphadenopathy (*).

retroperitoneal adenopathy (Fig 4). Lymph node biopsy demonstrated metastatic adenocarcinoma. As in case 1, immunohistochemistry demonstrated positivity for CK7, thyroid transcription factor 1, and Napsin-A (Fig 2); MSI analysis matched the donor (Fig 3). A p.L858R epidermal growth factor receptor mutation was present as well. Allograft nephrectomy was discussed; however, this was felt to be futile because of the presence of metastatic disease. The patient was discharged and relocated to another state.

DISCUSSION

Diagnosis and Treatment of Donor Transmitted Malignancy

If DTM is suspected, the origin of the tumor can be confirmed by MSI analysis [6−8]. In cases where the biological sex of the donor and recipient differs, the presence or absence of a Y chromosome by fluorescence in situ hybridization may be able to verify the origin of the tissue. Once confirmed, management depends on the organ involved and the presence of metastatic disease. If detected early, options include discontinuing immunosuppression and/or graft removal and retransplant [9,10]. This option is more practical in kidney transplantation since dialysis can be used for support in the intermin. In organs with no extracorporeal replacement therapies, the transplanted organ must be left in place, and immunosuppression is continued until a replacement organ is found.

In the case of our liver recipient, the allograft was left in place, immunosuppression continued, and osimertinib was trialed. Unfortunately, this was discontinued because of hepatotoxicity and disease progression. We identified 1 case report of DTM to the liver where yttrium^{90} radioembolization was used [11]. Yttrium^{90} is used to treat hepatocellular carcinoma and metastatic disease of the liver [12]. The patient had a poor clinical response in the referenced

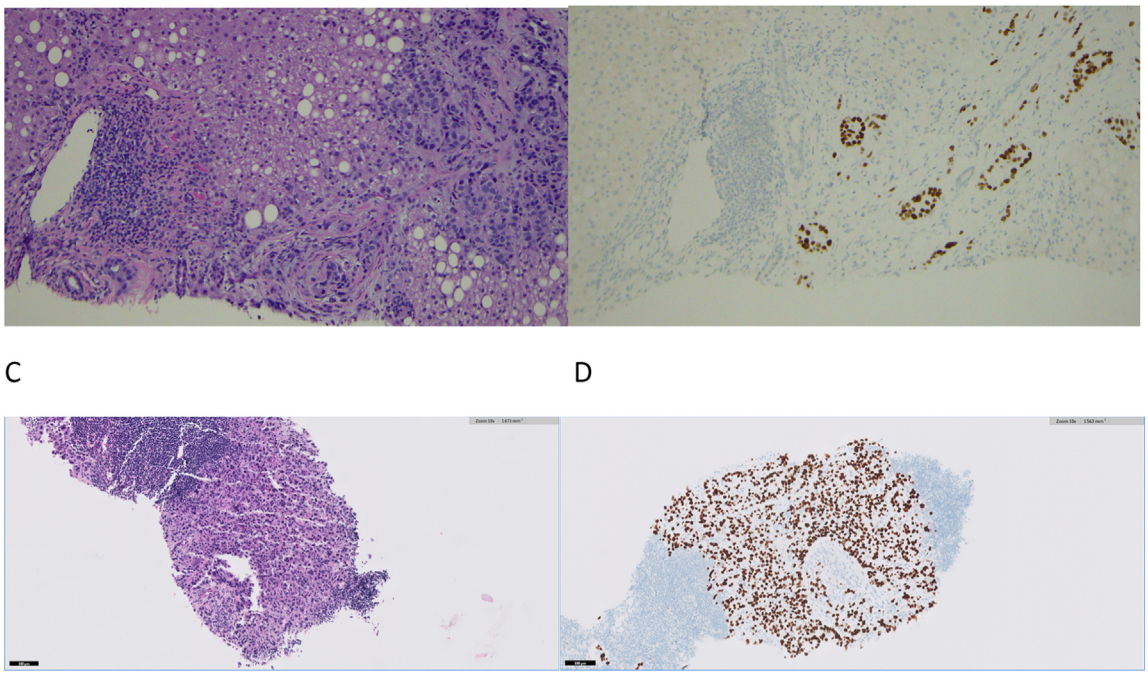

Fig 2. Histopathology liver biopsy in liver transplant recipient and retroperitoneal lymph node biopsy in kidney recipient. **(A)** Hematoxylin and eosin stain and thyroid transcription factor 1 immunohistochemistry **(B)** of liver biopsy. **(C)** Hematoxylin and eosin stain and thyroid transcription factor 1 immunohistochemistry **(D)** of lymph node.

case and passed away. In our renal transplant recipient, kidney removal was not performed because of the presence of metastases.

Implications for Multicancer Detection Techniques

Current practices exclude cancer via history, physical, and examination of internal organs during procurement. Tumors such as breast, melanoma, choriocarcinoma, colon, leukemia, and lymphoma have higher transmission rates because of their aggressive clinical nature [3,5]. Given organ scarcity, exceptions can be made for early-breast carcinoma (T1a/T1b) or T1 colon carcinoma in remission for at least 10 years [5]. Low-grade central nervous system tumors harbor low transmission rates; however, donation is not recommended if ventriculoperitoneal shunt, resection, chemotherapy, or radiation therapy has been performed. History should be obtained from family members, and any prior pathology should be reviewed for deceased donors. Attention should be given to donors with cerebral hemorrhage because some cases were later found to be due to intracranial metastases or aggressive central nervous system tumors [3].

Proposals for augmented cancer screening in solid organ transplantation focus on recipients because their risk of de novo malignancy is estimated to be 2- to 4-fold higher than the general population [12,13]. Chronic immunosuppression and decreased immune surveillance play roles in increased risk of de novo malignancy [14]. It is postulated there will be increased indolent malignancies in the donor pool because of increased life expectancy and donations in older people [15]. Also, traditional screening methods have a low yield. For example, colonoscopies have a yield of approximately one-half percent [4,16].

The risk-benefit ratio of cancer screening methods should be reevaluated given the availability of modern technologies [17], such as multicancer detection assays that analyze circulating cell-free DNA and circulating tumor DNA (ctDNA) [18]. Some companies, such as Grail and Thrive, offer early multicancer detection assays [19]. These tests are currently not approved by the Food and Drug Administration and are not without their limitations. First is the timing and availability of results. Samples must be sent to specialized laboratories; obtaining results takes weeks [20]. Although ctDNA could be used to screen living donors, the current processing time is impractical for deceased donors, representing the largest donor pool [21]. Also, the sensitivity in early-stage disease is underwhelming, though advances in future technology could overcome this [22]. One attempt to improve yield is identifying high-risk populations, as done in the SUMMIT trial, which evaluated the development of lung cancer in high-risk individuals with substantial smoking history [23]. Studies such as STRIVE (NCT03085888) and AI-EMERGE (NCT03688906) are

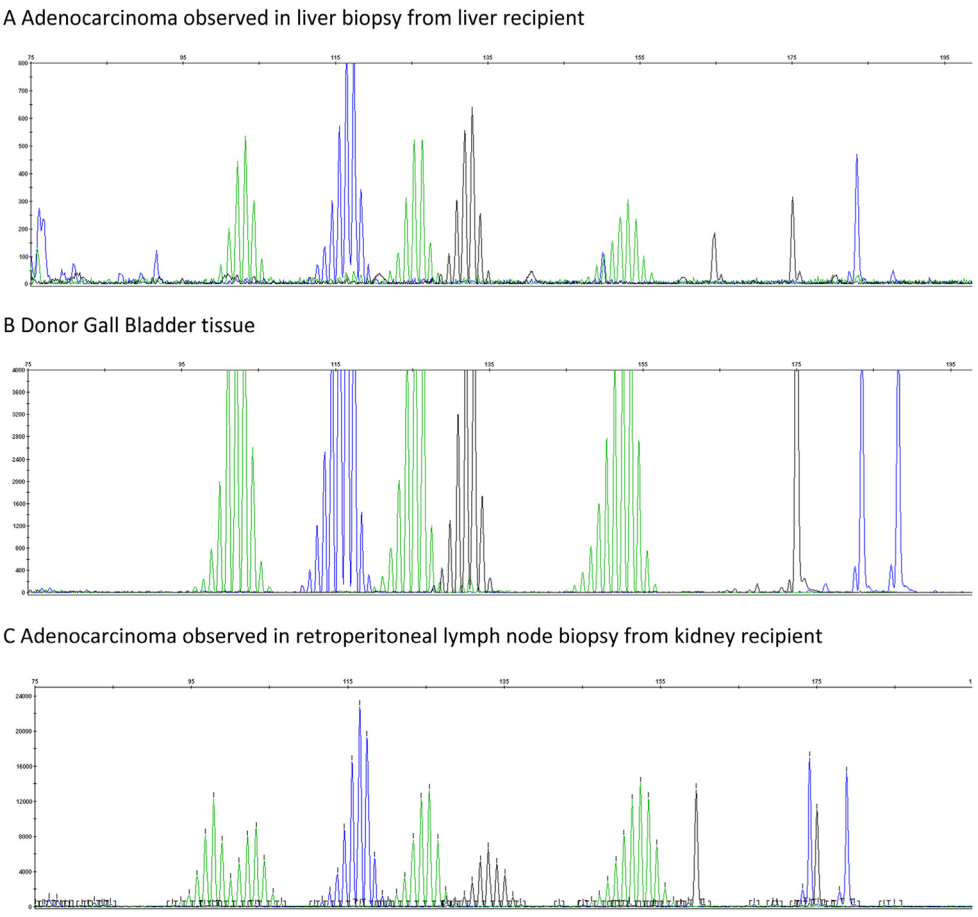

Fig 3. Microsatellite instability analysis of adenocarcinoma of liver recipient compared with normal donor tissue and adenocarcinoma of retroperitoneal lymph node biopsy from kidney recipient. **(A)** Electropherogram from adenocarcinoma detected in liver biopsy from liver transplant recipient. **(B)** Electropherogram of normal gall bladder tissue obtained from donor. **(C)** Electropherogram of adenocarcinoma obtained from retroperitoneal lymph node biopsy of kidney recipient.

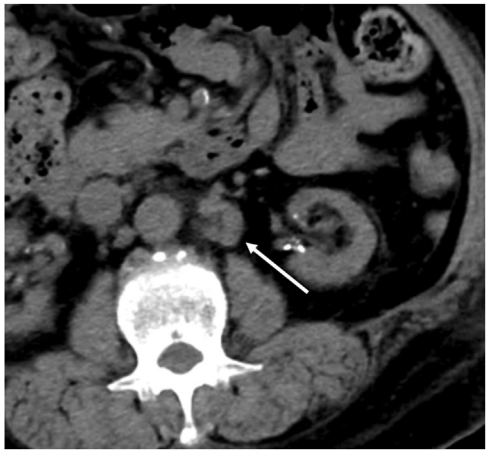

Fig 4. Noncontrast axial imaging on computed tomography demonstrates abnormal retroperitoneal lymphadenopathy including a left para-aortic lymph node (arrow) with abnormally thickened cortex and infiltration into the surrounding fat.

ongoing, evaluating cell-free DNA's role in early detection. Another application of ctDNA is surveillance for minimal residual disease [24]. These assays can detect recurrence months before imaging [25−27] and could be used in recipients or donors with a history of malignancy.

CONCLUSIONS

Donor-transmitted malignancy is rare but carries significant morbidity and mortality. Current guidelines limit these events by reviewing medical records, applying data on the risk of transmission, and physical examination of abdominal and thoracic viscera during procurement. As the donor pool increases in age, the incidence of DTMs may increase, and novel technologies such as ctDNA may augment eligible donors' screening and risk stratification. Although promising, these tools must be validated before integration into practice.

DATA AVAILABILITY

No data was used for the research described in the article.

DECLARATION OF COMPETING INTEREST

A.A. reports administrative support was provided by the University of Missouri−Kansas City. 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.

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