Donor-Derived Metastatic Melanoma in a Liver Transplant Recipient Established by DNA Fingerprinting

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Abstract

Metastatic melanoma is a donor-derived malignancy that has rarely been reported in liver allograft recipients. We present a case of a transmitted donor-derived melanoma to a liver allograft recipient in whom the diagnosis was established by polymerase chain reaction-based DNA fingerprinting.

A 52-year-old African-American man underwent a successful orthotropic liver transplant for alcohol-induced cirrhosis. One year after the orthotropic liver transplant, he presented at our institution with diffuse abdominal pain, and a computed tomography scan of the abdomen and chest showed innumerable masses diffusely involving the liver and multiple subcutaneous nodules in the abdominal and chest wall. A liver biopsy confirmed the diagnosis of metastatic melanoma. The origin of melanoma was traced to the donor by DNA fingerprinting of the native liver, the donor liver, and the donor gallbladder. Chemotherapy was initiated with temozolomide (75 mg/m² daily) and thalidomide (50 mg daily), to which he responded within 8 weeks with radiologic improvement in metastatic lesions. Tacrolimus was switched to sirolimus because of renal insufficiency as well as reported effectiveness against melanoma. Our patient survived for 9 months after the diagnosis of metastatic melanoma. He ultimately died of brain metastases.

Donor-derived metastatic melanoma is a rare cancer with the highest transmission and mortality rates, which requires better recognition. Prompt diagnosis of donor-derived melanoma is critical and can be achieved reliably with polymerase chain reaction-based DNA analysis. Management options after diagnosis include de-escalation of immunosuppression, with or without urgent organ removal or retransplant. The roles of chemotherapy, immunotherapy, and radiotherapy require further study.

Key words: *Donor derived malignancy, Liver transplant complications, DNA fingerprinting, Malignant melanoma*

Introduction

Transmission of donor-derived malignancy to an organ transplant recipient via the graft is a catastrophic outcome of an organ transplant.[1] Metastatic melanoma is a lethal donor-derived malignancy with a transmission rate of 74% and a mortality rate of 58%.[2] To date, only 4 case reports of metastatic melanoma involving liver allografts[3-6] were reported in search of the literature.

We report a case of this rare phenomenon of transmitted donor-derived melanoma to a liver allograft recipient where the diagnosis was established by polymerase chain reaction-based DNA fingerprinting. Our patient survived for 9 months after the diagnosis, after a change and reduction in the immunosuppressive regimen, combined with chemoradiation. This case serves to increase the clinical awareness regarding the need for strict donor screening to avoid potentially fatal outcomes from donor-derived melanoma, and outlines a treatment regimen that is associated with better-than-expected survival after diagnosis.

Case Report

A 52-year-old African-American man with a history of alcohol-induced cirrhosis underwent a successful orthotropic liver transplant at our center. His initial posttransplant course was unremarkable. Immunosuppression included induction with steroid-free rabbit antithymocyte globulin and maintenance with tacrolimus and mycophenolate mofetil. Mycophenolate mofetil was discontinued 3 months after the transplant, and tacrolimus was continued to maintain a trough level of 6 to 8 ng/mL during the first 3 months, 3 to 5 ng/mL during the second 3 months, 3 ng/mL between months 6 and 12, and 1 to 3 ng/mL 1 year after the transplant. The patient remained compliant with his immunosuppressive medications.

About 1 year after his orthotropic liver transplant, he presented to the emergency department with abdominal pain, shortness of breath, and low-grade fever of 1 week's duration. On admission, his vital signs all were within normal limits. He was alert and in no distress. Examination of his lungs and heart was unremarkable while abdominal examination revealed hepatosplenomegaly and right upper quadrant tenderness. His laboratory results showed a mild elevation in aspartate aminotransferase (96 U/L; normal range, 15 to 41 U/L). A computed tomography scan of the abdomen revealed diffuse retroperitoneal lymphadenopathy and innumerable masses diffusely involving the liver, suggestive of metastases (Figure 1A). A computed tomography scan of the chest showed mediastinal lymphadenopathy

Figure 1A. Computed Tomography Scan of the Abdomen

A computed tomography scan of the abdomen showing diffuse retroperitoneal lymphadenopathy and innumerable masses diffusely involving the liver suggestive of metastases (yellow arrows).

Figure 1B. Computed Tomography Scan of the Chest
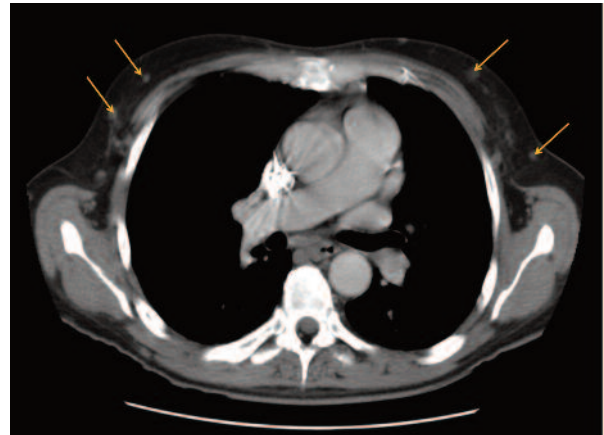
A computed tomography scan of the chest showing mediastinal lymphadenopathy and multiple subcutaneous nodules in the abdominal and chest wall, also suggestive of metastases (yellow arrows).

and multiple subcutaneous nodules in the abdominal and chest wall, also suggestive of metastases (Figure 1B). At this point in the assessment, posttransplant lymphoproliferative disorder was suspected. A computed tomography-guided core needle biopsy of a liver lesion revealed a monomorphic neoplastic infiltrate, morphologically suggestive of a posttransplant lymphoproliferative disorder. Hematoxylin and eosin staining revealed a population of cells with round-to-oval nuclei without apparent nucleoli and indistinct cell borders (Figure 2A). Pending further studies, tacrolimus was discontinued.

**Figure 2A.** Liver Biopsy With Hematoxylin and Eosin Staining
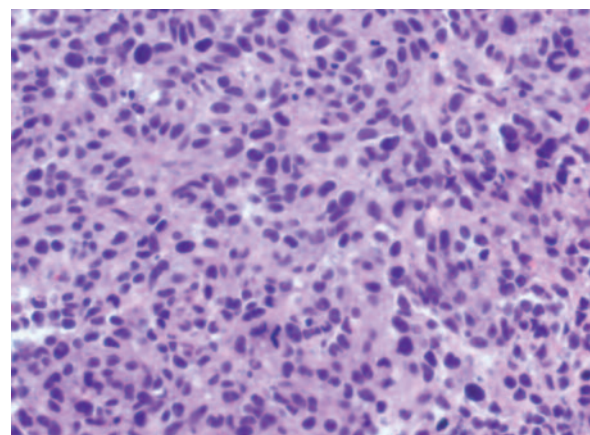
Liver biopsy with hematoxylin and eosin staining showing a population of cells with round-to-oval nuclei without apparent nucleoli and indistinct cell borders.

A portion of the liver biopsy was submitted for flow cytometric immunophenotyping. A minority of cells demonstrated lymphoid antigen

expression, the majority of which were T cells. No immunophenotypic evidence of a neoplastic lymphoid cell proliferation was demonstrated by flow cytometry. Immunohistochemical studies performed on formalin-fixed paraffin-embedded tissue of the liver biopsy, showed the infiltrate was reactive for Melan-A and S100 and lacked reactivity for CD45, pan-keratin, and synaptophysin, establishing a diagnosis of melanoma (Figure 2B).

Figure 2B. Immunohistochemical Studies Performed on a Formalin-Fixed Paraffin-Embedded Tissue From the Liver Biopsy
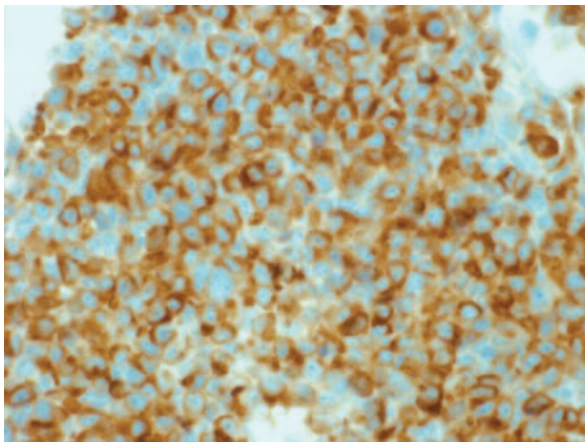
The infiltrate was reactive for Melan-A and S100 and lacked reactivity for CD45, pan-keratin, and synaptophysin, establishing a diagnosis of melanoma.

The patient denied any previous history of melanoma, and no suspicious cutaneous lesions were detected by physical examination before transplant, and at the time of this presentation. The organ donor was a 55-year-old morbidly obese, African-American man with a medical history of hypertension and atrial fibrillation and a large intracranial hemorrhage as the cause of death. As there was no prior history of melanoma in either the donor or recipient, DNA fingerprinting was done to determine if the tumor was of donor or recipient origin.

Four specimen types were analyzed for this purpose: native liver, donor gallbladder, allograft liver microscopically dissected from the liver lesion biopsy, and tumor (also microscopically dissected from the liver biopsy). Deoxyribonucleic acid was extracted from each and submitted for polymorphic marker analysis (Powerplex 16, Promega Corporation, Fitchburg, WI, USA). The results listed in Table 1 (bold indicates shared alleles) showed 14 of 16 markers were informative, clearly revealing alleles in the tumor that are different from the patient's native liver, but

identical with those within the donor gallbladder. These results show that the melanoma originated from donor tissue. The liver allograft demonstrated a mixture of both donor and recipient alleles, as recipient lymphocytes were present in the liver allograft.

Table 1. Results of DNA Fingerprinting

Marker	Native Liver	Donor Gallbladder	Liver Allograft	Tumor (Melanoma)
D3S1358	17	**16**	**16**,17	**16**
THO1	**7,8**	**7**,9	**7,8**,9	**7**,9
D21S11	30,32.2	24.2,**29**	24.2,**29**,30,32.2	**29**
D18S51	15,18	**14**,17	**14**,15,17,18	**14**
PENTA E	5,7	**12,17**	5,**12,17**	**12,17**
D5S818	**11**,13	**11,12**	**11,12**,13	**11,12**
D13S317	**12**	**11,12**	**11,12**	**11,12**
D7S820	9,**10**	**10,11**	9,**10,11**	**10,11**
D16S539	**11**	**8,11**	**8,11**	**8,11**
CSF1	9,**12**	**11,12**	9,**11,12**	**11,12**
PENTA D	8,9	7,**13**	7,8,9,**13**	**13**
VWA	17,**19**	**18**	17,**18,19**	**18**
D8S1179	10,15	**13**	10,**13**,15	**13**
TPOX	**8,11**	**8,11**	**8,11**	**8,11**
FGA	22,**26**	**20,22**	**20,22**,26	**20,22**
Amelogenin	XY	XY	XY	XY

After the diagnosis of melanoma was established, the patient was discharged home with a plan for outpatient chemotherapy with temozolomide (75 mg/m^2/d) and thalidomide (50 mg/d). The patient demonstrated a partial response to chemotherapy within 8 weeks, with a decrease in the size of the liver and subcutaneous metastatic nodules. One month later, routine laboratory studies showed elevations in transaminases, alkaline phosphatase, and total bilirubin, consistent with acute cellular rejection. Moderate acute cellular rejection was confirmed by liver biopsy and led to reinitiation of tacrolimus. Two weeks later, the patient presented at the hospital with an intractable headache associated with nausea, photophobia, and phonophobia. A computed tomographic scan and magnetic resonance imaging scan of brain were unremarkable. Temozolomide and tacrolimus were continued. The headache resolved with supportive management within a few days; however, because of acute renal insufficiency, temozolomide was held temporarily, and the patient's immunosuppression medications were switched from tacrolimus to sirolimus, which also reportedly has some activity against melanoma.[7]

After discussing the treatment options with the patient, decreased immunosuppression was planned to achieve a balance between preventing graft rejection and oncologic treatment for melanoma. During the next 5 months, the patient continued to feel better with no clinical evidence of graft rejection. A positron emission tomography scan done 5 months after the start of chemotherapy showed an 8-mm hypermetabolic cavitary lesion in the left lung, suspicious for cavitary metastasis. Hepatic and subcutaneous lesions decreased significantly in size, indicating a partial response to chemotherapy (Figures 3A and B).

Figure 3A. Computed Tomography Scan of the Abdomen

A computed tomography scan of abdomen showing significant decrease in size of hepatic lesions indicating partial response to chemotherapy (yellow arrows).

Figure 3B. Computed Tomography Scan of the Chest
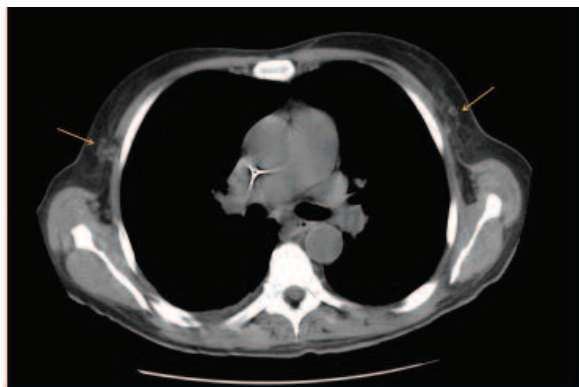
A computed tomography scan of chest showing significant decrease in size of subcutaneous lesions indicating partial response to chemotherapy (yellow arrows).

At approximately 8 months from the diagnosis of metastatic melanoma, the patient re-presented at the hospital with altered mental status, inability to ambulate, and at least 1 episode of a witnessed seizure. A physical examination was significant for dysmetria with no other focal neurologic deficit. A computed tomography scan of the head showed multiple mass lesions throughout the brain, both supratentorial and infratentorial, consistent with metastases. The brain metastases were treated with whole brain radiation therapy, for a total dosage of 30 Gy over 10 days along with temozolomide, thalidomide, sirolimus, and dexamethasone, resulting in improved mental status, no recurrence seizure activity, and his ability to return to work. However, 2 weeks after completing the radiation therapy, he presented with left arm weakness and dysphasia. A repeat computed tomography scan of the head showed innumerable brain lesions throughout both cerebral hemispheres, consistent with metastases, some with evidence of intralesional hemorrhage. At this point, the patient wished to be discharged to home on hospice care. He died shortly after discharge, as a direct result of metastatic melanoma.

Discussion

Donor-derived disease transmission, once a rare occurrence, is a growing problem with more liberal use of donors to meet the increased demand for solid-organ transplant. The incidence of transmission of undiagnosed malignancy in donor organs is estimated at around 0.02% to 0.2%.[8] However, the organ shortage has caused several transplant centers to expand the donor pool to include elderly donors, donors with infectious hepatitis, and donors with certain malignancies including low-grade skin cancers and primary central nervous system cancers.[8] A natural consequence of these expanded criteria is a rise in the incidence of donor-derived malignancy, calling for better understanding, increased vigilance, and stricter screening of donors.

Malignancy in a solid-organ recipient could arise in 3 ways. Most commonly, it is de novo development of malignancies, primarily nonmelanoma skin cancers and posttransplant lymphoproliferative disease. The second, is recurrence of previously treated malignancy. The third and least common way is inadvertent transmission of an undiagnosed primary tumor from the donor.[9,10] Transmission of malignancy and its propagation are facilitated, not only by the immunosuppressed state of the recipient, but also by

donor tissue type matching, which obviously is aimed toward successful graft function and survival.[11]

Metastatic melanoma is a rare posttransplant donor-derived malignancy demonstrating a transmission rate of 74%, a mortality rate of 58% in the first year,[2] and a 5-year survival rate of 5%.[12] Metastatic melanoma exhibits a complex biologic behavior with limited insight into its mechanisms of transmission, dormancy, and recurrence. Tumor dormancy and late recurrence remain clinical challenges, with recurrence reported as late as 35 years.[13] In the transplant setting, recurrence usually occurs much sooner with time to diagnosis ranging from 2.5 to 42 months (median, 10.5 mo).[9] Although it is almost impossible to predict the presence of an occult melanoma in a donor, elderly donors with idiopathic intracranial hemorrhage have been linked with the highest risk of transmission of donor melanoma.[9] This is based on the idea that unexplained hemorrhage could represent bleeding in an unrecognized metastatic melanoma deposit in the brain. The cause of death in our donor was similar.

Prompt and correct diagnosis of donor-derived melanoma is critical, especially in life-sustaining organ transplants, wherein reduction in immunosuppression and urgent retransplant may be the only possible strategies. In our patient, polymerase chain reaction-based DNA fingerprinting was used to identify the donor origin of metastatic melanoma. Polymerase chain reaction-based DNA fingerprinting of human tandem repeats is a sensitive, fast, and reliable test.[14] In this method, short repeated sequences of DNA called *short tandem repeats* are targeted by sequence-specific primers and amplified using polymerase chain reaction. Resulting DNA fragments are then separated and detected using electrophoresis. The pattern of alleles can distinguish between individuals extremely accurately.[14]

Management of liver transplant patients with donor-derived metastatic melanoma is not well defined owing to the lack of experience. In kidney/pancreas transplant patients, complete withdrawal of immunosuppressants to allow for organ rejection, followed by retransplant is an acceptable option. However, full organ rejection is not possible in liver recipients, given that the liver is a life-sustaining organ. This leaves reduction of immunosuppression, chemoradiation therapy, and consideration of urgent retransplant as the

only available treatment options.[5,9] The role of immunotherapy remains to be further studied. Switching from tacrolimus to sirolimus should be considered early, as it has been shown to be of some benefit against melanoma cells owing to its antitumor properties.[7] In our patient, in addition to reduction of immunosuppression and switching from tacrolimus to sirolimus, simultaneous chemotherapy was attempted with temozolomide and thalidomide followed by brain irradiation. With these measures, our patient survived 9 months after the diagnosis of metastatic melanoma.

The increasing risk of donor-derived malignancies in this era of organ transplant and expanding donor pools should be recognized. This risk can be minimized by an extensive review of the donor history, physical examination, essential laboratory values (including prostate specific-antigen and beta-human chorionic gonadotrophin in select cases), and radiologic data by the organ procurement organizations.[8] If possible, autopsy of all organ donors should follow organ procurement.[8] Donors with a history of melanoma (irrespective of the time of diagnosis, stage of disease, treatment rendered, and cancer-free duration) should be excluded from donation. Patients with a history of nonmelanoma skin cancer should be interviewed, and records should be obtained to confirm the nonmelanoma nature of cancer. Any idiopathic brain death should raise suspicion for metastatic deposit of malignancy,[2] in which case a limited cerebral postmortem examination could be used to identify undetected donor malignancy.[4] The diagnosis of malignancy in an organ recipient should prompt immediate investigations of other recipients from the same donor in multiorgan donations.[3]

In conclusion, donor-derived malignancies are rare, and metastatic melanoma is one such cancer with the highest transmission and mortality rates. Donors should undergo strict screening to minimize such transmission. Any possible donors with a history of, or current, lesion suspicious for melanoma should be excluded from the process. Early diagnosis with the use of polymerase chain reaction-based DNA analysis is imperative to ensure correct diagnosis of donor derivation and timely intervention. Management options after diagnosis include de-escalation of immunosuppression with or without urgent organ removal or retransplant. The role of chemotherapy, immunotherapy, or radiotherapy requires further study.

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