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Long-term survival of kidney-transplant recipient with donor-transmitted malignant melanoma after provoked rejection

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ABSTRACT

Donor-transmitted malignancy is a rare and often fatal complication of organ transplantation. We report a case of a 55-year old male kidney transplant recipient who was diagnosed with stage-IV donor-transmitted melanoma 5 months after transplantation with metastases in the liver, spleen, lung, and brain. Immunosuppression was discontinued, and encorafenib and binimetinib, inhibitors of a serine/threonine B-Raf proto-oncogene (BRAF) and mitogen-activated protein kinase kinase (MEK) respectively, were started. Severe rejection ensued and necessitated the start of hemodialysis as well as urgent graft nephrectomy. However, the tumor progressed and BRAF/MEK inhibition was replaced by immune-checkpoint inhibition with ipilimumab and nivolumab. When this also failed to slow disease progression and seizures occurred, therapy with encorafenib and binimetinib was reinstated. Afterwards, most of the metastases remained stable. The patient has now survived for more than 4 years in good general health, which is an exceptionally long survival with donor-transmitted, metastasized melanoma.

1. Introduction

Kidney transplanta recipients (KTR) are healthier and live longer than patients with end-stage kidney disease who remain on the waiting list for transplantation [1], but the immunosuppressive therapy that is required to prevent allograft rejection confers an increased risk of developing malignancy. Cancer may develop de novo in KTR, or it may be transmitted from the donor. Melanoma, lymphoma and renal cell cancer are the most commonly transmitted malignancies. 5-year survival rates of patients with donor-transmitted renal cell cancer or lymphoma are 93 % and 63 % respectively. By contrast, median survival with donor-transmitted melanoma is only 4 months [2].

Here we report the case of a KTR with donor-transmitted melanoma with metastases to the liver, spleen, lung, and brain who has survived for more than 4 years.

Case Report.

A 55-year old male patient with dialysis-dependent kidney disease due to hypertensive nephropathy received a kidney allograft from a deceased female donor with no history of malignancy. Chest x-ray and abdominal ultrasound of the donor revealed no focal lesions and the skin was reported free of scars, nevi or tattoos. The rectal and oral mucosa were likewise described as unremarkable.

After transplantation primary graft function was observed. The further course was unremarkable with a stable serum creatinine in the normal range and unsuspicious doppler ultrasound examinations of the allograft.

Five months after transplantation, the patient complained about a painful subcutaneous mass in the vicinity of the transplant scar. The mass was surgically removed, revealing a black color. The pathological diagnosis was malignant melanoma. A computerized axial tomography (CAT) scan of the chest and abdomen and a brain magnetic resonance imaging (MRI) scan showed lesions in the liver, spleen, lung and brain. There was a high level of circulating tumor marker S-100B (26.7 μg/l; normal range, <0.105 μg/l; Fig. 1). A clinical diagnosis of stage-IV

Abbreviations: BRAF, B-Raf proto-oncogene; CAT, computerized axial tomography; DSO, Deutsche Stiftung Organtransplantation (German organ procurement organization); KTR, kidney-transplant recipient(s); MEK, mitogen-activated protein kinase kinase; MRI, magnetic resonance imaging.

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melanoma was made. The consulting dermatologists and ophthalmologists did not find evidence of a primary melanoma in our patient. Genetic analysis confirmed transmission of the malignancy from the donor.

After interdisciplinary discussion, we decided to terminate immunosuppression and provoke allograft rejection, expecting an immune reaction to the donor's melanoma cells. Indeed, serum levels of S-100B dropped sharply in the absence of immunosuppression (Fig. 1). Acute allograft rejection occurred shortly thereafter (Fig. 1), and intermittent hemodialysis was started proactively before clinical uremia or hyperkalemia developed. Because of severe inflammation of the transplanted kidney, urgent graft nephrectomy was performed.

At the same time we initiated combination therapy with encorafenib and binimetinib. Encorafenib is a small molecule blocking a serine/threonine B-Raf proto-oncogene (BRAF) and binimetinib is an inhibitor of the mitogen-activated protein kinase kinase (MEK). Three months later, pulmonary metastases progressed. A switch to immune-checkpoint inhibition with ipilimumab and nivolumab was suggested, but the patient declined. Two months later, the patient experienced seizures, prompting radiation therapy of the cerebral metastases. Due to further seizures 12 months after diagnosis, dual checkpoint inhibition with ipilimumab and nivolumab was initiated. MEK/BRAF inhibition was simultaneously stopped.

Because of further progression of the lung and liver metastasis, therapy was changed back to encorafenib and binimetinib. This finally induced almost stable disease with only slowly progressing metastases. At the time of submission of this manuscript, the patient has survived for over 4 years and is in good general health without further seizures and despite maintenance hemodialysis three times per week. S100-B levels remain below the level of detection.

When the melanoma was first diagnosed, this was immediately reported to the German procurement organization DSO as a severe adverse event. The investigations that ensued led to the diagnosis of stage-IV melanoma in the recipient of the liver at our center as well as the recipient of the contralateral kidney at another center. Immunosuppression of the liver recipient was switched from mycophenolate mofetil (MMF) to everolimus, and BRAF/MEK inhibitors were started. Unfortunately, the recipient of the contralateral kidney died after a few weeks, and the liver recipient passed away 15 months after transplantation.

2. Discussion

Donor-transmitted malignancy is a rare but serious complication of organ transplantation. Melanoma is among the most frequently transmitted cancers. At the time of diagnosis, more than 80 % of patients have metastasis and only 50 % survive for 2 years [2]. Organs from donors with a history of non-melanoma cancer may be eligible for transplantation under certain conditions such as curative treatment and the absence of late recurrence. This has led to very low transmission rates of 0.012 % to 0.03 % [3,4]. By contrast, malignant melanoma may be transmitted even when the donor was considered cured for 16 or even 32 years prior to organ donation [5,6]. This has led to the exclusion of donors with any history of melanoma.

Contemporary cancer transmission occurs almost exclusively from donors without previous history of current evidence of malignancy, as in the case reported here The donor of our patient died due to intracerebral hemorrhage. While not evident, it cannot be ruled out that the hemorrhage was caused by an unrecognized cerebral metastasis [2]. Once tumor cells circulate in the blood stream, transmission may occur during organ transplantation [7].

The recommended management of donor-transmitted melanoma is to withdraw immunosuppression in order to induce rejection of any donor-derived tissues [8]. This may cure even metastatic disease, and it has enabled re-transplantation in one case [9].

With the use of immunotherapy and targeted therapies, the general prognosis of melanoma has considerably improved [10]. About 50 % of melanomas respond to immune-checkpoint inhibition with ipilimumab and nivolumab [10], highlighting the pivotal role of the immune system in the development of cancers. In combination with provoked allograft rejection, cases of complete remission of metastases in donor-transmitted melanoma have been reported [11,12].

Unfortunately, our patient did not achieve complete remission. The lack of success of immunotherapy could indicate that checkpoint inhibitors are unable to stimulate the immune system when it is already strongly activated by the presence of a kidney allograft.

The other kidney recipient died too quickly to receive any directed therapy, highlighting the grim prognosis of stage-IV donor-transmitted melanoma for most patients. In the case of liver transplants, provoked rejection and allograft removal are not feasible, and few treatment options remain. This raises the question whether a more thorough investigation of donor candidates could prevent such lethal outcomes. For instance, the use of mandatory CAT scans or tumor markers such as S-100B might increase the chances to detect occult cancers prior to procurement. These kinds of examinations are currently not mandatory for most organ procurement organizations, as is the case in Germany [13]. On the other hand, the overall risk of donor transmitted malignancy is very low, and it will be impossible to reduce the risk of transmission to zero [2,3]. Overall and despite the risk of developing de-novo or transmitted cancer, kidney transplantation remains the best available treatment for end-stage kidney disease.

CRediT authorship contribution statement

Andreas Kommer: Writing – original draft. **Stefan Holtz:** Investigation, Data curation. **Daniel Kraus:** Writing – review & editing,

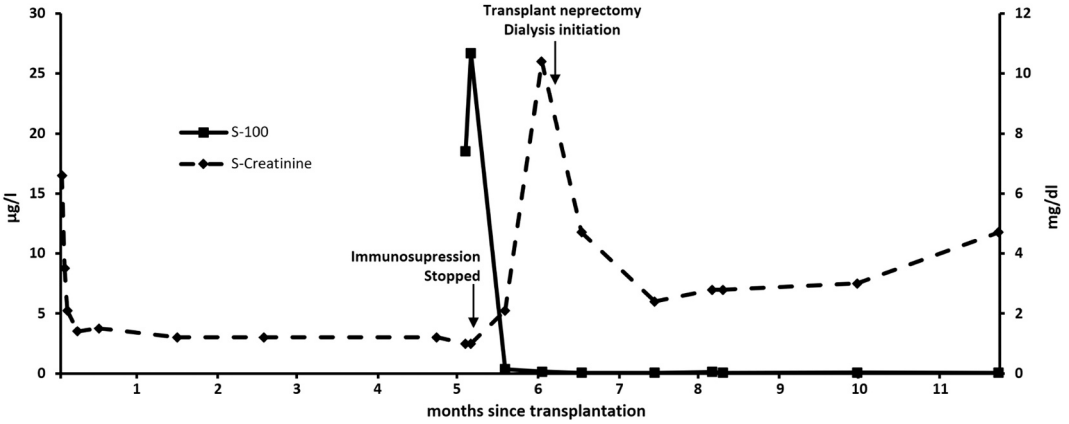

Fig. 1. Relationship between serum-creatinine and serum levels of S-100 tumor marker with good serological response after allograft rejection.

Supervision. **Simone Cosima Boedecker-Lips:** Writing – review & editing. **Martina Koch:** Writing – review & editing, Supervision. **Julia Weinmann-Menke:** Writing – review & editing, Resources.

Declaration of competing interest

The authors have no conflicts of interest regarding this manuscript.

Data availability

Data will be made available on request.

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