# Donor-Derived Metastatic Melanoma and Checkpoint Inhibition

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## ABSTRACT

Donor-derived malignancy, particularly melanoma, is a rare but known complication of organ transplantation. Here we describe a case of metastatic melanoma in a deceased-donor kidney transplant recipient. After diagnosis, the patient was successfully treated with cessation of immunosuppression, explantation of the renal allograft, and novel melanoma therapies, including the mutation-targeted agents dabrafenib and trametinib and the immune checkpoint inhibitor nivolumab. These 2 new classes of melanoma therapy have revolutionized the course of metastatic melanoma, altering it from one of nearly certain mortality to one of potential cure. This case reviews the mechanisms of action of these therapies and reports our experience with them in the rare setting of donor-derived melanoma in a dialysis-dependent patient.

DONOR-DERIVED melanoma from patients who are unknown to have malignancy at the time of donation is a very rare but known risk of kidney transplantation (KT). There have been ~20 reported cases in literature of donor-derived melanoma in KT recipients since 1972 [1]. KT recipients provide an immunologically permissive environment for "dormant" passenger malignant cells to grow within the recipient. The conventional approach to donor-derived cases has been to withdrawal immunosuppression to allow for allograft rejection, followed by surgical removal of the allograft and subsequent systemic chemotherapy. Historically, the vast majority of these patients died from metastatic disease within months of diagnosis, similarly to their de novo cutaneous melanoma counterparts [1].

However, novel agents are changing the landscape for metastatic melanoma, with the potential to transform a disease with devastatingly high mortality to one with potential for cure. These agents target tumors based on expressed mutations and block endogenous adaptive inhibitory mechanisms for tumor growth. Little is known about how these novel agents perform in a donor-derived setting, specifically in KT recipients. We describe here a KT recipient with donor-derived metastatic melanoma who was treated with dabrafenib, trametinib, and anti–programmed cell death protein 1 (PD1) inhibitor antibody, nivolumab. We review the mechanisms of action of these agents as well as relevant issues regarding drug metabolism in dialysis-dependent patients.

## CASE DESCRIPTION

The patient was a 57-year old man who had undergone deceased-donor KT. Fifteen years before undergoing KT, the patient himself was a kidney donor. Subsequent to donation, he developed chronic glomerulonephritis, requiring dialysis ~1 year before KT. Also, ~1.5 years before KT, he was diagnosed with prostatic adenocarcinoma that extended into the bladder neck (Gleason score, 8; pT3A; R1; N0; MX; stage III). He underwent radical prostatectomy and radiation therapy. The time of the transplantation relative to the prostate cancer treatment was discussed with the Israel Penn Tumor Registry.

His KT was from a male donor who died from cerebral hemorrhage and had no history of malignancy. The kidney allograft was placed in the right lower quadrant via standard surgical technique. It functioned within 4 hours and dialysis was never required. The patient received induction immunosuppression with thymoglobulin and steroids. Maintenance immunosuppression consisted of mycophenolate mofetil (MMF), tacrolimus, and prednisone. He was discharged on postoperative day 4 with a creatinine of 1.06 mg/dL after an uncomplicated course.

One month after KT, he presented with right thigh swelling and pain at the operative site. Evaluation with the use of ultrasound and computerized tomography (CT) revealed a small perinephric collection inferior and medial to the allograft between the bladder

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and the kidney. This underwent drainage by interventional radiology (~15 mL) with relief of symptoms. He presented 2 additional times with similar symptoms, requiring drainage of a recurrent periallograft effusion. With each episode, there was associated acute kidney injury, which resolved with drainage. At 4 months after KT, MMF was suspended owing to persistent leukopenia.

Approximately 6 months after KT, the patient reported severe fatigue and shortness of breath. He was afebrile and normotensive and in no acute distress, with mild tenderness to palpation in the right lower quadrant along the allograft site. His creatinine was 2.5 mg/dL (from 1.3 mg/dL 1 month earlier); white blood cell count, 2,800 cells/mm$^3$; platelets, 280,000 cells/mm$^3$; hemoglobin, 11.4 g/dL (from 14.4 g/dL 1 month earlier); 12-hour tacrolimus trough, 7.8 ng/dL; prostate-specific antigen, <0.01 ng/mL. There was no BK virus DNA detected in the blood, and urine culture was negative. Electrolytes and liver function tests were within normal limits. Ultrasound of the allograft demonstrated chronic mild hydronephrosis, normal resistive indices, and absence of a perinephric collection. CT of the abdomen and pelvis without intravenous contrast noted innumerable punctate nodules in the lungs, a 1.3-cm hypoattenuating lesion in the right hepatic dome, and scattered nonenlarged para-aortic lymph nodes. A CT-guided percutaneous biopsy of a left lower lobe pleural-based nodule was performed. Pathology revealed melanoma. Immunohistochemical stains were strongly positive for vimentin with focal staining for S-100, SOX-10, and melanin-A. In addition, the tumor was found to harbor a BRAF-V600E (c.1799T>A) mutation.

The patient underwent transplant nephrectomy. Operative findings demonstrated extensive tumor implants throughout the kidney allograft as well as invasion of the collecting system and vasculature, including encasement of the external iliac vessels. Pathology was consistent with necrotizing melanoma with lymphovascular invasion. There was no evidence of lymphocytic infiltration. HLA typing of the tumor cells matched that of the donor, indicating a diagnosis of donor-derived metastatic melanoma. The only other organ recipient from the same male donor, a female liver recipient, was also diagnosed with donor-derived metastatic melanoma as determined by identification of male karyotype in melanoma cells. In retrospect, the tumor growth and lymphatic invasion was likely responsible for the patient's recurrent symptoms of periallograft pain and effusion after KT.

According to American Joint Committee on Cancer criteria, the patient's melanoma stage was determined to be TX, NX, M1c (stage IV). Lactate dehydrogenase was elevated at 716 mg/dL. Targeted therapy directed against BRAF-V600E mutation–positive melanoma was initiated with the use of a BRAF inhibitor (150 mg dabrafenib twice daily) and a mitogen-activated protein kinase (MEK) inhibitor (2 mg trametinib once daily). There was early evidence of a clinical response. The patient exhibited anorexia and weight loss, necessitating a dose reduction (75 mg dabrafenib twice daily and discontinuation of trametinib). Despite these modifications, the side effects did not improve, leading to noncompliance and eventual discontinuation of these drugs. Nivolumab, a PD-1 inhibitor, was initiated at 3 mg/kg intravenously every 2 weeks. The patient tolerated this well without side effects. A restaging CT scan at 4 months after initiation of nivolumab demonstrated marked clinical response with resolution of liver metastases and significant shrinkage of multiple lung metastases. CT imaging 14 months after the initiation of nivolumab continued to demonstrate tumor regression. At the time of writing, the patient remains on nivolumab, every 2 weeks, without adverse events. He was managed on hemodialysis (HD).

## DISCUSSION

Recent advances have introduced novel alternatives to standard chemotherapy for metastatic melanoma that have shown significant improvement in mortality and the potential for cure. These include: 1) targeted therapy, in which tumors are treated based on specific expressed mutations; and 2) immunotherapy or "checkpoint inhibition," in which the adaptive inhibitory mechanisms of the immune system are blocked to allow endogenous immune cells to potentially recognize and eliminate cancer cells [2–5]. The patient described here is one of the first reported cases of donor-derived metastatic melanoma to be managed with the use of these novel therapies.

The Ras–Raf–MEK–mitogen-activated protein kinase signaling pathway is central to the pathogenesis of melanoma. Approximately 50% of patients with melanoma have a BRAF mutation. The BRAF-V600E mutation, which consists of a substitution of glutamic acid for valine at amino acid 600, is the most common mutation along this pathway, found in 50%–70% of melanomas. BRAF inhibitors shut down this melanoma-promoting pathway and are therefore an example of targeted therapy. Dabrafenib and vemurafenib are BRAF inhibitors, which have demonstrated 48% and 50% clinical response rates, respectively [4,5]. Despite these rapid and dramatic clinical responses, resistance to BRAF inhibitors can occur owing to up-regulation of parallel redundant pathways [6]. Trametinib (and cobimetinib) inhibits MEK, which works downstream of mutated BRAF and also has shown good clinical response [7]. When combined, BRAF and MEK inhibitors achieve even higher clinical responses (~65%) compared with either alone and can delay the problem of resistance to BRAF inhibitors [8,9].

Ipilimumab and nivolumab are examples of immunotherapy, also known as checkpoint inhibitor therapy. There are two main targets for immunotherapy in current clinical use: cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1. CTLA-4 is an antigen on cytotoxic T cells that competes with CD28, an activating factor for binding to B7 on antigen-presenting cells. Thus, CTLA-4 prevents sensitization of the T-cell to presented antigen by competitively inhibiting the function of CD28, serving as a "checkpoint" at which to block the immune system from destroying "self" [10]. PD-1 is a receptor on T cells that binds a ligand on tumor cells (PD-L1) and in turn inhibits immune-targeting of the tumor cells [3]. Therefore, by blocking either CTLA-4 or PD-1, the immune system can bypass innate barriers which, in a healthy state, prevent self-injury, but in a malignant state, allow for propagation of cancer cells [2]. Ipilimumab, a CTLA-4 inhibitor approved in 2011, was the first medication to demonstrate a survival advantage in melanoma. Collectively, ipilimumab and anti–PD-1 antibodies pembrolizumab and nivolumab have demonstrated unprecedented success in treating metastatic melanoma [11–13]. The use of ipilimumab, in a patient with donor-derived metastatic melanoma on hemodialysis has

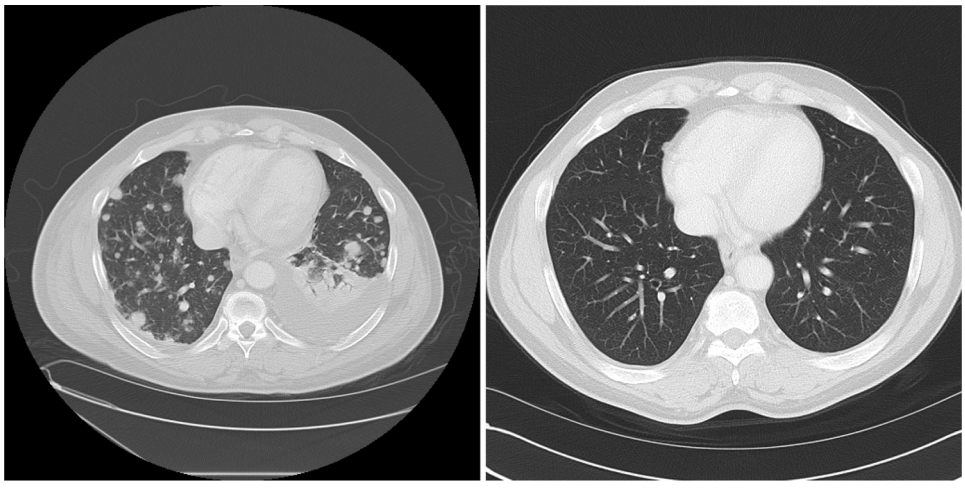

**Fig 1.** Computerized tomographic scan of lung at diagnosis (right) and at 14 months after initiation of nivolumab.

previously been reported [14]. However, to our knowledge, the present case is the first reported of donor-derived melanoma in a kidney transplant recipient to be treated with the BRAF/MEK inhibition combination of dabrafenib and trametinib and the anti-PD1 antibody, nivolumab.

Given that patients with donor-derived melanoma likely require withdrawal of immunosuppression and transplant nephrectomy, they will be managed on dialysis. Few guidelines exist regarding the use of anticancer therapeutics in patients on dialysis. Clinical trials usually exclude patients with chronic kidney disease (CKD; glomerular filtration rate, <60 mL/min). To date, there have been no studies on BRAF inhibitor dosing in patients on dialysis. However, caution has been advised owing to potential toxicity seen in a patient on dialysis receiving vemurafenib [15]. Nausea and diarrhea are relatively common with the dabrafenib-trametinib combination, encountered in up to 35% of all patients. Recommended dose reductions have been published in patients experiencing side effects [16]. Whether or not the adverse effects profile of dabrafenib is more pronounced in patients on dialysis is currently unknown. Our patient experienced intractable gastrointestinal side effects on these drugs but the contribution of dialysis dependence to this was likely minimal. Dabrafenib and vemurafenib are primarily metabolized by cytochrome P450 isoenzymes (CYP2C8 and CYP3A4), whereas trametinib and cobimetinib are metabolized by hydrolytic enzymes resulting in fecal elimination. Only ~20% of each drug is cleared by the kidney. In addition, because both these drugs are highly bound to plasma proteins, dialysis is not likely to remove them effectively [17,18].

Nivolumab and pembrolizumab are large proteins, and elimination of these drugs is less well understood but may include proteolysis, endocytosis, and target-mediated disposition [19,20]. Therefore, these monoclonal antibodies are not eliminated via traditional pathways and are likely to be relatively unaffected by CKD or dialysis. There is no clinically significant difference in nivolumab clearance in patients with CKD compared with control patients [21].

The presented patient had an early clinical response to combined BRAF-MEK inhibition but found treatment intolerable. After only 1.5 months of therapy with dabrafenib and trametinib, he received a PD-1 inhibitor immunotherapeutic, nivolumab, on January 12, 2016. He had evidence of a radiographic response. The most recent imaging, on February 9, 2017, indicated an ongoing response (Fig 1). Although this patient had a robust response to BRAF-MEK inhibition, radiographic evidence indicates that he is responding to PD-1 inhibition as well, given that he would have been expected to demonstrate progressive disease off BRAF-MEK therapy without another effective line of therapy at his disposal. Whether or not there exists a more robust response to checkpoint inhibition in donor-derived versus de novo cancer is unknown and can not be observed from this case. However, it demonstrates that checkpoint inhibitor therapy can be well tolerated and effective for donor-derived cancer in the absence of a transplant immunosuppression regimen. Furthermore, this case suggests that nivolumab can be used in patients on HD without regard to dose or interval and without regard to HD timing. It also underscores that clinicians must maintain a high index of suspicion for donor-derived malignancy in patients who have atypical presentations after KT such as the one described here. Early detection of malignancy affords more rapid administration of anticancer therapy. Explantation of the allograft and suspension of immunosuppressive therapy should be strongly considered.

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