

Acute Kidney Transplant Rejection After Administration of Nivolumab in a Dialysis Patient With a Failed Graft



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INTRODUCTION

Immune checkpoint inhibitors (ICIs) are monoclonal antibody drugs that block the binding of specific regulatory proteins located on T cells. Cytotoxic T lymphocyte-associated antigen-4 and programmed cell death protein 1 (PD-1) are the main targets of ICIs. In healthy individuals, the binding of ICIs to their ligands on antigen-presenting cells and peripheral tissues deactivates T cells and prevents autoimmunity.¹ Therefore, blocking this binding by ICIs allows the immune system to destroy the malignant cells. During the last decade, the advent of ICIs has dramatically improved outcomes in patients with metastatic melanoma and many other types of cancer, and they have arisen as first-line therapies. However, severe complications have come to light following the use of these agents affecting almost every organ and system including native kidneys and kidney allografts. They are commonly referred to as immune-related adverse effects, occur in >50% of patients, can become life-threatening, and may result in treatment discontinuation or failure.²

Kidney transplantation provides overall improved survival and quality of life in patients with end-stage kidney disease (ESKD). The use of immunosuppressive drugs, although mandatory to minimize the risk of allograft rejection, increases the incidence of *de novo* malignancies up to 4-fold among kidney transplant recipients (KTRs). Common practice after the diagnosis of malignancy in KTRs is to minimize or even withhold immunosuppression. This practice, along with the institution of immunotherapy in KTRs, further

increases the risk of allograft rejection in part because of the inhibition of regulatory signals and subsequent increase of T cell activation. The evidence on the safety and benefits of ICIs in KTRs is limited because this patient population has been excluded from clinical trials. To our knowledge, no specific recommendations for the use of ICIs in KTRs are currently available, and the relevant published literature reports only a few cases of KTRs treated with ICIs.

We report a unique case of acute transplant rejection after treatment with anti-PD-1 for a metastatic renal cell carcinoma in a previously transplanted patient with a nonfunctioning kidney graft who was on peritoneal dialysis for the last 2 years.

CASE REPORT

A 41-year-old woman with ESKD was admitted to the nephrology ward with fever and kidney graft tenderness. She had a history of ESKD of unknown etiology since 2001 when she started hemodialysis. Seven years later, in 2008, she underwent deceased donor kidney transplantation with 2 human leukocyte antigen mismatches. After induction treatment with basiliximab she began a course of methylprednisolone, cyclosporin, and mycophenolate mofetil. Four years later, she was diagnosed with biopsy-proven cell-mediated rejection related to medication nonadherence, whereas a titer of panel reactive antibodies remained low (both immunoglobulin G classes I and II < 5%) with no donor-specific antibodies. Despite receiving adequate antirejection treatment, she progressively developed chronic allograft injury and by October 2017 she was started on

peritoneal dialysis. The immunosuppression was gradually reduced, and she was maintained on 4 mg of methylprednisolone every other day.

In February 2019, in the context of an evaluation of uncontrolled hypertension, a computed tomography scan of her abdomen was performed and a large, solitary, 5-cm mass was found in the left native kidney. Left nephrectomy was performed a month later and the kidney with the perirenal fat and an 8-cm section of the ureter were resected. A neoplastic mass of maximal diameter of 5 cm was isolated and proceeded to further evaluation. The microscopic examination revealed a clear cell renal cell carcinoma nuclear grade 2, according to the World Health Organization grading system. The tumor extended into the renal vein's segmental branches but did not invade the perirenal fat and the Gerota fascia (T3a). A subsequent abdominal and thoracic computed tomography scan revealed multiple pulmonary lesions indicating metastatic disease (NOM1). The patient initially received sunitinib in April 2019, an anti-vascular endothelial growth factor drug that further deteriorated the patient's hypertension and was therefore discontinued after 6 months of therapy.

In August 2019, the patient underwent a second computed tomography scan that showed no improvement in the pre-existing pulmonary lesions with the remainder of the findings unremarkable. The patient opted to proceed with nivolumab 3 mg/kg, an anti-PD-1 antibody, in November 2019. Two weeks after the first cycle of treatment, she reported fever ≤ 38.5 °C, and 2 days later marked allograft pain. On presentation, her blood pressure was 145/90 mm Hg, her heart rate was 110 beats/min, and her temperature was 38.2 °C. The physical examination revealed marked tenderness and enlargement of the kidney graft and peripheral edema; the rest of the examination was unremarkable. Blood cultures were negative. Laboratory tests revealed an increase in the inflammatory markers, a white blood cell count of 16.550 cells/mm³ (with 90.4% polymorphonuclear leukocytes), a C-reactive protein of 137 mg/l (reference range 0–6 mg/L), and anemia (hemoglobin 8.3 g/dl). Electrolytes and liver function tests were within normal limits. Ultrasound was performed and confirmed the graft enlargement with no hydronephrosis or perinephric fluid collection; no other findings indicating intra-abdominal pathology were noted. Further imaging concerning renal vessels (i.e., angiography) was not performed because the patient was anuric long before the current event. Testing for human leukocyte antigen donor-specific antibodies was not available at the time of the event.

Medications on admission included methylprednisolone 4 mg every other day, atorvastatin 20 mg daily,

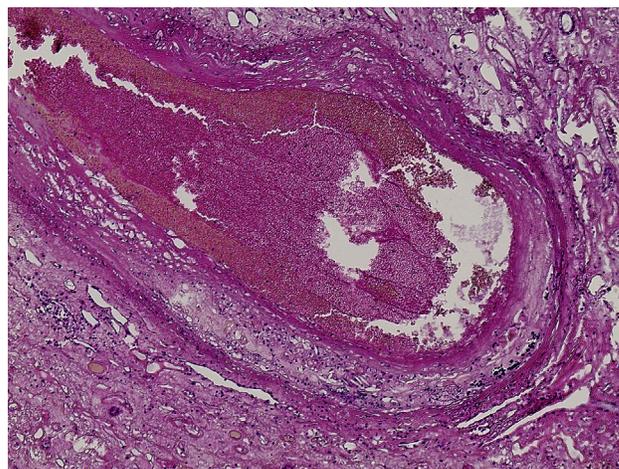


Figure 1. Large thrombus obstructing the lumen of an interlobar artery. Many inflammatory cells can be appreciated in the vessel wall (hematoxylin and eosin stain; original magnification $\times 100$).

carvedilol 12.5 mg twice a day, omeprazole 20 mg daily, moxonidine 0.4 mg twice a day, irbesartan 300 mg daily, sevelamer 800 mg 2 tabs, 3 times a day, and darbepoetin 60 μ g/weekly subcutaneously. With the clinical suspicion of graft rejection, the patient received treatment with intravenous pulse methylprednisolone (500 mg/day for 3 days), followed by oral prednisolone 32 mg/day, which was gradually tapered. After treatment with pulses of steroids, a rapid resolution of symptoms and a remarkable fall of inflammation markers (white blood cell count and C-reactive protein) was observed, and the patient was discharged in a week. A month later, the patient underwent transplant nephrectomy, and the biopsy specimen was consistent with mixed T cell and antibody-mediated rejection. Pathology examination revealed massive, ischemic type necrosis of renal parenchyma caused by large vessel thromboses (Figure 1). In addition, diffuse hemorrhagic infiltrations were noted in the interstitium, while endarteritis and transmural arteritis (Figure 2) were found in many arteries, in a background of severe tubular atrophy, interstitial fibrosis, and glomerulosclerosis (involving $\sim 50\%$ of the cortical parenchyma). Sparse lymphocytic infiltrates were also seen in the renal cortex and a small to moderate number of inflammatory cells were occasionally seen in the peritubular capillaries. According to Banff guidelines, areas of severe interstitial fibrosis (scarred areas), ischemic necrosis, and hemorrhage should be avoided for the evaluation of C4d immunohistochemical marker. Since no well-preserved area of renal parenchyma was available for C4d evaluation, C4d immunohistochemical assay was performed only for research purposes, but it was negative. Nevertheless, the presence of renal vessel thromboses, endarteritis, and transmural arteritis, as well as the diffuse interstitial hemorrhage, were highly suggestive features of a mixed,

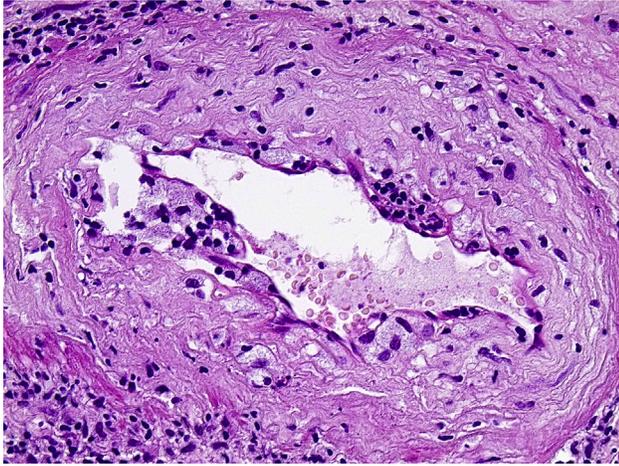


Figure 2. Several inflammatory cells, mostly lymphocytes and foamy cells, not limited only in the subendothelial space but also involving the muscular wall of an interlobular artery, in an example of transmural arteritis (hematoxylin and eosin stain; original magnification $\times 400$).

acute T cell- and antibody-mediated rejection, in a background of severe chronic kidney damage.

After nephrectomy, the patient was started on hemodialysis, her overall condition improved, and she was transferred back to peritoneal dialysis. A repeated abdominal and thoracic computed tomography scan and a positron emission tomography scan detected no evidence of cancer relapse, spread to lymph nodes, or metastases, except for the pulmonary lesions that were stable in number and size. To define the true nature of the lung lesions, oncologists recommended a lung biopsy procedure that the patient refused. Based on the above findings and the fact that patient experienced serious side effects from both previous therapeutic regimens (anti-vascular endothelial growth factor and ICIs), the oncologists decided not to proceed with further treatment and to continue to monitor the patient. Fifteen months after her last anticancer treatment, the patient is in stable clinical condition.

DISCUSSION

Accumulating evidence as presented by several case reports, case series, and systematic reviews has shed light on the allograft-associated immunologic complications of ICI therapy in KTRs with malignancies, all of them indicating high rejection rates and worsened allograft outcomes.^{3,4} Accordingly, a recent multicenter retrospective cohort study of KTRs with cancer receiving ICIs showed that 42% of patients developed acute graft rejection of which 65.5% progressed to ESKD requiring dialysis.⁵

Instead, the published data regarding ICI utilization, safety, and efficacy in patients receiving maintenance dialysis, including those with failed kidney allografts,

are scarce. Evidence from a recent systematic review based on the characteristics of 54 case reports regarding ICI use in different populations of patients with chronic kidney disease indicates that ICI efficacy and toxicity profiles including immune-related adverse effects do not appear to be significantly different in dialysis compared with nondialysis patients.⁶ In addition, a report of 19 dialysis patients who received ICI therapy between 2013 and 2019 showed that although 32% of the patients experienced diverse immune-related adverse effects, none of the 4 patients with previous failed kidney allografts included in the study had clinical evidence of rejection.⁷

We report a single case of kidney graft rejection of a long-term nonfunctioning graft 14 days after the first cycle of therapy with the PD-1 inhibitor nivolumab. To our knowledge, this is the first case of acute transplant rejection in a previously transplanted anuric patient being on peritoneal dialysis for a long period of time.

Hirsch et al.⁸ have described a similar case of a patient with a history of kidney allograft failure on hemodialysis for 3 years who developed hepatocellular cancer and who also received nivolumab, experienced acute rejection, and then suffered from cancer progression.

Likewise, Mejia et al.⁹ recently reported a 66-year-old patient with a failed kidney allograft undergoing hemodialysis who received combination immunotherapy with anti-PD-1 (nivolumab) and anti-cytotoxic T lymphocyte-associated antigen-4 (ipilimumab) for metastatic papillary renal and urothelial cancer. The patient's clinical course was complicated by development of gross hematuria and pain over the allograft, and a histopathologic evaluation after transplant nephrectomy revealed chronic active T cell-mediated rejection.⁹

Our patient presented with symptoms consistent with acute rejection 2 weeks after the first dose of nivolumab. The timing of allograft rejection is typical, occurring within 4 weeks after ICI administration as currently described in KTRs, whereas the occurrence of ICI-associated acute interstitial nephritis in native kidneys is of delayed onset, presenting after a median of 14 weeks.⁵ A T cell-mediated rejection is an almost universal finding whenever a biopsy specimen is obtained, with approximately 50% of cases representing mixed acute T cell-mediated and antibody-mediated rejection whereas pure T cell-mediated rejection is diagnosed in the other 50%.^{6,7} Of note, a considerable percentage of cases remained unspecified in most studies.⁴ Our patient's biopsy specimen revealed lesions highly suggestive of mixed acute rejection in accordance with the aforementioned pathologic patterns described in patients with functioning kidney

Table 1. Teaching points

The use of immune checkpoint inhibitors in kidney transplant recipients is associated with substantially high rates of acute rejection.
Notably, rejection can occur even in a nonfunctional kidney graft.
Data are inconsistent to support the use of higher-dose steroids for rejection prophylaxis.
Clinical experience on immune checkpoint inhibitor treatment in transplant recipients is limited; therefore, prescription of these drugs should be cautious and under close monitoring of the patient and kidney function.

grafts. Activation and proliferation of pre-existing kidney allograft antigen-specific memory T cells elicited by ICI, further potentiated by immunosuppression withdrawal, as occurred with our patient, have been suggested as a potential underlying mechanism.⁵

Graft loss and initiation of dialysis are indications for immunosuppression withdrawal irrespective of cancer presence. Our patient was maintained in a small alternative-day dose of methylprednisolone because she was planning to be retransplanted with a live related kidney graft from her mother. Patient survival is the main priority in KTRs with functioning grafts, and clinical research is ongoing so as to find appropriate immunosuppressive regimens that maintain the equilibrium between adequate responses to immunotherapy while simultaneously protecting the kidney allograft. More specifically, maintaining the same level of immunosuppression together with the administration of the most effective oncologic regimen, utilization of mammalian target of rapamycin inhibitors because of their combined immunosuppressive and antitumor effects, and the use of higher maintenance or pulsed dose steroids have all been recommended and are currently under clinical evaluation as possible strategies. Available evidence regarding prophylactic coadministration of corticosteroids is controversial, with some reporting lower efficacy of ICIs in this setting, whereas d'Izarny-Gargas et al.⁵¹⁰ reported beneficial effects on preservation of allograft function without attenuating the antitumor effects of ICIs. On the other hand, therapeutic decision making in patients with failed allografts undergoing dialysis is more straightforward because of the withdrawal of immunosuppression while there are no concerns regarding preservation of graft function. Yet although transplant nephrectomy is the standard management approach in acute rejection of a failed allograft, its effects on patient sensitization need to be considered. Furthermore, recent guidelines recommend against excluding transplant candidates with a history of metastatic cancer who have been administered potentially curative therapy and have achieved complete remission. Successful kidney retransplantation in a KTR who experienced both a complete antitumor response and allograft rejection after pembrolizumab

(anti-PD-1) administration, in the setting of metastatic cutaneous squamous cell carcinoma has been recently described by Lipson et al.⁵¹³ Conducting larger studies is a challenging task both because of the small number of patients and because of the poor prognosis of these patients in general. However, evaluation of similar reports in the future might provide insight on the durability of the immune-mediated tumor control in KTRs who are administered ICIs as well as better delineate benefits and risks associated with retransplantation in terms of allograft survival and tumor relapse.

The present case shows that the role of the PD-1 pathway in the maintenance of tolerance to transplanted organs is critical even in a patient with ESKD. The initiation of nivolumab triggered the cascade of events which led to acute rejection in a long-term nonfunctioning kidney graft. In the rare case of a dialysis patient with a failed kidney graft with an indication for ICI therapy, caregivers should take into consideration several variables, including the risk of acute allograft rejection and the future potential for retransplantation (Table 1). A thorough patient update about the possible side effects is imperative. Until prospective studies with sufficient patient numbers become available, prophylactic administration of corticosteroids in this setting should be individualized.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The patient has signed a consent statement in which she gave the full permission for the publication of her data.

AUTHOR CONTRIBUTIONS

All authors participated in the clinical care and assembling of data and contributed to the intellectual content and the writing of the case report. They all actively reviewed and edited the content

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Supplementary References.

Figure S1. A severely atrophic area of renal parenchyma, containing ischemic glomeruli and an artery with endarteritis (hematoxylin and eosin stain, original magnification $\times 100$).

Figure S2. In this area, severe glomerulosclerosis, tubular atrophy, and interstitial fibrosis in association with inflammation can be appreciated (hematoxylin and eosin stain, original magnification $\times 20$).

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