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Case Report

Acute Kidney Allograft Rejection Precipitated by Lenalidomide Treatment for Multiple Myeloma

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Patients who develop malignancy after kidney transplantation typically undergo a reduction in immunosuppression and referral to an oncologist for chemotherapeutic considerations for the management of their malignancy. Traditional cytotoxic chemotherapy agents can result in kidney transplant injury, but the decision about which agents to be used has largely been determined by oncologists without the involvement of nephrologists. More recently, several classes of drugs with immunomodulatory actions have been approved for the treatment of cancer, including multiple myeloma. Activation of the immune system against malignant cells may have unintended consequences in solid-organ transplant recipients, who require suppression of the immune system to avoid transplant rejection. In this report, we present a case of acute kidney transplant rejection in a 65-year-old woman following administration of the newer immunomodulatory agent lenalidomide for the treatment of multiple myeloma. A greater awareness of the mechanisms of newly introduced chemotherapy agents and discussion with the treating oncologist and patient are paramount in caring for patients who develop malignancy following transplantation.
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INDEX WORDS: Kidney allograft rejection; lenalidomide; multiple myeloma; kidney transplant; acute renal allograft rejection; immunomodulatory chemotherapy agent; chemotherapy regimen; malignancy; immunosuppression withdrawal; case report.

Malignancy is a major cause of morbidity and mortality following kidney transplantation.[1-3] The necessity of immunosuppression for successful kidney transplantation results in impairment of the normal immune surveillance mechanisms that prevent the growth and development of malignancies. More recently, it has been shown that immunosuppressive agents may also have specific carcinogenic effects.[4]

The management of patients who develop malignancy after kidney transplantation is challenging. Reduction in overall immunosuppression is the cornerstone of therapy; however, reduction in immunosuppression may precipitate acute kidney rejection. Treatment of rejection in the setting of malignancy is limited due to the need for augmented immunosuppression to manage rejection, which can have catastrophic effects on the progression of the underlying malignancy. In clinical practice, the severity of malignancy in kidney transplant recipients often dictates the aggressiveness of immunosuppression withdrawal by the nephrologist. Aside from immunosuppression management, the actual treatment and management of the malignancy has traditionally been under the realm of the oncologist.

Intravenous cytotoxic chemotherapy has been the mainstay in cancer treatment since the first patient was treated with nitrogen mustard in 1942.[5] These medications target rapidly dividing cancer cells, resulting in cellular death. However, normal tissue may also be affected, resulting in the severe toxicities associated with systemic chemotherapy. More recently, novel anticancer agents that stimulate the immune system have shown efficacy across tumor types (Table 1). However, trials of these new agents have traditionally excluded organ transplant recipients because activation in the immune system may result in immune-mediated toxicities, which may be particularly relevant in the organ transplantation setting. We present a case of renal transplant rejection following the administration of the newer immunotherapy chemotherapy agent lenalidomide in a patient with multiple myeloma after kidney transplantation.

CASE REPORT

A 65-year-old woman with end-stage kidney disease secondary to autosomal dominant polycystic kidney disease had received a living unrelated kidney transplant from a friend and underwent induction with basiliximab followed by maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and steroids. After transplantation, her creatinine level was in the range of 0.7 to 0.8 mg/dL (estimated glomerular filtration rate [eGFR], calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation, was 90-105 mL/min/1.73 m^2).

Five years after transplantation, the patient experienced a mechanical fall resulting in a fracture of the lesser trochanter of the left femur. Pelvic imaging also revealed lytic bone lesions of the

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Table 1. Mechanism of Action of Immunomodulatory Chemotherapy Agents

Chemotherapy agent	Mechanism of Action	Malignancy Treated
Ipilimumab	CTLA4 monoclonal antibody	Metastatic melanoma
Nivolumab, pembrolizumab, atezolizumab	Antibody to PD-1	Renal cell carcinoma; non–small cell lung cancer; metastatic melanoma
Lenalidomide, thalidomide, pomalidomide	Thalidomide derivatives	Multiple myeloma; myelodysplastic syndrome; light chain amyloidosis
Interleukin 2	T-cell cytokine	Metastatic melanoma; renal cell carcinoma
Sipuleucel-T	Dendritic cell therapy; cells are removed from the patient and grown with prostatic acid phosphatase to induce immunity against prostatic acid phosphatase, which is seen only on prostate tissue	Prostate cancer
Interferon	Cytokines produced by the immune system	Hairy cell leukemia; AIDS-related Kaposi sarcoma; melanoma; follicular lymphoma; chronic myeloid leukemia

Abbreviations: CTLA4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1.

right and left femora. Bone marrow biopsy revealed normocellular marrow with large plasma cell aggregates occupying 25% to 30% of the marrow. Staining with CD138 revealed a 30% plasma cell population, consistent with a plasma cell dyscrasia. Stage 1 κ light chain multiple myeloma was diagnosed, mycophenolate mofetil treatment was discontinued, and she was maintained on prednisone and tacrolimus treatment for 2 months prior to starting chemotherapy.

The patient was started on lenalidomide and dexamethasone for the treatment of the multiple myeloma. She tolerated her first cycle well and received a second dose 1 month later. One week following her second session of chemotherapy, she developed worsening edema and nausea. A basic metabolic panel performed by her primary care physician revealed an increased creatinine level from 0.9 mg/dL (eGFR, 78 mL/min/1.73 m^2) 2 days prior to 5.9 mg/dL (eGFR, 8 mL/min/1.73 m^2). A biopsy was performed and showed heavy interstitial lymphocytic inflammation with accompanying edema. Severe tubulitis with more than 20 lymphocytes (Fig 1) and intimal arteritis (not shown) were also present. C4d-positive staining was positive and HLA antibody testing detected a de novo donor-specific antibody to DQ5 with a median fluorescence intensity of 5,181. Banff 2A cellular rejection and antibody-mediated rejection were diagnosed.

Discussions with the patient revealed that her primary wish was to avoid the development of kidney failure and return to dialysis therapy. She received intravenous immunoglobulin for the antibody-mediated rejection and 9 doses of antithymocyte globulin for the Banff 2A cellular rejection; her creatinine level improved to 1.4 mg/dL (eGFR, 36 mL/min/1.73 m^2). The chemotherapy regimen was changed to dexamethasone and bortezomib.

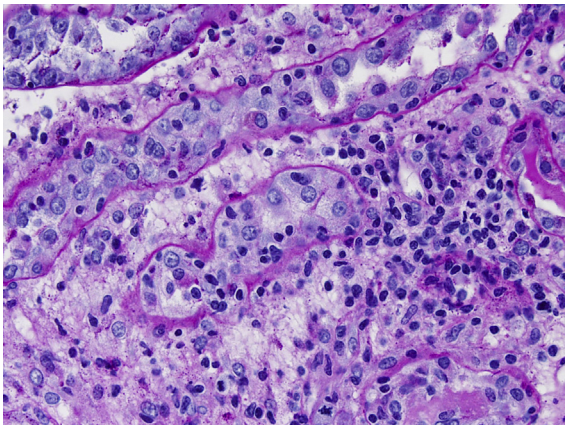

Figure 1. Light microscopy of tubules from kidney biopsy specimen. Interstitial inflammation and tubulitis are present (periodic acid−Schiff stain; original magnification, ×40).

DISCUSSION

The importance of the immune system in controlling and eradicating cancers has been known for decades. Manipulation of the immune system to improve cancer treatment was first demonstrated in 1891 when William Coley injected bacteria into tumors followed by the use of intravesicular bacillus Calmette-Guérin for the treatment of bladder cancer. This was followed by allogenic bone marrow transplantation for the treatment of leukemia and the administration of interleukin 2 (IL-2), a cytokine that stimulates T cells, to treat malignant melanoma and advanced renal cell carcinoma.[6-8]

The patient described in this report developed severe transplant dysfunction following administration of lenalidomide, a newer immunomodulatory chemotherapy agent. Lenalidomide is a synthetic derivative of thalidomide, which is synthesized from glutamic acid. Thalidomide is an effective sedative and hypnotic antiemetic drug, which was used to treat first-trimester morning sickness. However, the drug is teratogenic, resulting in phocomelia, and was subsequently banned by the US Food and Drug Administration (FDA). The FDA reapproved the drug in 1998 for limited use in patients with erythema nodosum leprosum when it was demonstrated that thalidomide had immunomodulatory properties, which could be used to effectively treat that condition.[9,10] Thalidomide was initially used to treat relapsed and refractory multiple myeloma, but its use has been limited by its multiple systemic toxicities, including neuropathy, deep vein thrombosis, and sedation. Lenalidomide was developed as a more