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Cost of Paid Transplantation Abroad: Possible Donor-Origin Early Multiple Myeloma in a Renal Transplant Recipient Treated Using Bortezomib

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ABSTRACT

The incidence of cancer is greater in transplant recipients compared with the general population. Posttransplantation lymphoproliferative disorder (PTLD) is the second most common cancer in these patients. Non-Hodgkin lymphoma is most commonly observed, and multiple myeloma (PTLD-MM) accounts for less than 4% of PTLDs. Most reported PTLD-MM is of recipient origin, and to date, few cases of donor-origin PTLD-MM have been reported. Bortezomib is a protease inhibitor that has been used successfully to treat multiple myeloma. Herein, we describe the case of a patient in whom multiple myeloma developed shortly after paid living-unrelated renal transplantation performed abroad (in Egypt). The patient had no apparent risk factors for PTLD-MM. Thus, it was supposed that PTLD-MM was of donor origin, considering its early development, lack of recipient risk factors, and no available donor medical status. To our knowledge, this report is the first to describe the use of bortezomib in this setting. Although bortezomib plus dexamethasone therapy resulted in hematologic remission, the patient remained dialysis-dependent.

AN INCREASED INCIDENCE of neoplasia is a well-recognized complication of long-term immunosuppression therapy. The prevalence of neoplasia is reportedly 14% in the fist 10 years posttransplantation, and increases to 40% by 20 years.[1] The causes of posttransplantation cancer are multifactorial and include impaired immunosurveillance of neoplastic cells, direct cancer-promoting effects of immunosuppression drugs, latent or acquired viral infections with decreased antiviral immunity, and genetic and acquired risk factors.[2] In adults, posttransplantation lymphoproliferative disorder (PTLD) is the second most common cancer, accounting for as many as 12% of posttransplantation cancers.[3] Non-Hodgkin lymphomas constitute the largest group of PTLD cases, whereas multiple myeloma (PTLD-MM) accounts for less than 4% of PTLDs. While most PTLD-MM cases are recipient-originated, a few cases of donor-origin PTLD-MM have been reported.[4,5] Herein, we report the case of a patient who developed a possibly donor-origin PTLD-MM early after living-unrelated renal transplantation performed abroad (in Egypt), which was treated successfully using bortezomib.

CASE REPORT

A 46-year-old man underwent paid living-unrelated kidney transplantation in Egypt, against medical advice. The recipient had no knowledge of the identify or medical status of the donor, but was told only that the donor's health was "good." He was not given a medical discharge report describing the perioperative period or whether an induction regimen had been used. The patient had been diagnosed with end-stage kidney disease, and had been receiving maintenance dialysis therapy 3 times a week for 7 months before transplantation. The native kidney disease was unknown; urine and serum protein electrophoresis yielded normal results. The patient had done well posttransplantation with a regimen of tacrolimus, prednisone, and mycophenolate mofetil. He began to experience severe backache and extensive bone pain, along with deterioration of graft function. A renal allograft biopsy specimen revealed cast nephropathy. A serum biochemistry panel and complete blood cell counts at biopsy were as follows: serum calcium, 9.2 mg/dL; phosphorus, 4.8 mg/dL; albumin, 3.6 g/dL, total protein, 5.2 mg/dL; urea, 97 mg/dL; creatinine, 4.98 mg/dL, lactate dehydrogenase, 197; hemoglobin, 10.9 g/dL; white blood cell count, 10.900/mm^3; and platelet count, 344,000/mm^3. Because of progressive uremia, hemodialysis therapy was reinstituted. A bone survey revealed

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extensive lytic lesions. There were 100% plasma cells at bone marrow aspiration. Bone marrow biopsy revealed 30% plasma cells with lambda light-chain expression. Serum protein electrophoresis with immunofixation revealed a band compatible with lambda light chains. Two cycles of combination therapy using vincristine, adriamycin, and dexamethasone (VAD) were administered and cessation of immunosuppression drugs. Because remission could not be achieved, 7 cycles of bortezomib-dexamethasone therapy were administered. Hematologic remission was achieved; however, the patient remained dialysis-dependent.

DISCUSSION

Posttransplantation lymphoproliferative disorders are a heterogeneous group of lymphoid proliferations ranging from benign hyperplastic lesions to malignant lymphoma. Currently, the classification is based on the Society of Hematopathology system, which identifies 4 major categories of PTLD: lymphoid hyperplasias, or "early" lesions; polymorphic PTLD; lymphomatous or monomorphic PTLD including T-cell lymphoma; and other lymphoproliferative disorders including myeloma and Hodgkin lymphoma.[6] They are most often of B-cell origin, and commonly contain the Epstein-Barr virus (EBV).[7] In contrast to the high incidence of posttransplantation lymphomas, PTLD manifesting as PTLD-MM is rare, accounting for less than 4% of PTLDs and less than 1% of posttransplantation malignant lesions. Nevertheless, compared with the general population, renal transplant recipients are at 4.4-fold higher risk of developing multiple myeloma.[1] Recently, Caillard et al[8] reviewed the medical records for 66,159 patients in the United States Renal Data System. Lymphoid proliferations were diagnosed in 1169 patients (1.8%). Of these, 823 (1.6%) were non-Hodgkin lymphoma, 160 (0.24%) were myeloma, 60 (0.1%) were Hodgkin disease, and 126 (0.19%) were lymphoid leukemia.[8] Compared with patients with non-Hodgkin lymphoma, those with myeloma were older, less often were multiple-organ recipients, and more frequently were positive for hepatitis C virus before transplantation. Therapy with OKT3 and azathioprine was used less frequently, and with mycophenolate mofetil was used more often. Patients with myeloma more frequently received a cadaver organ. Treatment with antithymocyte globulin was used more frequently, and with anti-IL2-R was used less often. Insofar as risk factors, there was no association between EBV status and myeloma.[8] Our patient was younger, tested negative for hepatitis C virus before transplantation, received a living- unrelated donor kidney, apparently did not receive an induction regimen, and was positive for EBV IgG antibody.

Posttransplantation lymphoproliferative disorder with multiple myeloma can occur at a variety of sites including the oral cavity, maxillary antrum, scalp, thigh, abdominal and chest walls, skull base, bone marrow, and the allograft.[9] Plasma cell myeloma in the nontransplantation setting typically manifests as bone marrow–based multifocal plasma cell proliferations associated with lytic bone lesions and serum or urine monoclonal proteins. In the absence of these typical findings, diagnosis of plasma cell myeloma posttransplantation is difficult because other histologic types of PTLD share some clinical, laboratory, and pathologic features of plasma cell PTLD.[10]

Most reported cases of PTLD-MM are of recipient origin; however, a few cases have been reported in which the myeloma was related to the donor.[4,5] In one of these cases,[4] PTLD-MM manifested at 18 months posttransplantation as a pararenal mass, with multifocal marrow involvement. The patient was a 67-year-old woman who was seronegative for EBV.[4] At fluorescence in situ hybridization (FISH), Y chromosomes were observed in the cells of the pararenal mass. In the other case,[5] IgA myeloma developed at 7 years after allogeneic renal transplantation in a 31-year-old male recipient of a 59-year-old female cadaver organ. Seven years later, he reported left-sided back pain and hypercalcemia. A skeletal survey revealed multiple lytic bone lesions. The authors confirmed donor origin via DNA fingerprinting of myeloma cells of recipient and donor spleen cells. We did not perform FISH because our patient was a man, and we could not use DNA fingerprinting because of lack of access to donor data. However, we supposed that the myeloma was of donor origin because of the relatively short time to development after transplantation and the relatively low risk of myeloma development coupled with no data about the identity or medical condition of the living-unrelated donor. Medical complication rates and allograft and patient loss are higher in living paid transplantation procedures.[11] This case clearly illustrated an additional cost of paid transplantation abroad where the procedure is legal and little or no information is provided to recipients about the donor.

Treatment methods of multiple myeloma include decrease of immunosuppression, use of cyclophosphamide alone or with prednisolone, or VAD. If graft function had deteriorated from myeloma, cyclosporine or tacrolimus dosage can be decreased or discontinued. The survival rate with myeloma is generally lower than with other PTLD subtypes.[8] Remission could not be achieved with VAD; thus, bortezomib plus dexamethasone was administered. Bortezomib is a modified dipeptidyl boronic acid analogue that binds 26S proteosomes,[12] inhibition of which prevents degradation of key proteins, ultimately leading to cell death. A number of studies have demonstrated the efficacy of bortezomib in combination with dexamethasone or thalidomide in patients with naïve[13] or refractory or relapsed[12] multiple myeloma. Kaposztas et al[14] reported light-chain deposition disease in a patient successfully treated with bortezomib and thalidomide before renal transplantation. However, soon after transplantation, the disease recurred, and the patient continued to receive dialysis therapy until successful treatment with bortezomib.

To our knowledge, this is the first case report describing successful treatment of donor-derived PTLD-MM using bortezomib. However, despite hematologic remission, kidney function did not recover sufficiently that hemodialysis therapy could be discontinued.

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