Treatment of Primary Central Nervous System Posttransplant Lymphoproliferative Disorder in an Adult Kidney Transplant Recipient: A Case Report

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Abstract
Posttransplant lymphoproliferative disorder is a serious complication of solid-organ transplant. Extraneural involvement is common; however, isolated involvement of the central nervous system is extremely rare and represents a particularly difficult therapeutic challenge with no current consensus on optimal treatment. Here, we describe a 70-year-old woman who developed Epstein-Barr virus-related primary central nervous system lymphoma 19 months after kidney transplant. Immunosuppression was reduced, and the patient was started on high-dose methotrexate, which was complicated by acute kidney injury and discontinued. She then received a rituximab and temozolomide chemotherapeutic regimen and achieved complete clinical response. Seventeen months after diagnosis, she is alive and has not developed any other posttransplant lymphoproliferative disorder. We review the current literature and discuss treatment options for patients with primary central nervous system posttransplant lymphoproliferative disorder following kidney transplant.

Key words: Central nervous system lymphoma, Renal transplantation, Rituximab

Introduction
Posttransplant lymphoproliferative disorder (PTLD) with central nervous system (CNS) involvement is a rare and serious complication of solid-organ transplant (SOT). Although kidney transplant recipients develop PTLD at much lower rates than other SOT recipients, they have been associated with the highest risk for CNS involvement.1,2 High-dose methotrexate (HD-MTX) is the treatment of choice in patients with CNS lymphomas; however, its nephrotoxicity poses a unique challenge in patients with chronic allograft nephropathy. Here, we report an adult SOT recipient who developed primary CNS PTLD in the setting of chronic allograft nephropathy and underwent successful treatment with an aggressive chemotherapeutic regimen that preserved allograft function.

Case Report
A 70-year-old white female patient underwent a deceased-donor kidney transplant for end-stage renal disease secondary to hypertension. The recipient was both Epstein-Barr virus (EBV) and cytomegalovirus seropositive. She was started on immunosuppressive therapy with thymoglobulin, tacrolimus, mycophenolate mofetil, and prednisone. Allograft function was stable, but postoperative recovery was complicated by cytomegaloviremia on day 44 posttransplant; this was treated adequately with valganciclovir. Recovery was further complicated by recurrent methicillin-susceptible Staphylococcus aureus bacteremia; despite treatment with cefazolin, on day 251 she developed septic emboli to the brain and lungs, causing a transient expressive aphasia and pneumonia. Imaging studies revealed multiple ring-enhancing lesions throughout the bilateral cerebral and cerebellar hemispheres consistent with abscesses. A right atrial pacemaker lead showing methicillin-susceptible Staphylococcus aureus vegetative endocarditis with coexisting patent foramen ovale were identified as the infection source. The pacemaker lead was explanted; 2 weeks into her course of antibiotics, imaging displayed marked radiologic improvement. During her long course of antibiotics,
which included nafcillin, cephalaxin, micafungin, and fluconazole, she developed no new neurologic findings, and brain imaging continued to show radiologic improvement with no new lesions.

Antibiotic treatment was then complicated by acute kidney injury (AKI) in the setting of stage IV chronic kidney disease, thus prohibiting postcontrast visualization with serial magnetic resonance imaging (MRI). During the AKI, serum creatinine and serum urea nitrogen levels rose from a baseline of 152 μmol/L and 6.8 mmol/L to a peak of 223 μmol/L and 15.7 mmol/L, which then recovered to 154 μmol/L and 12.5 mmol/L on repeat measurements 1 month later. Immunosuppressive doses were maintained at 500 mg mycophenolate mofetil twice daily, 1 mg tacrolimus twice daily, and 5 mg prednisone once daily.

On day 579, brain MRI revealed a new 1.4 × 1.3-cm mass in the right frontal lobe with adjacent edema (Figure 1A and 1B). Total spine MRI demonstrated no evidence of additional lesions or leptomeningeal involvement. A diagnostic lumbar puncture demonstrated normal protein level of 0.42 g/L, glucose level of 3.61 mmol/L, and white blood cell count of $5 \times 10^9$/L with 85% lymphocytes, 13% mononuclear cells, and 2% polymorphonuclear cells. Cerebrospinal fluid was positive for EBV by polymerase chain reaction, and cytology did not reveal any malignant cells. Serum lactate dehydrogenase was elevated at 6.7 μkat/L and albumin was normal at 40 g/L.

Given the prolonged course of antibiotics and negative infectious workup, a neoplastic process was highly suspected. Immunosuppressive agents were tapered to 250 mg mycophenolate mofetil twice daily, 1 mg tacrolimus twice daily, and 5 mg prednisone once daily, and plans were made for biopsy and resection. Preoperative MRI on day 626 revealed interim growth of the lesion to 2.0 × 2.3 cm (Figure 1C). Biopsy of the lesion and dura confirmed a monomorphic CD19-positive, CD20-positive, CD30-positive (10%), CD200-positive, PAX-5-positive, BCL-2-positive, MUM-1-positive, EBV-positive, CD10-negative, BCL-6-negative, c-MYC-negative, CD3-negative, high-grade ABC type diffuse large

Figure 1. Composition of Overweight and Obese Patients

(A) Axial T2-weighted image at diagnosis demonstrated a lesion of intermediate signal in the anterior right frontal lobe, surrounded by perilesional edema. (B) This lesion showed high signal on the diffusion-weighted image, consistent with high cellularity. (C) Axial T2-weighted image on day of biopsy demonstrated interval growth of the lesion to 2.0 × 2.3 cm. (D) Axial T2-weighted image obtained after completion of chemotherapy revealed resolution of the mass lesion and encephalomalacia in the right frontal lobe from surgery and chemotherapy.

Figure 2. Pathology Results of Lesion

(A) Hematoxylin and eosin-stained section demonstrating effacement of the brain parenchyma by an atypical lymphoid infiltrate composed of large atypical lymphoid cells. The atypical lymphoid cells show round to irregular nuclei with hyperchromatic to vesicular chromatin, occasional nucleoli, and indistinct cytoplasmic borders (×200). (B) Negative expression of CD3 (×200). (C) Bright positive expression of CD20 (×200). (D) Bright positive expression of BCL-2 (×200). (E) Negative expression of BCL-6 (×200). (F) Positive expression of MUM-1 (> 80%; ×200). (G) Positive expression of Epstein-Barr virus by in situ hybridization (×200).
B-cell lymphoma with a Ki-67 proliferation index of 40% to 50% (Figure 2). Positron emission tomography scan, bone marrow biopsy, and peripheral blood smear showed no evidence of nodal or systemic involvement of the PTLD, confirming the disease was a primary CNS PTLD. The patient’s surgical resection was complicated by hemorrhagic stroke with left upper extremity weakness that gradually resolved with long-term physical therapy.

With the diagnosis of EBV-positive primary CNS PTLD, all immunosuppressives, including prednisone, were discontinued, and the patient was started on dexamethasone 4 mg three times daily to decrease cerebral edema. Chemotherapy was initiated on day 641 and consisted of 4 g/m² HD-MTX and 0.1 g/m² leucovorin. However, treatment was complicated by AKI and prolonged clearance of MTX, prompting a glucarpidase rescue on day 4 of chemotherapy and discontinuation of HD-MTX treatment. Kidney function stabilized from peak serum creatinine and serum urea nitrogen levels during the AKI of 288 μmol/L and 27.5 mmol/L to 137 μmol/L and 9.3 mmol/L on repeat measurements 2 weeks later. Dexamethasone was then tapered, and on day 677 she was started on a temozolomide and rituximab regimen given its nonnephrotoxic profile.

Induction consisted of 0.375 mg/m² rituximab for 1 day and temozolomide 0.150 mg/m² for 5 consecutive days every 28 days for 4 cycles, followed by consolidation phase with temozolomide alone for 5 consecutive days every 28 days for 8 cycles.3 The patient’s treatment was complicated by episodes of bacteremia and urinary tract infections but was otherwise well tolerated without any myelotoxicity. Brain MRI after completion of induction and consolidation therapy on day 1025 demonstrated a complete radiographic response (Figure 1D). She did not require any radiation therapy, and 17 months after diagnosis remains in complete clinical response without evidence of any other PTLD. Allograft function was stable without evidence of rejection, and she continues on 5 mg of daily prednisone.

Discussion

Posttransplant lymphoproliferative disorder is a well-recognized but uncommon complication of adult SOT and hematopoietic stem cell transplant and is associated with significant morbidity and mortality.4 This disorder encompasses a heterogeneous group of disorders that can range from an indolent polyclonal proliferation to aggressive lymphomas.5 Posttransplant lymphoproliferative disorder is thought to be the result of immunosuppressive-induced impairment of T-cell immunity, leading to an uncontrolled proliferation of EBV-transformed B lymphocytes. Risk factors associated with PTLD include duration and dosage of immunosuppressives, EBV infection, and host genetic variation.6 Central nervous system involvement is reported in 7% to 15% of cases and is recognized as a poor prognostic factor.5 7 The 2 largest international multicenter retrospective studies on primary CNS PTLD by Evens and associates and Cavaliere and associates reported the outcomes of 84 and 34 patients. The authors found that the median time from SOT to primary CNS PTLD was 54 and 53 months, median overall survival (OS) was 17 and 47 months, 79% and 76% of patients had kidney transplant, and 94% and 92% of tumors were EBV positive.5 8

Given the rarity of primary CNS PTLD and the complexities of the patient population, there is no consensus on optimal treatment. Treatment modalities include antiviral therapy, surgery, radiation, reduction of immunosuppressives, anti-CD20 monoclonal antibodies, cytotoxic chemotherapy, and possibly cellular immunotherapy; despite these options, overall prognosis remains poor.6 9 10 Evens and associates studied the largest cohort of patients with primary CNS PTLD. By correlating quality of response with clinical outcome, they reported that 3-year progression-free survival (PFS) and OS for patients who achieved complete remission were 63% and 77%, with rates of 30% and 45% for those who achieved partial remission and rates of 0% and 0% for those with stable disease. On a multivariate analysis, response to therapy (complete and/or partial response) was the most significant prognostic factor for survival, followed by elevated lactate dehydrogenase levels in cerebrospinal fluid.5 Therefore, it is our opinion that aggressive treatment with an effective first-line therapy is critical to improve patient outcomes.

Successful treatment of primary CNS PTLD through reduction of immunosuppressive agents and chemotherapy with HD-MTX or a rituximab-based regimen has been well documented in SOT recipients and is considered first-line treatment. However, the
nephrotoxicity of HD-MTX remains an important consideration in this patient population, where durable renal dysfunction and allograft loss after treatment remain serious complications.11,12 Our patient was initially started on HD-MTX; however, because of renal toxicity during her first cycle requiring glucarpidase rescue, we switched her to rituximab plus temozolomide, a nonnephrotoxic regimen that she tolerated well.

The CD20 monoclonal antibody rituximab has shown excellent clinical activity in the treatment of both systemic and primary CNS PTLD, given that most PTLDs are CD20-positive diffuse large B-cell lymphomas.4,10,13 Prospective and retrospective studies using rituximab with temozolomide in primary CNS lymphoma have shown it to be an effective and well-tolerated treatment modality.3,14 Evens and associates showed by univariate analysis that treatment with rituximab was associated with a significant improvement in PFS.5 In a retrospective study of 81 patients with primary CNS lymphoma treated with HD-MTX, the addition of rituximab was associated with improved complete response, PFS, and OS rates.15 In our experience, rituximab with temozolomide is an effective therapeutic regimen for primary CNS PTLD, especially in patients who cannot tolerate HD-MTX. Despite significant mortality, primary CNS PTLD patients should be treated with curative intent, as those who achieve complete remission have excellent prognoses.

References