Post-Transplant Lymphoproliferative Disorder in a Kidney Transplant Recipient

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Introduction
A 53-year-old man with ESKD underwent living donor kidney transplantation from his spouse who had a positive serum PCR for Epstein-Barr virus (EBV) at the time of donation. He received rabbit antithymocyte globulin induction and rapid corticosteroid taper with maintenance immunosuppressive therapy of sirolimus (target trough 8–12 ng/ml) and tacrolimus (target trough 8–11 ng/ml). The patient was seronegative for EBV. At 1 month post-transplant, the patient had a serum creatinine of 0.8 mg/dl, and serum EBV and cytomegalovirus PCR were negative.

At 3 months post-transplant, he presented with 4 kg weight loss attributed to gastroparesis and serum creatinine of 1.5 mg/dl. His LDH was mildly elevated (338 IU/ml), but remaining liver enzymes were normal. His sirolimus dose was reduced to achieve a trough level of 6 ng/ml. Over the next 2 weeks, he lost an additional 2 kg. Serum creatinine rose to 1.7 mg/dl, and LDH rose to 1005 IU/ml; tacrolimus and sirolimus levels were stable. Serum EBV PCR was positive at 7×10^6 copies per 1 ml.

He was admitted to the hospital for additional management. On examination, he had a temperature of 37.8°C, normal heart rate, BP of 122/82 mm Hg without orthostasis, shotty cervical lymph nodes, clear lungs, normal cardiac examination, and mildly distended abdomen with a nontender but palpable kidney allograft. Laboratory testing showed serum creatinine of 1.7 mg/dl, blood glucose of 357 mg/dl, LDH of 1500 IU/ml, tacrolimus trough level of 5.0 ng/ml, and sirolimus trough of 6.0 ng/ml. Urinalysis showed a specific gravity of 1015, 1+ protein/3+ glucose/2+ ketones on dipstick, and negative microscopy.

Question 1
What is the most likely cause of the AKI in this patient?

A. Acute cellular rejection
B. Antibody-mediated rejection
C. Tacrolimus toxicity
D. Urinary tract obstruction
E. Volume depletion

Discussion of Question 1
The correct answer is E. There is no evidence to suggest early rejection (A or B), except perhaps the intentional reduction in immunosuppression. Tacrolimus toxicity (C) is unlikely. Without abdominal pain and urinary complaints, D is less likely. With his poor appetite, weight loss, and glucosuria, E is the best choice.

Clinical Course
Admission chest x-ray (Figure 1A) demonstrated mediastinal and paratracheal adenopathy confirmed on computerized tomography (Figure 1B). Head computerized tomography showed no masses. Immunosuppression was discontinued, because EBV PCR rose to 15×10^6 copies per 1 ml. Because of a creatinine of 2.6 mg/dl, a kidney biopsy was performed. This revealed interstitial lymphocytic infiltrates (Figure 1, C and D), which stained positive for CD3 (Figure 1E), CD20 (Figure 1F), and EBV-encoded RNA (Figures 1, G and H). Lymph node and bone marrow biopsies were positive for monomorphic B cell infiltrates. Positron emission tomography scan confirmed tumor in the liver, spleen, and sinuses. A diagnosis of post-transplant monomorphic (large B cell lymphoma) lymphoproliferative disorder (PTLD) was made.

Question 2
Which of the following statements is true about PTLD?

A. The greatest risk of EBV-PTLD is in kidney transplant recipients.
B. It is more common in EBV-mismatched transplant with donor positive and recipient negative for EBV immunity.
C. There is an increased risk when using T cell–depleting induction therapy.
D. Risk of development is reduced with sirolimus therapy.

Discussion of Question 2
The correct answer is B. The risk of PTLD is lowest after kidney transplant (0.8%–2.5%) and highest in
small bowel transplants (≤20%) (1). C is incorrect, because both rabbit antithymocyte globulin and alemtuzumab have uncertain effects on PTLD risk (2). D is incorrect, because sirolimus has been associated with higher rather than lower risk for PTLD (3).

**Additional Clinical Course**

The patient was transferred to the intensive care unit with hypotension, hyperkalemia, worsening anion gap metabolic acidosis, and rising serum creatinine of 5.9 mg/dl. He was started on dialysis and ultimately intubated. He received chemotherapy with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride. He became severely pancytopenic, with LDH 7000 IU/ml and ferritin of 10,000 ng/ml. Over the ensuing week, he required platelet and red blood cell transfusions and developed pulmonary infiltrates. Bronchoscopy demonstrated fungal hyphal elements, and antifungal therapy was added to a regimen of broad spectrum antibiotics. EBV viral load fell dramatically postchemotherapy to 0.1×10⁶ copies per 1 ml, but repeat bone marrow biopsy showed ongoing lymphoma and hemophagocytic syndrome. On hospital day 32, his family withdrew intensive support, and he died 4.6 months post-transplant.

**Discussion**

Solid organ transplant recipients have a threefold higher risk of cancer, particularly virally mediated cancers, compared with the general population (4). PTLD represents 21% of all cancers in solid organ transplants recipients compared with 4%-5% in the immunocompetent population (1). Among the solid organs transplanted, kidney recipients have the lowest risk of PTLD (1), with a bimodal incidence in the early post-transplant period and a second peak later 10–14 years post-transplant. Early-onset PTLD is more common in children (2.4%-15% incidence), and it is characterized by EBV tissue positivity, extranodal disease, and a monomorphic subtype (5). EBV seronegative recipients receiving an EBV-positive organ have a 10- to 75-fold higher risk compared with seropositive recipients (5).
Interestingly, the vast majority of tumors in solid organ transplantation originate from the recipient cells (6).

Clinical presentation of PTLD is variable. It may be asymptomatic, or it may present with pleiotropic symptoms affecting any or multiple sites, including skin, solid organs, brain, and bone, and B symptoms of fatigue, night sweats, weight loss, and low-grade fever. In contrast to other non-Hodgkin lymphomas, PTLD carries a high incidence of extranodal involvement, including the gastrointestinal tract (20%–30% of patients), the solid allograft (10%–15% of patients), and the central nervous system (5%–20% of patients) (5).

The diagnosis of PTLD is made by histopathologic tissue examination and characterized by the World Health Organization 2017 classification (reviewed in ref. 5). PTLD is classified into nondestructive, polymorphic, monomorphic PTLD and Hodgkin lymphoma–like PTLD. The EBV-encoded RNA in situ hybridization assay is recommended in all patients, although the frequency of patients who are EBV negative has increased and now represents 48% of all PTLD (7). Compared with EBV-positive PTLD, EBV-negative PTLD occurs later post-transplant, has monomorphic histology, is diagnosed often at an advanced stage, and is diagnosed often with central nervous system involvement, but it does not carry a worse prognosis. It responds equally to therapy, achieving similar rates of complete remission (7).

The treatment options for PTLD include a reduction in immunosuppression, often with a combination of chemotherapy and rituximab; surgical excision and radiotherapy are reserved for localized disease. Immunosuppression reduction restores EBV-specific cellular immunity and leads to a partial or complete remission in 12.5%–50% of the patients (7). In patients with high-risk features, such as older age (>50 years old), elevated LDH, severe organ dysfunction, the presence of B symptoms (fever, night sweats, and weight loss), and multiorgan involvement at the time of diagnosis, response rate is poor. The reduction in immunosuppression is on the basis of the extent of the disease, and it is typically achieved by reduction of the calcineurin inhibitor by 25%–50%, cessation of the antimetabolite (azathioprine or mycophenolate), and continuation of prednisone at 10 mg daily (8). Response to reduction occurs within 2–4 weeks. In the critically ill patient, all immunosuppression is discontinued. It is essential to monitor graft function during immunosuppression reduction, because there is a 38% risk of rejection. In patients who do not respond to reduction of immunosuppression, the standard therapy is rituximab alone, with a complete response rate of 25% (9). In nonresponders, rituximab is followed by four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy, with a complete response rate of 70%. The PTLD-1 prospective trial established a risk-stratified sequential treatment approach with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone as the standard therapy for PTLD irrespective of EBV status (9).

In the current era, the overall median survival is 6.6 years post-PTLD diagnosis (9). Retransplantation after treatment is considered in select patients after 1 year of complete remission. The risk for PTLD recurrence is <2% after retransplantation (10). Here, the patient had all of the poor prognostic features associated with PTLD with severe allograft dysfunction and multiorgan involvement, and even with early detection and aggressive therapy, the disease was fatal.

Acknowledgments
We appreciate the clinical support and management by Drs. Alan Kirk, S. John Swanson, and Douglas Hale and the entire National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases intramural kidney transplant program. Dr. Mannon serves on the editorial board of JASN.

This case was presented at the American Society of Nephrology Kidney Week 2018 Nephrology Quiz and Questionnaire, San Diego, CA, October 26, 2018.

Disclosures
Dr. Mannon reports grants from Quark Pharmaceuticals, CSL Behring, Mallinckrodt, and Transplant Genomics and personal fees from Sanofi outside the submitted work. Dr. Agarwal has nothing to disclose.

References

Published online ahead of print. Publication date available at www.cjasn.org.