Title

An Interesting Case of PTLD After Kidney Transplantation

Journal

Proceedings of the UCLA Department of Medicine, 18(1)

Authors

Reddy, Uttam G.
Lum, Erik

Publication Date

2014-08-08

CLINICAL VIGNETTE

An Interesting Case of PTLD After Kidney Transplantation

Uttam G. Reddy, MD and Erik Lum, MD

Introduction

Post-transplant lymphoproliferative disorders (PTLD) are proliferations of lymphoid and/or plasmacytic cells that occur due to therapeutic immunosuppression after solid organ or allogeneic hematopoietic stem cell transplantation. PTLD is the most common malignancy, with the exception of skin cancer, after solid organ transplant in adults and occurs in up to 10% of patients. In most cases, PTLD is associated with Epstein Barr Virus (EBV) infection of B cells, either as a consequence of reactivation of the virus post-transplantation or from primary EBV infection. More than half of PTLD cases present with extra-nodal masses. Involvement of the allograft itself accounts for almost 25% of the cases of PTLD. Other involved organs include the gastrointestinal tract, lungs, skin, liver, and central nervous system. In this case report, we present a 62-year-old recent renal transplant recipient who presented with hyperkalemia and acute kidney injury, and was found to have a large peri-hilar mass infiltrating his right lower abdominal kidney allograft.

Case Presentation

A 62-year-old male with ESRD due to hypertension, with history of a benign bladder tumor in 1992 underwent successful deceased donor renal transplantation. He was induced with basiliximab, an IL2 receptor blocker. His post-transplant course was complicated by low-level cytomegalovirus (CMV) viremia, which responded to three weeks of valganciclovir therapy, and BK viremia, which resolved following reduction in the dose of mycophenolate mofetil. Throughout this time, patient's renal function remained excellent with his baseline creatinine in the 1.1-1.3 range.

Seven months after transplantation, the patient presented to clinic with complaints of fatigue and decreased appetite. He noted right lower abdominal pain that was intermittent and not associated with activity. He denied any vomiting or diarrhea, but did complain of nausea. He was found to have acute kidney injury with a creatinine of 1.8 and hyperkalemia with a K+ of 6.4. Given the degree of his electrolyte abnormalities, he was admitted for a renal transplant biopsy and acute management of his hyperkalemia. The patient had an ultrasound of his kidney allograft prior to biopsy, which showed evidence for a slightly distended collecting system with a slightly thickened urothelium. A focus of the soft tissues in the renal hilum of uncertain significance was seen. After discussion with Urology regarding this questionable hilar mass, the decision was made to proceed with allograft biopsy. The patient underwent allograft biopsy which showed acute cellular rejection 1a based on Banff criteria. There was also no evidence of BK nephropathy. The patient was treated with intravenous steroids for a three days. His renal function improved slightly and after discussion with Radiology, the patient underwent an MRA abdomen/pelvis with and without contrast to better evaluate the questionable peri-hilar mass seen on ultrasound at the time of kidney biopsy. The MRA revealed a hilar enhancing mass infiltrating the allograft and surrounding tissues that measured up to 9.5 cm, which likely represented post-transplant lymphoproliferative disease (Figure 1) A dedicated CT guided biopsy of the peri-hilar mass was then performed by Radiology. The biopsy revealed a monomorphic post-transplant lymphoproliferative disorder, plasmablastic lymphoma type (Figure 2a). Immunohistochemical stains demonstrated that the lymphoma cells were positive for CD20, PAX5 (weak), BCL2, BCL6, MUM1, CD138, CD45, and EBV EBER with lambda light chain restriction and a Ki67 proliferative index of 60-70% (Figure 2b). Flow cytometry demonstrated a small population of large B-cells with lambda light chain restriction. Serum EBV PCR was negative. A PET scan was then done showing a large heterogeneous mass with intense FDG uptake (7.824 Max SUV) in the transplant kidney located in the right pelvis. This was consistent with the biopsy proven lymphoma. No FDG uptake was seen in the urinary bladder.

Given his newly diagnosed malignancy his immunosuppression was reduced. Mycophenolate was discontinued altogether and patient was switched from tacrolimus to low dose sirolimus. He was also received chemotherapy in the form of rituximab, cyclophosphamide, and prednisone. This was followed by 6 cycles of dose adjusted R-EPOCH

(rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin). After cycle #2 of da-REPOCH, patient underwent repeat MRI, which showed an interval decrease in size of pri-hilar enhancing mass (Figure 3). A repeat PET scan was ordered which showed persistent amorphous soft tissue stranding and thickening surrounding the renal hilum and anterior parenchyma of the right lower quadrant renal transplant, but without definite FDG uptake, suggesting resolution of his lymphoma.

Discussion

Post-transplant lymphoproliferative disease (PTLD) refers to a syndrome of abnormal hyperplastic and neoplastic lymphocyte growths following organ transplantation, ranging from a benign self-limited form of lymphoproliferation to an aggressive, widely disseminated disease[1]. It is a well-recognized potentially fatal complication after solid organ transplantation.

The 2008 WHO classification system characterizes PTLD into four general types – 1) Plasmacytic hyperplasia and infectious mononucleosis-like PTLD (early lesions) – polyclonal B cell proliferation without evidence of malignant transformation 2) polymorphic PTLD -monoclonal or polyclonal lymphoid infiltrates that demonstrate evidence of malignant transformation but do not meet all of the criteria for one of the B cell or T/NK cell lymphomas recognized in immunocompetent patients 3) monomorphic PTLD - monoclonal lymphoid proliferations that meet the criteria for one of the B cell or T/NK cell lymphomas recognized in immunocompetent patients and 4) Classical Hodgkin lymphoma- like PTLD. The patient presented in the case above had the monomorphic type of PTLD. Monomorphic PTLD is further classified according to the subtype. The most common is diffuse large B cell lymphoma (DLBCL), while Burkitt lymphoma or a plasma cell neoplasm are less common[2].

Approximately 90% of PTLD are of B-cell origin, and 90% to 95% containing the Epstein-Barr virus (EBV) [3]. EBV infection results in a polyclonal expansion of B cells hosting the virus. These B cells express viral antigens which elicit a T cell response that removes the vast majority of the infected B cells. However, a small subpopulation of the infected B cells down-regulates viral antigen expression and escapes immune surveillance. These latently infected B cells persist, and if T cell immunity wanes such as with immunosuppression, this can give rise to lymphoproliferative disorders such as PTLD. The EBV infected B cells that give rise to PTLD can originate in the recipient (host) or the donor. Following solid organ transplantation, host-derived PTLD is most common[4]. In these patients, host-derived PTLD is typically a multisystem disease, whereas donor-derived PTLD is more commonly limited to the allograft tissue[5]. In the patient presented in this case, it is not known whether the PTLD was host or donor derived, as a chromosome analysis of the biopsy tissue was not done.

The primary risk factors associated with developing PTLD are related to the degree of immunosuppression and the EBV status of the recipient[6]. Additional risk factors include recipient age less than 25 and Caucasian race[7]. T cell immunity, particularly, is thought to play a major role in the development of PTLD[8]. Interestingly, it is during the first year after transplantation when immunosuppression is the strongest, when the incidence of PTLD is the highest[9]. Highlighting the importance of T cell immunity, it has been shown that induction agents that suppress T cell activity (such as thymogloblin) are associated with higher rates of PTLD[10]. There is an increased risk of PTLD among EBV-negative recipients receiving organs from EBV-positive donor organs as well, as was the case in our patient.

The clinical presentation of PTLD is heterogeneous - depending on the degree of PTLD, location of involvement, and other co-morbidities affecting the patient. The most common presenting symptoms include fever, weight loss, and fatigue. An unexplained infectious syndrome in a transplant recipient should raise the suspicion of a PTLD. More than half of PTLD presents with extra-nodal masses – namely the stomach, intestine, lungs, skin, liver, central nervous system, and the allograft itself[11]. Often times, if the allograft is involved, it can lead to ultimate failure or dysfunction of the allograft. In general, EBV negative tumors tend to present much later (after 6 years) and have an overall more aggressive course[12].

Diagnosing PTLD is usually dependent on the clinicians' level of suspicion based on patient history. Reasons to suspect PTLD include constitutional symptoms, lymphadenopathy, allograft dysfunction, and/or abnormal imaging studies. Laboratory testing in patients with PTLD may show one or more of the following: 1) unexplained anemia, thrombocytopenia, or leukopenia 2) elevated level of serum lactate dehydrogenase 3) hypercalcemia 4) hyperuricemia and/or 5) monoclonal protein in the serum or urine. If PTLD is suspected, imaging of the area in question is recommended as well as consideration of a positron

emission tomography (PET) scan if the diagnosis is highly suspected. EBV viral load should be tested. To definitively make the diagnosis, a tissue biopsy is necessary in which the morphology, immunophenotype, EBER, and molecular genetic studies and antigen receptor genes are suggested[13].

Management of PTLD varies significantly according to the type of lymphoproliferative disease present. Reduction of immunotherapy is the primary and most immediate focus of therapy. For most patients with early lesions, reduction of immunosuppression alone is usually all that is necessary. In CD20 positive patients who cannot tolerate a reduction of immunosuppression or for those who have residual disease, rituximab may be considered as an option[14]. In polymorphic PTLD (CD20+), the use of rituximab in addition to reduction of immunosuppression is the cornerstone of therapy[15]. Our patient had evidence of monomorphic CD20+ PTLD. Such cases are treated with rituximab in combination with chemotherapy, and reduction of immunosuppression[16]. Our patient was able to control his aggressive PTLD, with 6 cycles of rituximab, chemotherapy (EPOCH) and a reduction of his immunosuppression to low dose Sirolimus and prednisone. Patients whose tumors do not express CD20 are not candidates for rituximab therapy and are therefore treated with combination chemotherapy plus immuno-suppression reduction. Surgery is reserved for patients with complications such as perforation or obstruction. Lastly, for most patients with classical Hodgkin lymphoma-like PTLD, management with chemotherapy plus/minus radiation therapy according to protocols used for classical Hodgkin lymphoma is suggested.

Post-transplant lymphoproliferative disorders remain one of the most adverse consequences following both solid organ and stem cell transplantation. We present a remarkable case of a kidney transplant recipient who developed a large peri-hilar mass infiltrating into the allograft that was found to be a monomorphic type of PTLD, which was effectively treated with rituximab and chemotherapy. We highlight the importance of having a clinical suspicion of such a diagnosis, and provide a better understanding of the evaluation and management of post-transplant lymphoproliferative diseases.

Figure 1: MRI of abdomen/pelvis

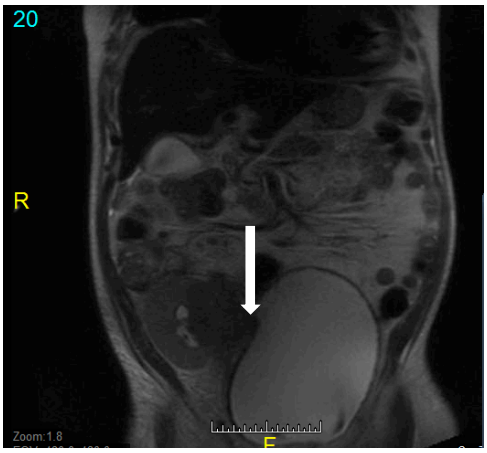
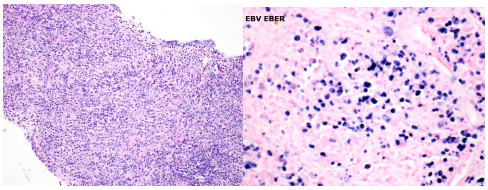
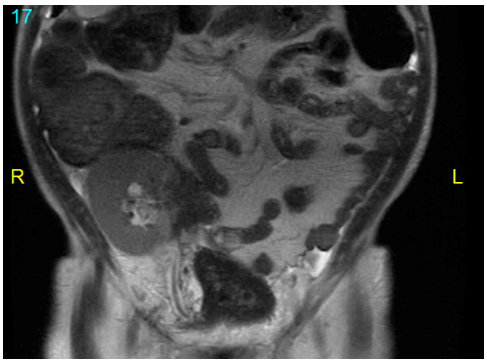


Figure 2



(A. H & E stain of hilar mass showing significant inflammation
(B. EBV EBER stain positive showing involvement of EBV virus)

Figure 3: Repeat MRI Abdomen/Pelvis shows significantly decreased size of the peri-hilar mass



REFERENCES

1. **Harris NL, Ferry JA, Swerdlow SH**. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology Workshop. *Semin Diagn Pathol*. 1997 Feb;14(1):8-14. PubMed PMID: 9044505.
2. **Swerdlow SH, Campo E, Harris NL, et al**. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon 2008.
3. **Penn I**. The problem of cancer in organ transplant recipients: an overview. *Transplant Sci*. 1994 Sep;4(1):23-32. Review. PubMed PMID: 7804694.
4. **Weissmann DJ, Ferry JA, Harris NL, Louis DN, Delmonico F, Spiro I**. Posttransplantation lymphoproliferative disorders in solid organ recipients are predominantly aggressive tumors of host origin. *Am J Clin Pathol*. 1995 Jun;103(6):748-55. PubMed PMID: 7785662.
5. **Petit B, Le Meur Y, Jaccard A, Paraf F, Robert CL, Bordessoule D, Labrousse F, Drouet M**. Influence of host-recipient origin on clinical aspects of posttransplantation lymphoproliferative disorders in kidney transplantation *Transplantation*. 2002 Jan 27;73(2):265-71. PubMed PMID: 11821742.
6. **Caillard S, Lelong C, Pessione F, Moulin B**; French PTLD Working Group. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. *Am J Transplant*. 2006 Nov;6(11):2735-42. PubMed PMID: 17049061.
7. **Smith JM, Rudser K, Gillen D, Kestenbaum B, Seliger S, Weiss N, McDonald RA, Davis CL, Stehmen-Breen C**. Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. *Transplantation*. 2006 Jan 27;81(2):175-80. PubMed PMID: 16436959.
8. **Lucas KG, Small TN, Heller G, Dupont B, O'Reilly RJ**. The development of cellular immunity to Epstein-Barr virus after allogeneic bone marrow transplantation. *Blood*. 1996 Mar 15;87(6):2594-603. PubMed PMID: 8630428.
9. **Opelz G, Henderson R**. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet*. 1993 Dec 18-25;342(8886-8887):1514-6. PubMed PMID: 7902900.
10. **Opelz G, Naujokat C, Daniel V, Terness P, Döhler B**. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. *Transplantation*. 2006 May 15;81(9):1227-33. PubMed PMID: 16699447.
11. **Nalesnik MA, Jaffe R, Starzl TE, Demetris AJ, Porter K, Burnham JA, Makowka L, Ho M, Locker J**. The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. *Am J Pathol*. 1988 Oct;133(1):173-92. PubMed PMID: 2845789; PubMed Central PMCID: PMC1880655.
12. **Leblond V, Davi F, Charlotte F, Dorent R, Bitker MO, Sutton L, Gandjbakhch I, Binet JL, Raphael M**. Posttransplant lymphoproliferative disorders not associated with Epstein-Barr virus: a distinct entity? *J Clin Oncol*. 1998 Jun;16(6):2052-9. PubMed PMID: 9626203.
13. **Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, Marcus R, Parameshwar J, Ramsay A, Newstead C**; Haemato-oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. *Br J Haematol*. 2010 Jun;149(5):675-92. doi: 10.1111/j.1365-2141.2010.08161.x. Epub 2010 Apr 16. Review. PubMed PMID: 20408847.
14. **Jagadeesh D, Woda BA, Draper J, Evens AM**. Post transplant lymphoproliferative disorders: risk, classification, and therapeutic recommendations. *Curr Treat Options Oncol*. 2012 Mar;13(1):122-36. doi: 10.1007/s11864-011-0177-x. Review. PubMed PMID: 22241590.
15. **Tsai DE, Hardy CL, Tomaszewski JE, Kotloff RM, Oltoff KM, Somer BG, Schuster SJ, Porter DL, Montone KT, Stadtmauer EA**. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation*. 2001 Apr 27;71(8):1076-88. PubMed PMID: 11374406.
16. **Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, Marcus R, Parameshwar J, Ramsay A, Newstead C**; Haemato-oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. *Br J Haematol*. 2010 Jun;149(5):693-705. doi: 10.1111/j.1365-2141.2010.08160.x. Epub 2010 Apr 16. Review. PubMed PMID: 20408848.

Submitted on August 8, 2014