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Post Transplant Lymphoproliferative Disorder of The Renal Allograft : A Case Report

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ABSTRACT

Patients receiving a solid organ transplant have an increased risk of developing Post Transplant Lymphoproliferative disorder (PTLD). Incidence of PTLD is 1% in renal allograft recipients. Most of the PTLDs are of B cell origin, and are found to have evidence of Epstein–Barr virus (EBV) infection. The immunosuppressant mediated decrease in activity of the natural cytotoxic T–cells is probably one of the contributing factors. We report a case of PTLD occurring in the transplanted kidney of a 45 year old male, 7 years after transplant who presented with graft dysfunction. The graft biopsy revealed presence of lymphoid proliferation, confirmed by histochemistry and a diagnosis of monomorphic B-cell lymphoma was made. He was treated by reducing the immunosuppression and is doing well on follow up.

KEYWORDS Post transplant lymphoproliferative disorder, lymphoma, renal allograft, Epstein Barr virus

Introduction

Patients receiving a solid organ transplant have an increased risk of developing lympho-proliferative disorders, commonly referred to as Post Transplant Lymphoproliferative disorder (PTLD) and are characterized by abnormal lymphoid proliferation. Incidence of PTLD is 1% in renal allograft recipients.[1]

There was an initial rise in the incidence of PTLD following widespread use of cyclosporine. However, this effect was found to decrease following the monitoring of the drug dose using drug levels, which led to a significant decrease in the cyclosporine dosage.2 Further, there is no significant difference in the incidence of PTLD following tacrolimus use, as compared to cyclosporine.3

Most of the PTLDs are of B cell origin, and are found to have evidence of Epstein–Barr virus (EBV) infection. The immunosuppressant mediated decrease in activity of the natural cytotoxic T-cells is probably one of the factors leading to uncontrolled proliferation of B-cells by the EBV.4 EBV attaches to the receptor for the complement fragment C3d, and thereby its effects are seen in the cells which have this receptor. The common sites or cells expressing this receptor are the squamous epithelial cells present in the oropharynx, as also, the B-lymphocytes, with the lymphocyte infection being commonly latent. The attachment of the virus to the C3d receptor and its effects leads to transformation of these cells into lymphoblastoid lines, with almost infinite growth potential.[5] We report a case of PTLD occurring in the transplanted kidney of a 45 year old male, 7 years after transplant.

Case presentation:

We present a case of a 45 year old male, who received a live related renal transplant 7 years back, with the mother being the donor. He had 50% (3/6) HLA match, and negative cross match with the mother. He was not given any induction therapy and was started on triple immunosuppression, including Tacrolimus, Mycophenolate Mofetil and Prednisolone. He had a stable post-operative course, with a discharge creatinine of 0.9mg/dl at POD-8. He had come for routine follow up this visit, and was found to have graft dysfunction, with the creatinine increasing to 3.1mg/dl from a baseline of 1.8mg/dl. He did not have any symptoms of fever, night sweats, anorexia or weight loss. His post-transplant course was significant for one episode of acute borderline t-cell mediated rejection, 6 months post transplant and was treated with pulse doses of methyl prednisolone. Following treatment, the graft function improved with creatinine decreasing to 1.2mg/dl from 2.2mg/dl. His current CMV and BKV status was found to be negative, and blood and urine cultures were sterile. There was no evidence of any active focus of infection, or dehydration. There was no anemia, and no lymphadenopathy.

For evaluation, he underwent a percutaneous graft biopsy. The graft biopsy revealed 18 glomeruli, with mesangial prominence and open capillary lumina, with normal glomerular basement membrane on light microscopy. Tubules were mildly degenerated. Interstitium was markedly prominent for diffuse mononuclear cell infiltration with presence of large nodular aggregates and sheets of monomorphic large round cells (Figure 1,2). The mononuclear cells had hyperchromatic coarse nuclei and prominent nucleoli and occasional atypical mitotic figures. Blood vessels were unremarkable.

The biopsy was subjected for immunohistochemistry, and revealed that the nodular aggregates and mononuclear cells were positive for CD20 (Figure 3) and negative for CD4, SV40 and CD138. Immunofluorescence revealed no significant immunofluorescence with anti human IgG, IgA, IgM, C1q and C4d antisera.

Figure 1: Mildly degenerated tubules with prominent interstitial mononuclear cell infiltration with nodular aggregates.

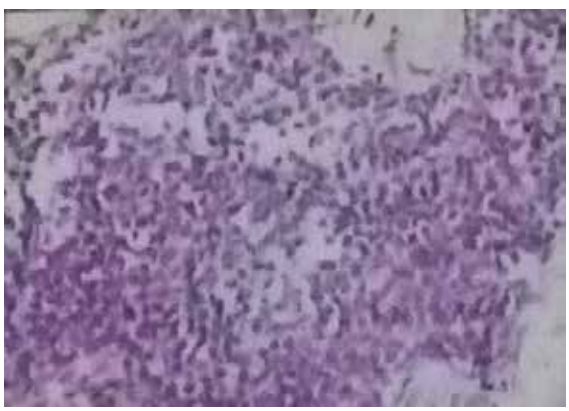

Figure 2: Interstitial cell aggregates with plenty of monomorphic large round cells

Figure 3: Immunohistochemistry showing presence of CD-20 positive cells

Thus, he was diagnosed as a case of monomorphic B cell lymphoma/PTLD (B-cell type) occurring within the renal allograft. He was submitted for plain CT scan of chest and abdomen, which did not show any significant abnormality or lymphadenopathy. His PCR for EBV DNA was negative.
He was treated by reducing the degree of immunosuppression, and was switched over to two drug immunosuppression. Currently, at 8 months follow up, the patient is doing well with stable graft function, with creatinine of 2.0mg/dl, and is on Sirolimus 1mg and prednisolone 5mg.

Discussion:
PTLD comprises a spectrum of diseases, ranging from infectious mononucleosis and lymphoid hyperplasia to highly aggressive lymphoma. The risk factors for developing PTLD are seronegative status of EBV, degree of immunosuppression, use of monoclonal and polyclonal antibodies, acute rejection treatment and CMV disease.

PTLDs with isolated renal allograft involvement usually develop early in the post-transplant period, while PTLD affecting the gastrointestinal system develops at a later period after transplant[6] and therefore emphasizes the need to look for any initial signs of the disease.[7] PTLD developing in the renal allograft commonly presents graft dysfunction. The importance lies in the fact that early and localized PTLD can be cured completely by appropriate surgery. On the other hand,[8] PTLD diagnosed at a later time can result in presentation with disseminated disease, and increase in morbidity and mortality. Therefore, all patients with worsening of allograft function should be diagnosed with renal biopsy, to rule out allograft PTLD, apart from rejections.[9,10] It has been found that survival is better for patients with graft PTLD, as compared to PTLD involving other localizations.[11] Early diagnosis of PTLD localized to the renal allograft leads to earlier evaluation, and this may be one of the possible factors for the better survival of patients with PTLD localized to the renal allograft as compared to other localizations. It is suggested that EBV infection of the kidney may be a possible etiology for the localization of PTLD to the renal allograft.[12] The characteristics of PTLDs can vary from polymorphic polyclonal hyperplasia to monomorphic monoclonal lymphomas.[13-16] It has been shown that hyperplastic lesions frequently have a polyclonal pattern, while lymphomatous lesions commonly demonstrate a monoclonal pattern.[17] The prognosis of patients with hyperplasia and polymorphic PTLD has been reported to be superior compared to patients with monomorphic PTLD.[18] The mainstay of treatment of PTLD is reduction or cessation of immunosuppression. Estimated survival rates are variable, ranging from 25-60%.

Conclusion:
PTLD is a potentially serious problem, noted after solid organ transplantation. Efforts to improve early detection and other preventive strategies will improve the outcome in such cases. Based on our findings, and other literature, we suggest that allograft dysfunction in renal transplant recipients should have a detailed evaluation, including for PTLD involving the allograft. PTLD limited to the renal allograft in renal transplant patients has a benign behavior; therefore it is important to screen renal recipients with allograft dysfunction for early diagnosis of PTLDs.

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