Posttransplant Lymphoproliferative Disorder: Experience from a Pediatric Nephrology Unit in North India

Abstract

Posttransplant lymphoproliferative disorder (PTLD) is reported in 1%–3% among pediatric renal allograft recipients. We report the experience of PTLD among pediatric renal allograft recipients at a pediatric nephrology center in North India. Four cases of PTLD were identified from among records of 95 pediatric renal allograft recipients over a period of 21 years. Constitutional and localizing symptoms were present in three patients each. The diagnosis was suggested on positron emission tomography in three patients and confirmed by histopathology in all. Sites affected included tonsils, cervical lymph nodes, duodenum, and para-aortic lymph nodes in one patient each. The lymphocytic infiltrate was polymorphic in three patients and monomorphic in one. Immunostaining suggested B-cell origin in all patients. There was evidence of Epstein–Barr virus infection in only one patient. The patients were successfully managed with reduction of immunosuppression (in all), rituximab (in 3), and excision of affected tissue (in 1). Over a follow-up period of 30–88 months, there were no episodes of disease recurrence or allograft rejection, and renal function was preserved.

Keywords: *Pediatric, posttransplant lymphoproliferative disorder, renal allograft*

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Introduction

Posttransplant lymphoproliferative disorder (PTLD) has an estimated incidence of 1%–3% among pediatric renal allograft recipients.[1,2] In India, access to renal transplantation is limited due to lack of resources. Consequently, there is a paucity of data on pediatric renal transplantation and consequently on PTLD following renal transplantation.[3] The experience with PTLD in our center is reported.

Case Reports

We retrospectively reviewed the clinical records of all 98 renal transplantations in 95 renal allograft recipients aged 4.2–18 years, who underwent renal transplantation between January 1995 and December 2015 and were diagnosed with PTLD based on tissue histology and immunohistochemistry for B-cell origin. Fifty-seven (58.2%), 12 (12.2%), 25 (25.5%), and 4 (4.1%) transplant recipients received no induction, daclizumab, basiliximab, and anti-thymocyte globulin, respectively. Initial calcineurin inhibitor used was cyclosporine for 28 (28.6%) and tacrolimus for 70 (71.4%) transplantations. Initial antimetabolite used was azathioprine for 24 (24.5%) and mycophenolate for 74 (75.5%) transplant recipients. Patients who received daclizumab underwent early steroid withdrawal; all others received steroids throughout their follow-up. Antiviral prophylaxis for cytomegalovirus (CMV) was administered to 19 (19.4%); surveillance for Epstein–Barr virus infection was not performed. Four (4.2%) of 95 pediatric renal allograft recipients developed PTLD at a median age of 12.9 (7.6–23.1) years and 1.1 (0.25-8.1) years from transplantation. Clinical details of these patients are as below and summarized in Table 1.

Patient 1

Patient 1 was a 15-year-old male who developed end-stage renal disease (ESRD) due to reflux nephropathy at the age of 15 years, 1 month; he underwent live-related renal transplantation (LRRT) with his father as donor 4 months after the initiation of dialysis. After an uneventful initial posttransplant period, he developed a painless unilateral swelling in the right tonsil 97 months after the transplantation. Excision biopsy was performed; tissue histology was suggestive of diffuse large B-cell lymphoma. Reduction of immunosuppression was in

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How to cite this article: Thergaonkar RW, Bhardwaj S, Sinha A, Dinda AK, Kumar R, Bagga A, *et al.* Posttransplant lymphoproliferative disorder: Experience from a pediatric nephrology unit in North India. Indian J Nephrol 2018;28:374-7.

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Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_143_17

Quick Response Code:

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Table 1: Clinical characteristics of pediatric renal allograft recipients with posttransplant lymphoproliferative disorder

Clinical characteristic	Patient 1	Patient 2	Patient 3	Patient 4
EBV serology: Donor/recipient	Not known	Not known	Positive/positive	Negative/negative
CMV serology: Donor/recipient	Not known	Positive/positive	Positive/positive	Positive/positive
Induction	None	None	Daclizumab: 9 doses	None
Maintenance therapy	Cyclosporine, azathioprine, prednisolone	Tacrolimus, MMF, prednisolone	Tacrolimus, MMF	Tacrolimus, MMF, prednisolone
Duration since transplantation	97 months	6.5 months	19 months	3 months
Symptoms	Large right tonsil	Fever, lymphadenopathy	Fever, nausea, diarrhea	Fever, pain abdomen
Localization on PET scan	Not done	Cervical lymph nodes	Duodenum, adenoids, tonsils	Para-aortic lymph nodes
Histology	Monomorphic; diffuse large B-cell lymphoma	Polymorphic	Polymorphic	Polymorphic
EBV LMP1	Not done	Not done	Negative	Positive
EBV by PCR	Not done	Negative	Negative	Negative
Relapse	No	No	No	No
Follow-up period	88 months	84 months	54 months	30 months

CMV: Cytomegalovirus, EBV: Epstein–Barr virus, MMF: Mycophenolate mofetil, PCR: Polymerase chain reaction, PET: Positron emission tomography, LMP1: Latent membrane protein 1

the form of reduction in the dose of cyclosporine from 3.5 to 3 mg/kg/day to reduce 2-h concentration (C2) levels from 555 to 232 ng/ml along with the reduction of dose of azathioprine from 1.5 to 1 mg/kg/day. Rituximab could not be offered since it was not available.

Patient 2

Patient 2, a female underwent LRRT at the age of 17 years with mother as donor after 10 months of peritoneal dialysis for ESRD of unknown cause. She had been treated for pulmonary tuberculosis during dialysis. She developed a swelling in her left submandibular region associated with fever 6½ months after renal transplantation. There was an initial reduction in size of the lymph node after empirical antibiotic therapy, but the size increased another 2 months later. Positron emission tomography (PET) scan showed increased uptake of 2-deoxy-2-(fluorine-18)-fluoro-D-glucose (FDG) at submandibular lymph nodes and in addition in retroperitoneal and presacral nodes as well as the spleen. Contrast-enhanced computerized tomography (CT) showed similar findings. An excision biopsy at this stage showed polymorphic B-cell disease.

Patient 3

Patient 3, a male, a case of ESRD due to reflux nephropathy, underwent preemptive LRRT with his mother as a donor at the age of 6 years. He received antiviral chemoprophylaxis with valganciclovir. After an uneventful posttransplantation period of 19 months, he developed fever and nausea. PET-CT scan showed increased FDG uptake in the tonsils; however, after adenotonsillectomy, tonsillar and adenoid tissues did not show any histological evidence of PTLD. Meanwhile, the patient continued to have constitutional symptoms and in addition had epigastric pain. A repeat PET-CT scan 3 months later showed increased FDG uptake in the duodenum; an endoscopic duodenal biopsy showed polymorphic B-cell disease.

Patient 4

Patient 4, a case of Frasier syndrome, had undergone gonadectomy for arrhenoblastoma in her early childhood. She developed ESRD due to steroid-resistant nephrotic syndrome and underwent preemptive LRRT with her grandfather as a donor at the age of 9½ years. Three months after renal transplantation, she developed recurrent abdominal pain and anorexia. A para-aortic node showed increased FDG uptake on PET-CT scan; lymph node biopsy showed polymorphic B-cell disease.

In Patients 2, 3 and 4, therapy with mycophenolate mofetil (MMF) was ceased and the dose of tacrolimus reduced from 0.16, 0.24, and 0.26 mg/kg to 0.1, 0.17, and 0.15 mg/kg/day, thus reducing trough levels from 7.66, 5.60, and 8.47 ng/ml to 5.6, 3.4, and 7.21 ng/ml, respectively. These three patients also received intravenous rituximab, at a dose of 375 mg/m^2 once a week for four doses. Therapy resulted in symptomatic improvement, disappearance of palpable lymph nodes (Patient 2), resolution of lesions on ultrasonography (Patients 2 and 3), and loss of enhancement on follow-up FDG-PET scans, performed 3 months (Patient 2) and 6 months (Patients 3 and 4) after

diagnosis. Chemotherapy or radiation was not required in any patient.

There was no clinical suggestion of recurrence on follow-up in all four cases. Scintigraphy, beyond 12-month follow-up, did not show enhancement in Patients 1, 2, and 4. Repeat scanning in Patient 3 at 12 months after diagnosis showed increase in duodenal FDG uptake, but a repeat biopsy did not show evidence of PTLD.

Discussion

The present case series summarizes the 21-year experience with PTLD in pediatric renal allograft recipients at our center. PTLD occurred in 4.2% of patients with polymorphic variant as the chief histological type. In the Indian experience of Sakhuja *et al*. of 2000 adult renal allograft recipients, 29 (1.45%) developed PTLD; however, only two patients had polymorphic B-cell disease while 18, 2, and 7 patients had monomorphic B-cell, monomorphic T-cell, and plasma cell myeloma, respectively.[4] This is consistent with the existing literature that PTLD is more common but more often polymorphic in children as compared to adults.[2] Given the fact that two of our patients were above 15 years of age, it seems possible that this pattern of disease continues in adolescence. No risk factors were obvious, including the age at transplantation or immunosuppressive agents used. Antiviral prophylaxis for CMV was used in 19/95 renal allograft recipients; of these, one patient (5.3%) developed PTLD. A systematic review and meta-analysis including nine studies and over 2000 subjects could not show any difference in the incidence of PTLD in patients receiving or not receiving antivirals with a risk ratio of 0.95 (95% confidence interval 0.58–1.54).[5] In the present study, the chief symptoms of PTLD were either constitutional or those localized to the organ involved. Symptoms of PTLD include those related to viral infection, mass effect, organ dysfunction, or lymphoma-related B symptoms.[6,7] The profile of our patients seemed to be one of somewhat less severe disease as compared to the Irish childhood series in which 4/10 had monomorphic disease and 8/10 had Stage III or IV disease as per the St. Jude's Staging System.[8] We found that PET-CT scan was useful for diagnosis as well as assessment of response to therapy. PET-CT has been reported to have a sensitivity of 88.2% and specificity of 91.3% in the diagnosis of PTLD.[9] PET and CT scan have been shown to be complementary to each other at initial diagnosis.[10] The diagnosis was confirmed in all our patients by histopathology with immunostaining suggesting B-cell origin. In one of our patients, reduction in immunosuppression after excision biopsy alone had been therapeutic despite the monomorphic nature of the disease. As per the present guidelines, the initial step is reduction in immunosuppression to the lowest tolerated levels.[11] A common strategy is reduction of the dose of the calcineurin inhibitor and discontinuation of the antimetabolite;[12] this was used in three of our patients. The use of rituximab in three patients was preemptive and in keeping with the overall impression that rituximab is effective in B-cell neoplasias in a posttransplant setting.[11] All patients had a good outcome in our study, without relapses, rejection, or need for chemotherapy in the medium term. This suggests that close clinical surveillance and timely diagnosis, reduction in immunosuppression and rituximab may be effective strategies for management of PTLD.

Conclusion

We conclude from our experience that PTLD in Indian pediatric renal allograft recipients occurs in <5% patients, can be diagnosed with PET-CT scan followed by tissue biopsy in patients with constitutional and/or localizing symptoms, and is amenable to therapy with excision of affected part if possible, reduction in immunosuppression and anti-CD20 biological therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Opelz G, Döhler B. Pediatric kidney transplantation: Analysis of donor age, HLA match, and posttransplant non-Hodgkin lymphoma: A collaborative transplant study report. Transplantation 2010;90:292-7.
2. Mynarek M, Schober T, Behrends U, Maecker-Kolhoff B. Posttransplant lymphoproliferative disease after pediatric solid organ transplantation. Clin Dev Immunol 2013;2013:814973.
3. Sethi SK, Sinha R, Rohatgi S, Kher V, Iyengar A, Bagga A. Pediatric renal transplant practices in India. Pediatr Transplant. 2017;21:e12892.
4. Sakhuja V, Ramachandran R, Kohli HS, Jha V, Gupta KL, Rathi M, *et al.* Spectrum of lymphoproliferative disorders following renal transplantation in North India. Indian J Nephrol 2013;23:287-91.
5. AlDabbagh MA, Gitman MR, Kumar D, Humar A, Rotstein C, Husain S, *et al.* The role of antiviral prophylaxis for the prevention of Epstein-Barr virus-associated posttransplant lymphoproliferative disease in solid organ transplant recipients: a systematic review. Am J Transplant 2017;17:770-81.
6. Loren AW, Porter DL, Stadtmauer EA, Tsai DE. Post-transplant lymphoproliferative disorder: A review. Bone Marrow Transplant 2003;31:145-55.
7. Nassi L, Gaidano G. II. Challenges in the management of post-transplant lymphoproliferative disorder. Hematol Oncol 2015;33 (Suppl 1):S96-S99. doi: 10.1002/hon.2234.
8. Malone A, Kennedy G, Storey L, O'Marcaigh A, McDermott M, Broderick AM, *et al.* Post-transplant lymphoproliferative disorder in paediatric patients: The Irish perspective-a single centre experience. Ir J Med Sci 2017;186:339-43.
9. Panagiotidis E, Quigley AM, Pencharz D, Ardeshna K, Syed R, Sajjan R, *et al.* (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in diagnosis of post-transplant lymphoproliferative disorder. Leuk Lymphoma 2014;55:515-9.
10. Vali R, Punnett A, Bajno L, Moineddin R, Shammas A. The

value of 18F-FDG PET in pediatric patients with post-transplant lymphoproliferative disorder at initial diagnosis. Pediatr Transplant 2015;19:932-9.

11. Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, *et al.* Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients – BCSH and BTS guidelines. Br J Haematol 2010;149:693-705.
12. Paya CV, Fung JJ, Nalesnik MA, Kieff E, Green M, Gores G, *et al*. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD task force and the Mayo Clinic Organized International Consensus Development Meeting. Transplantation 1999;68:1517-25.