Posttransplant Lymphoproliferative Disorder in Pediatric Solid Organ Transplant Recipients: A Seven-Year Single-Center Analysis

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Introduction

- The price of chronic immunosuppression after solid organ transplantation is development of malign diseases.
- There is reduced immune response to viruses and potential transformation to malignancy or Post-transplant Lymphoproliferative Disorder (PTLD)
- Most PTLD cases are associated with EBV, usually occur in patients who are EBV seronegative before transplant
- EBV transforms and immortalizes B cells.
- Immunosupressive treatment cause defective cytotoxic T cell control on virus infected B cells.

*L'Huillier AG et al. Am J Transplant. 2019 Oct;19(10):2764-2774

The aim of our study

- This study analyzes the experience of a single center in managing pediatric PTLD cases over a 7-year period.
- The investigation focuses on PTLD incidence, anatomical sites involved, and the outcome of the patients.
- The primary objective is to explore clinical features and treatment outcomes in pediatric PTLD patients, emphasizing patient survival and associated clinical ramifications.

Methods

- Retrospective analysis of medical records from pediatric SOT recipients (liver and kidney) at Baskent University Ankara Hospital Organ Transplantation Center between January 1, 2017-January 1, 2024.
- The study was approved by the Institutional Review Board (KA24/63).
- Identified PTLD cases based on persistent lymphadenopathy or tumorous lesions, confirmed through pathological examination.
- Early PTLD was defined within the initial year post-transplantation.
- EBV association was determined through EBER in situ hybridization test, PCR, and serology.

Results

- 10 patients (LiverT/KidneyT, 9/1; M/F,3/7)
- The incidence of PTLD for pediatric LT (8.7%) (of total 9/103 LT recipients).
- 77.8% of the PTLD cases were EBV naive before transplantation.
- Most common complaints were fever, lymphadenopathy, hepatosplenomegaly, dyspnea and diarrhea.
- Mean time of follow-up was 22.9 months
- The most common involved sites of lymphadenopathy were mediastinal , abdominal and cervical regions.
- Most of the biopsies (90%) revealed Early Polymorphic Form of PTLD with both CD20 and EBER positivity.
- One patient who was admitted after kidney T was diagnosed with abdominal Burkitt Lymphoma.
- EBV PCR was positive in all patients at the time of diagnosis.
- Immunuspressive treatment at the time of PTLD diagnosis was tacrolimus in 70% and tacrolimus + mycofenolate mofetil in 30% of patients.
- Tacrolimus was changed to everolimus in 40% and to sirolimus in 60% patients.

Results

Characteristic	Value
Sex	
M/F	7:3
Diagnosis	
Biliary atresia	5
PFIC2	2
Glycogen storage disease type 1a	1
Crigler Najjar Diseasse	1
Renal artery stenosis chronic kidney disease	1
Organ tansplanted (LT/KT)	9:1
Age at transplantation	21.5 months (6-84)
Age at PTLD	46.4 months (10-120)
Time from transplantation (mean)	21.2 months
Donor Type	
Living-related	10
Early/late	4:6
EBV serologic status (D/R)	
EBV VCA Ig G (-/+)	1
EBV VCA Ig G (+/-)	2
EBV VCA Ig G (NA/-)	5
EBV VCA Ig G (+/+)	2
History of acute rejection (+/-)	4:6

Results

Characteristic	Value
Presentation	
Fever	10/10
Lymphadenopathy (cervical, axillary, intraabdominal, mediastenal, inguinal)	10/10
Hepatosplenomegaly	6/10
Diarrhea	2/10
Mass in abdomen	1/10
Dyspnea	2/10
Treatment	
Rituximab 375 mg/m2/week for 4 weeks	7/10
Decrease of immunesupression only + weekly IVIG	2/10
NHL-90 (Non-Hodgkin Lymphoma 90) chemoterapy	1/10
Long term IVIG prophylaxis	2/10
Resolution of PTLD	10/10

Results

Case No/ Sex/ Age (months) at diagnosis	Underlying disease/type of SOT***/ time (months) from SOT*** to PTLD	Presentation	Involved site	EBV Status of Donor/ Recipient	Histologic Diagnosis	Initial EBV**** viral load at presentation (copies/ ml whole blood)	Change in immunsupressive therapy (Initial treatment/ Treatment during PTLD)	Antiviral treatment/ Type	Specific treatment	Outcome of PTLD	OS** (months)
1/M/24	Biliary atresia/LT$^{\Delta}$/ 11	Fever, dyspnea,HSM§	Mediastinal,paraaortic, paracaval, mesenteric LAP§§, HSM,GIS§§§	+/-	PTLD-Early polymorphic form	81,7x10^3	Tacrolimus/ Everolimus	Yes/ Gancyclovir	Rituximab 375 mg/m^2/ week x2	Resolved	3
2/F/21	Biliary atresia/LT/ 2	Fever, dyspnea,HSM, mediastenal mass	Mediastinal,paraaortic, mesenteric LAP,HSM	-/+	PTLD-Early polymorphic form	1,43 X10^5	Tacrolimus/ Everolimus	Yes/ Gancyclovir	Rituximab 375 mg/m^2/ week x4	Resolved	12
3/M/72	PFIC$^{\Psi}$2/LT /60	Fever, diarhhea	GIS (colon, stomach) ,HSM	Not known/ Not known	PTLD-Early polymorphic form	positive	Tacrolimus/ Everolimus	Yes/ Gancyclovir	Rituximab 375 mg/m^2/ week x4 +IVIG	Resolved	12
4/F/11	PFIC2/LT/ 3	Fever, HSM, axillary, abdominal, cervical LAP, exanthema	Cervical, axillary,HSM aksiller LAP,HSM	Not known/-	PTLD-Early polymorphic form	positive	Tacrolimus/ Everolimus	Yes/ Gancyclovir	Rituximab 375 mg/m^2/ week x2 + IVIG$^{\Psi\Psi}$	Resolved	33
5/F/51	Biliary atresia/LT/ 36	Fever, cervical LAP	Cervical LAP	+/-	PTLD-Early polymorphic form	637	Tacrolimus+MMF$^{\Psi\Psi\Psi}$/ Everolimus	Yes/ Gancyclovir	Decrease of immunosupression only	Resolved	21

Clinical features at the time of presentation of PTLD, 1st line treatment, and outcome

Case No/ Sex/ Age (months) at diagnosis	Underlying disease/type of SOT/time (months)from SOT to PTLD	Presentation	Involved site	Histologic Dx	Initial EBV viral load at presentation (copies/ml whole blood)	Change in immunsupressive therapy (Initial treatment/ Treatment during PTLD)	Antiviral treatment/ Type	Specific treatment	Outcome of PTLD	OS (months)
5/M/37	Glycogen storage disease typa1A/LT/ 24	Fever, diarhhea, HSM	GIS(Terminal ileum) HSM	+/-	PTLD-Early polymorphic form	2,42X10^{2}	Tacrolimus+MMF/Sirolimus	Yes/ Valgancyclovir	Rituximab 375 mg/m^{2}/ week x4+IVIG	Resolved	18
7/F/120	Biliary atresia/LT/ 12	Fever, cervical, axillary LAP, HSM	Cervical, axillary lap, HSM	+/-	PTLD-Early polymorphic form	positive	Tacrolimus/ Sirolimus	Yes/ Acyclovir	Dexamethasone + IVIG	Resolved	60
8/F/84	Renal artery stenosis/RT / 36	Fever, mass in abdomen, abdominal LAP	Mass in abdomen, abdominal LAP	+/-	PTLD-Burkitt lymphoma	1,13 X10^{5}	Tacrolimus/NHL-BFM©-90 Chemotherapy	No	NHL-BFM©-90 chemotherapy	Treated with chemotherapy	36
9/F/10	Biliary atresia/LT/ 4	Fever, axillary, abdominal, cervical LAP	Abdominal, axillary, cervical LAP, HSM	Not known/-	PTLD-Early polymorphic form	3,3 X10^{3}	Tacrolimus+MMF/Sirolimus	No	Rituximab 375 mg/m^{2}/ week x4	Resolved	26
10/F/34	Crigler Najjar Syndrome/ LT/24	Fever, abdominal LAP	abdominal LAP, SM	+/+	PTLD-Early polymorphic form	2,89 X10^{3}	Tacrolimus/ Sirolimus	Yes/ Acyclovir	Rituximab 375 mg/m^{2}/ week x4	Resolved	8

Discussion

- The incidence of PTLD was more in LT compared to KT.
- Time to PTLD since transplantation was longer than previous reports and most of the cases were early polymorphic forms.
- Tacrolimus and being EBV seonegative before LT is an important risk factor for PTLD
- 2 of our patients were treated with change and decrease in IS, 1 with chemotherapy and 7 with Rituximab therapy,
- All of the PTLD attacks were resolved with success, and there was no organ rejection due to decreased IS.

*Jeong JH et alt. Korean J Pediatr 2017;60(3):86-93
**Heo JS et al. Transplant Proc 2004;36:2307-8
*** Karakoyun M et al. Turk J Gastroenterol 2018; 29: 89-93.