original research report

Lymphoproliferative disorders in pediatric liver allograft recipients: a review of 212 cases

Hossein Khedmat,[a] Saeed Taheri[b]

From the Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences and [b]Dr. Taheri Medical Research Group, Tehran, Iran

Correspondence: Hossein Khedmat · Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran, Iran · khedmat.h@gmail.com

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BACKGROUND AND OBJECTIVES: Due to the limited incidence of posttransplant lymphoproliferative disorders (PTLD) in pediatric liver graft recipients, there is a scarcity of data on the characteristics of the disease in this population. We aimed to analyze the special features and behavior of PTLD arising after pediatric liver transplantation.

DESIGN: A comprehensive search of the literature was conducted for the available data on PTLD in pediatric liver recipients pediatric PTLD through a search of Pubmed and Google Scholar using appropriate terms.

METHODS: We sought data on liver recipients younger than 18 years of age at the time of transplantation. From 51 reports, 43 fulfilled the inclusion criteria. Overall 250 cases of PTLD (212 pediatric PTLD) were found from 43 reports. Data on pediatric patients was compared to adults.

RESULTS: Pediatric PTLD lesions were more likely of the polymorphic type (P=.004) and polyclonal (when age cut-off was defined at 12 years; P=.023). Remission rates, metastasis frequency and organ involvements were not different between the groups (P>.1 for all). Survival analysis showed no disparity between pediatric PTLD and adult patients (P>.1); but when data was reanalyzed for patients surviving at least 4 months post diagnosis, the log rank test showed that pediatric patients have a superior outcome compared to adults (P=.045).

CONCLUSIONS: Pediatric liver recipients developing PTLD have relatively better disease presentation and behavior than that in adults. Stomach involvement was also more frequently seen in patients younger than 12 years, and should be more intensively evaluated. Future studies with a prospective approach and larger population size are needed for confirming our results.

Posttransplant lymphoproliferative disorders (PTLD) are increasingly recognized as a life threatening complication of transplantation. Complicating range from polyclonal hyperplasia of the lymphoid system to monoclonal non-Hodgkin lymphoma.[1-3] PTLD is associated with a high rate of graft loss and patient mortality, due to its devastating, unpredictable and often treatment-irresponsive nature of the disease.[4,5] The main pathogenesis of the disease arises from defects that usually occur in T-cell regulation processes leading to uncontrolled proliferation of B or T lymphocytes, generally in response to Epstein-Barr virus (EBV), or some other viral infections.[6,7]

Compared to lymphomas developing in the normal population, PTLD usually represent a more unfavorable histopathological presentation, a more aggressive clinical course, lesser responsiveness to conventional interventions, and a poorer outcome.[8] These unwanted features of PTLD become more prominent in the pediatric transplant population, where data scarcity exists on the clinical course and safety and effectiveness of conventional therapies in managing the disease. Due to the overall higher number of adults undergoing organ transplantation, most of the available data in the current literature address PTLD arising in adult patients, and available data in the pediatric context are limited.

PTLD has been shown the most common tumor in solid organ transplanted children, with an overall incidence rate of 5% to 15% in different series whose share in the frequency of post-transplant malignancies is over 50% of all tumors.[9,10] The reported rate of mortality for this population is also extremely high (up to

60%) although reports with lower mortality rates also exist.[9,11,12] Some of the recommended reasons for these elevated risks in pediatric transplant context are young age, transplant time, EBV seronegativity, and long-term immunosuppression.

As mentioned, most of the data available in the literature on PTLD have been derived from adult populations, and data on children are mostly from single- or multicenter reports of small series. We conducted a very comprehensive and thorough search to find all individual pediatric cases in series whose data were presented by authors who tried to standardize their data and acccumulate their data to find potential clinical and histopathological features of lesions, and prognoses specifically associated with PTLD in this patient population.

METHODS

Pubmed and Google Scholar were comprehensively searched for reports on lymphoproliferative disorders developing in liver transplanted children. Keywords used included "lymphoproliferative disorders + transplantation + liver + pediatric" "lymphoproliferative disorders + liver + transplantation + children" "lymphoproliferative disorder + liver + transplantation + childhood" "lymphoproliferative disorders + liver + transplantation + young". The search was empowered by following the citations of each article, and our previous searches on liver transplantation. Wherever the full text of the articles were not obtainable, we contacted correspondent authors of each article through their email addresses requesting the article. Then we included reports in which data for each patient was presented individually, into the database. Lymphoproliferative disorders occurring after liver transplantation in children (pediatric PTLD) were considered as our case group and adult liver transplant recipients developing PTLD were included as controls. Controls were selected from the same studies as the case group. Pediatric patients were defined as younger than 18 years of age; patients 18 years or older were considered adults. A questionnaire was developed to collect data from the included series. Data from 43 previously published studies were included in the analysis.[11, 13-54]

Due to the inconsistencies in data presentations as well as approaches used in the studies included into this survey, it was not possible to get all data we needed from all the included patients. So, we tried to standardize data of different studies by implementing new definition criteria. Disseminated lymphoma was diagnosed when it was declared by the authors or at least three different organs (Different lymph node areas were excluded from analysis due to lack of knowledge categorization) were involved by PTLD, reported in 26 (23.9%; 141 unreported) patients. Multiorgan involvement, defined as involvement of more than a unique organ as well as more than one lymphatic region, was available in 80 (53%; 99 unreported) patients.

Response to treatment termed "remission" was defined as any favorable change in the cancer measures as well as patients' clinical condition; we also developed new criteria for defining remission rates for the study population; while remission episode was presumed available when patients were alive after their 24th month of PTLD diagnosis (since, reported cases having this criterion had at least one confirmed remission episode) and no remission was defined when a patient died within the first month post-PTLD diagnosis (because among reported cases there were no patients dying at the first post-transplant month and reported to have any remission episodes).

Software used for data analyses was SPSS v.13.0. Statistical differences between patient subgroups were performed by using chi-square and the Fisher exact test for proportions and the *t* test for continuous data. Survival analysis was done with life tables and Kaplan-Meier methods and log-rank test. All statistical tests were performed at the .05 significance level.

RESULTS

Data on 250 liver transplant recipients who developed lymphoproliferative disorders were enrolled into analysis, of which 212 (84.8%) were children ≤18 years. Seventy-three (51%) of the study participants were male and 70 (50%) were female (107 unreported). Mean age and standard deviation at diagnosis of PTLD was 9.9 (15.7) years (**Table 1**). The mean (SD) interval between transplantation and the diagnosis of PTLD was 28.7 (35.1) months whereas follow-up time after diagnosis of PTLD was 34.5 (39.1) months. Two hundred and twelve (84.8%) patients had undergone liver transplantation at a pediatric age, while the remaining 38 (15.2%) recipients were adults. Patient EBV infection status was documented in 114 (45.6%) patients of whom 95 (83.3%) were positive. According to remission criteria, 120 (48%) patients represented data on remission of whom 96 (80%) had at least one remission episode, irrespective of their future disease behavior. Overall mortality was 56 (35.4% of the reported cases; 92 unreported) patients; 35 (72.9%) of the mortality was due to PTLD disease (8 (14.3%) unreported data).

Chi square tests showed that pediatric PTLD lesions were significantly more frequent of early histo-

Table 1. Characteristics of liver transplant recipients of pediatric and adult age.

Variables	Pediatric PTLD		Controls		*P*		Available data (n)
	<18 yr	<12 yr	<18 yr	<12 yr	<18 yr	<12 yr	
Age (SD) in years	4.4 (4.6)	-	44.3 (16.6)	-	-	-	250
Gender male (%)	56 (50.5)	52 (52.5)	17 (53.1)	21 (47.7)	.843	.362	143
Time to PTLD development (SD) in months	29.5 (34.7)	26.8 (33.2)	25.5 (36.7)	35.0 (40.3)	.547	.112	172
Early onset disease (%)	69 (50.4)	66 (53.7)	18 (51.4)	19 (41.3)	.531	.104	172
Multiorgan involvement (%)[a]	66 (54.5)	60 (55.6)	12 (46.2)	18 (46.2)	.518	.206	147
Disseminated PTLD (%)[a]	20 (23.8)	16 (21.6)	6 (26.1)	10 (30.3)	.79	.233	107
B cell type (%)	35 (89.7)	29 (87.9)	17 (100)	23 (100)	.303	.111	56
Morphology							
Early lesion (Plasmacytic hyperplasia)	7 (5.6)	7 (6.5)	0	0			
Polymorphic B cell lymphoma	68 (54)	61 (56.5)	12 (38.7)	17 (37.8)	.09	.004	157
Monomorphic PTLD	44 (34.9)	33 (30.6)	18 (58.1)	27 (60)			
Hodgkin lymphoma	7 (5.6)	7 (6.5)	1 (3.2)	1 (2.2)			
EBV status (%)	72 (82.8)	64 (81)	20 (83.3)	28 (87.5)	.609	.301	111
Author defined remission episode (%)	38 (82.6)	35 (83.3)	13 (81.3)	16 (80)	.585	.502	62
Remission (%)[a]	74 (79.6)	67 (78.8)	20 (80)	27 (81.8)	.604	.466	118
Polyclonal lesions - vs. monoclonal (%)	18 (48.6)	13 (41.9)	11 (73.3)	16 (76.2)	.093	.023	52
Death due to PTLD (% of mortality)	25 (73.5)	24 (25.8)	10 (71.4)	11 (28.2)	.765	.476	48

[a]based on the defined criteria;

pathological features (*P*=.037). When age cut-off point was decreased to 12 years, pediatric PTLD lesions were more likely to be both polymorphic (*P*=.004) and polyclonal (*P*=.023). Pediatric PTLD were comparable to their adult counterparts lesions cell types (*P*=.303), rate of EBV infection (*P*=.609), multiorgan involvement (according to the defined criteria; *P*=.518), disseminated PTLD (according to the defined criteria; *P*=.79), and in representing any remission episodes in their disease course (*P*=.604) (**Table 1**).

Table 2 summarizes different organ involvements by PTLD in pediatric PTLD patients and compares them with the adult group. No priority for organ complication by PTLD was detected for pediatric patients. When age cut-off was defined at 12 years, pediatric patients were significantly more likely to complicate the stomach (*P*=.035). Time from transplantation to PTLD development was also comparable between the study groups (*P*=.531).

At the last follow, 56 (35.4%) patients were dead. Survival analysis showed no significant difference in the outcome of PTLD in pediatric versus adult patients (*P*=.244; **Figure 1**). However, after the very early post transplantation time, the survival curve of pediatric PTLD goes upward, indicating better survival. Thus, we reanalyzed data censoring mortalities within the early months, and increased the time interval step by step. We found that after censoring events before the 4th post diagnosis month, the survival difference between pediatric PTLD and adult PTLD liver recipients reached to the significance level (*P*=.041; **Figure 2**). One and 5-year survival rates for the pediatric PTLD patients were 76% and 64%, respectively; compared to 73% and 57%, respectively, for the controls.

Study participants were categorized based on the time of PTLD development (versus time at transplan-

Table 2. Comparison of frequencies of organ involvements by PTLD in the study patient groups.

Involved organs	Pediatric PTLD[a]	Controls	*P*
Orbit	2 (1.5)	0	.695
Skin	2 (1.6)	0	.68
Stomach[b]	11 (10)	0	.035
Genitalia	1 (1)	1 (4)	.312
CNS	6 (4)	1 (4)	.696
Spleen	13 (10)	2 (8)	.557
Renal involvement	3 (2)	1 (4)	.524
Respiratory system	16 (12.4)	5 (19.2)	.353
Liver	32 (24)	9 (35)	.329
Bone marrow	8 (6.2)	3 (11.5)	.396
Small intestine	23 (19)	4 (16)	.503
Colon	4(3)	2(8)	.278

[a]Pediatric liver recipients developing PTLD; [b]age cut off at 12 years;

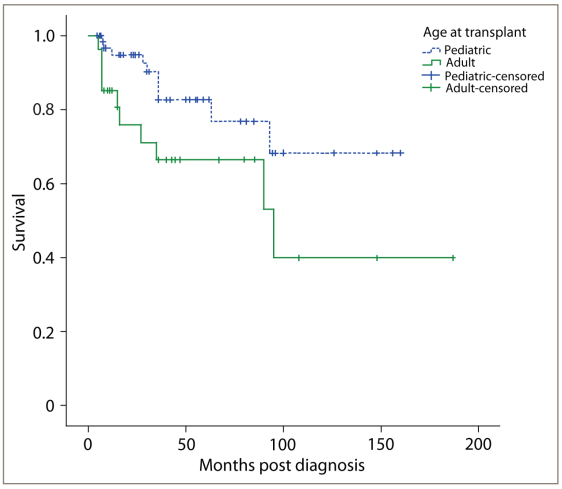

Figure 2. Survival curves of liver recipients of pediatric or adult age after censoring events occurring within the first 4 months.

tation). According to the new categorization, PTLD lesions developing in pediatric liver recipients were more likely to be polyclonal (56% vs. 23%; *P*=0.035) and polymorphic (58% vs. 40%; *P*=.045). However, survival analysis showed no significant outcome difference (*P*=.667; **Figure 3**). Finally data was reanalyzed excluding adult patients. Survival analysis showed that T-cell type PTLD lesions (*P*=.002) as well as multiorgan involvement (P=.048; **Figure 4**) were significantly associated with inferior outcome.

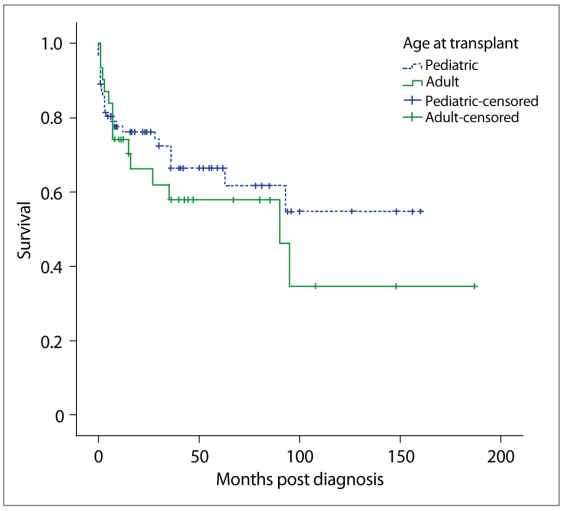

Figure 1. Survival curves of liver transplant recipients developing PTLD by age at transplantation.

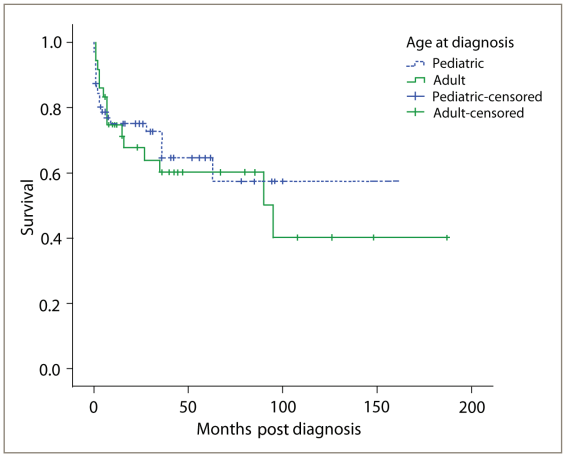

Figure 3. Survival curves of liver recipients whose PTLD lesions developed when they were at pediatric or adult age.

DISCUSSION

The practice of transplantation witnessed significant improvement when new immunosuppressive agents were introduced. However, using the newly developed potent immunosuppressants was associated with the development of post-transplant malignancies including PTLD, which immensely threatens the lives of organ transplant recipients. The rate of PTLD developing in liver recipients is considered comparable to renal graft recipients and lower than most other organ transplant patients. In the pediatric setting, the overall incidence of PTLD has been reportedly up to 1.2% of all recipients or 298/100 000 posttransplantation years of follow-up.[34,55] This might mean that our study population can be considered representative of over 18 000 pedi-

atric liver transplant population; or over 71 000 years of posttransplant follow up. This shows the magnitude of the findings of the present article. Moreover, when considering the frequency of liver transplantation in children, our study population will more prominently come into view.

In this study, we tried to eliminate the limitation of data existing in individual and multicenter reports, while trying to find and accumulate all the retrievable existing data available to form a database. Thus, we conducted a very through and comprehensive search for all cases of pediatric liver transplants that developed PTLD. We believe that our study represents the largest investigation of liver transplant pediatric PTLD patients.

Epstein Barr-virus (EBV) infection has been proposed as a significant risk factor in inducing PTLD especially in the pediatric transplant setting. Guthery et al, proposed that younger age is associated with EBV-associated PTLD development in pediatric liver transplantation, although they did not exclude detection bias as an explanation for their observation. [56] The proposed rationale behind this finding is that the seronegativity of children places them at a higher risk of seroconversion and PTLD as a consequence. Controversial observations have also been reported where older children were more likely to develop EBV-associated PTLD. [57] In this study, however, we found no association between EBV serology and younger age, although our observation was not able to show seroconversion.

Previous studies have shown better PTLD outcomes in younger children.[57,58] Survival analysis of our study population, however, showed no outcome difference related to patient age. Nevertheless, a precise look at the survival curves shows an improvement in pediatric patients. After a survival reanalysis after censoring events occurring within the early months, we found that for patients who survive the first 4 post transplant months, pediatric PTLD patients have a superior outcome compared to adults (>18 years).

Histopathological features of PTLD among pediatric PTLD patients were of significantly more benign types. Moreover, reanalysis of data on lower age cut-off points showed a larger significant difference. This finding is in concordance with our previous knowledge as well as our finding of better survival of pediatric PTLD patients compared to their adult counterparts, while it has been shown that polymorphic PTLD lesions in children respond better to antimalignancy therapies than monomophic ones.[59] However, data on histo-

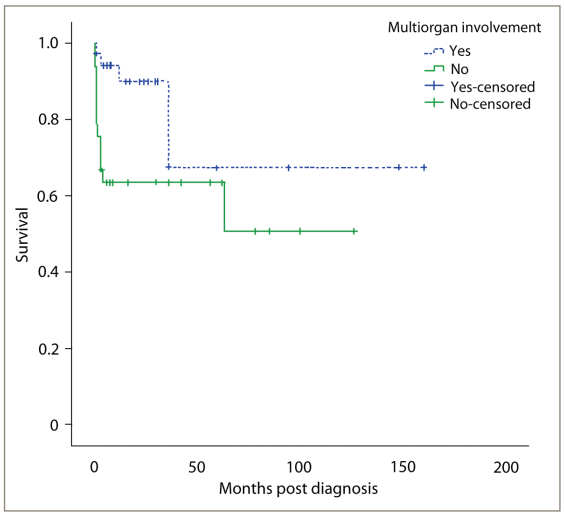

Figure 4. Survival curves of pediatric liver recipients developing PTLD regarding their disease extent.

pathological disparities in PTLD lesions related to age is controversial. In renal graft recipients, Shapiro et al found no significant difference in the histopathology of PTLD lesions by age groups with both groups having more monomorphic lesions.[58] While Cacciarelli et al showed that 75% of lesions in pediatric PTLD liver recipients were early lesions. Polyclonal lesions were also more frequently seen in pediatric patients.[11] This can also provide another explanation for the superior survival observed in pediatric PTLD patients.

This study has several limitations. First, data for this study was accumulated from different published reports whose approaches were not essentially consistent. For example, a report of any response to treatment was presented very dissimilarly in different studies, while in one study partial and complete remission were used to translate the results, while in another only "response to treatment" was used and in some others no specific terminology was employed. Thus, we ought to invent new methods to standardize different data presentation types to be able to accumulate the existing data for analysis.

In conclusion, this study showed that pediatric liver transplant recipients developing PTLD are more likely to develop lesions with more favorable histopathological features. Except for the very early post-transplant period, they also have better survival compared to older liver transplant patients. Future prospective studies with larger patient population and more controlled conditions are needed for confirming our findings.

REFERENCES

1. Khedmat H, Taheri S. Early versus late outset of lymphoproliferative disorders post-heart and lung transplantation: The PTLD.Int Survey. Hematol Oncol Stem Cell Ther. 2011;4(1):10-6.
2. Khedmat H, Taheri S. Post-Transplantation Lymphoproliferative disorders localizing in the adenotonsillar region: Report from the PTLD.Int survey. Ann Transplant. 2011 Mar 23;16(1):109-16.
3. Izadi M, Taheri S. Features, predictors and prognosis of lymphoproliferative disorders post-liver transplantation regarding disease presentation time: Report from the PTLD.Int. survey. Ann Transplant. 2011 Mar 23;16(1):39-47.
4. Khedmat H, Taheri S. Characteristics and prognosis of post-transplant lymphoproliferative disorders within renal allograft: Report from the PTLD. Int. Survey. Ann Transplant. 2010 Sep 28;15(3):80-6.
5. Izadi M, Fazel M, Saadat SH, Taheri S. Hepatic involvement by lymphoproliferative disorders post liver transplantation: PTLD.Int. Survey. Hepatol Int. 2011 Sep;5(3):759-66.
6. Izadi M, Taheri S. Significance of in situ hybridization results for EBV-encoded RNA in post-transplantation lymphoproliferative disorder setting: Report from the PTLD.Int Survey. Ann Transplant. 2010 Dec 22;15(4):102-9.
7. Khedmat H, Alavian SM, Taheri S. Significance of Epstein-Barr virus infection in the outcome of renal transplant patients with lymphoproliferative disorders. Ann Transplant, 2010; 15(2): 40-44.
8. Magrath IT, Rowe M, Filipovich AH, et al. Advances in understanding of EBV associated lymphoproliferative disorders. In Ablashi DV, ed. EBV and human disease. Clifton, NJ: Human Press, 1991; 243.
9. Smets F, Sokal EM. Epstein-Barr virus-related lymphoproliferation in children after liver transplant: role of immunity, diagnosis, and management. Pediatr Transplant 2002; 6: 280–287.
10. Penn I. De novo malignancies in pediatric organ transplant recipients. Pediatr Transplant 1998; 2: 56–63.
11. Cacciarelli TV, Green M, Jaffe R, Mazariegos GV, Jain A, Fung JJ, Reyes J. Management of posttransplant lymphoproliferative disease in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. Transplantation. 1998 Oct 27;66(8):1047-52.
12. Younes BS, McDiarmid SV, Martin MG et al. The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. Transplantation 2000; 70: 94–99.
13. Berg LC, Copenhaver CM, Morrison VA, Gruber SA, Dunn DL, Gajl-Peczalska K, Strickler JG. B-cell lymphoproliferative disorders in solid-organ transplant patients: detection of Epstein-Barr virus by in situ hybridization. Hum Pathol. 1992 Feb;23(2):159-63.
14. Kogan-Liberman D, Burroughs M, Emre S, Moscona A, Shneider BL. The role of quantitative Epstein-Barr virus polymerase chain reaction and preemptive immunosuppression reduction in pediatric liver transplantation: a preliminary experience. J Ped Gastroenterol 2001;33:445 – 449.
15. Arbus GS, Grisaru S, Segal O, Dosch M, Pop M, Lala P, Nutikka A, Lingwood CA. Verotoxin targets lymphoma infiltrates of patients with post-transplant lymphoproliferative disease. Leuk Res. 2000 Oct;24(10):857-64.
16. Roque J, Rios G, Humeres R, Volpi C, Herrera JM, Schultz M, Rios H, Rius M, Salgado C, Hepp J. Early posttransplant lymphoproliferative disease in pediatric liver transplant recipients. Transplant Proc. 2006 Apr;38(3):930-1.
17. Huang RY, Shapiro NL. Adenotonsillar enlargement in pediatric patients following solid organ transplantation. Arch Otolaryngol Head Neck Surg. 2000 Feb;126(2):159-64.
18. Wu JF, Ho MC, Ni YH, Chen HL, Lu CY, Hsu HY, Lee PH, Chang MH. Timing of Epstein-Barr virus acquisition and the course of posttransplantation lymphoproliferative disorder in children. Transplantation. 2009 Mar 15;87(5):758-62.
19. Uribe M, Hunter B, Alba A, Calabrán L, Flores L, Soto P, Herzog C. Posttransplant lymphoproliferative disorder in pediatric liver transplantation. Transplant Proc. 2009 Jul-Aug;41(6):2679-81.
20. Porter CC, Liang X, Gralla J, McGavran L, Albano EA. BCL6 expression correlates with monomorphic histology in children with posttransplantation lymphoproliferative disease. J Pediatr Hematol Oncol. 2008 Sep;30(9):684-8.
21. Gheorghe G, Albano EA, Porter CC, McGavran L, Wei Q, Meltesen L, Danielson SM, Liang X. Posttransplant Hodgkin lymphoma preceded by polymorphic posttransplant lymphoproliferative disorder: report of a pediatric case and review of the literature. J Pediatr Hematol Oncol. 2007 Feb;29(2):112-6.
22. De Diego JI, Prim MP, Hardisson D, Verdaguer JM, Jara P. Post-transplant lymphoproliferative disease in tonsils of children with liver transplantation. Int J Pediatr Otorhinolaryngol. 2001 Apr 27;58(2):113-8.
23. Collins MH, Montone KT, Leahey AM, et al. Post-transplant lymphoproliferative disease in children. Pediatr Transplant. 2001;5:250–257.
24. Kerkar N, Morotti RA, Madan RP, Shneider B, Herold BC, Dugan C, Miloh T, Karabicak I, Strauchen JA, Emre S. The changing face of post-transplant lymphoproliferative disease in the era of molecular EBV monitoring. Pediatr Transplant. 2010 Jun;14(4):504-11. Epub 2010 Jan 7.
25. Djokic M, Le Beau MM, Swinnen LJ, Smith SM, Rubin CM, Anastasi J, Carlson KM. Post-transplant lymphoproliferative disorder subtypes correlate with different recurring chromosomal abnormalities. Genes Chromosomes Cancer. 2006 Mar;45(3):313-8.
26. Allen UD, Farkas G, Hebert D, et al. Risk factors for post-transplant lymphoproliferative disorder in pediatric patients: a case– control study. Pediatr Transplant 2005;9:450-5.
27. Praghakaran K, Wise B, Chen A et al. Rational management of posttransplant lymphoproliferative disorder in pediatric recipients. J Pediatr Surg 1999: 34: 112–116.
28. Norin S, Kimby E, Ericzon BG, Christensson B, Sander B, Söderdahl G, Hägglund H. Post-transplant lymphoma--a single-center experience of 500 liver transplantations. Med Oncol. 2004;21(3):273-84.
29. Jens Martin Rohrbach. EBV-induced polymorphic lymphoproliferative disorder of the iris after heart transplantation. Graefes Arch Clin Exp Ophthalmol. 2004 Jan;242(1):44-50. Epub 2003 Dec 9.
30. Sharon. Increased Levels of Circulating Epstein-Barr Virus (EBV)-Infected Lymphocytes and Decreased EBV Nuclear Antigen Antibody Responses Are Associated With the Development of Posttransplant Lymphoproliferative Disease in Solid-Organ Transplant Recipients
31. Castellano-Sanchez AA, Li S, Qian J, Lagoo A, Weir E, Brat DJ. Primary central nervous system post-transplant lymphoproliferative disorders. Am J Clin Pathol. 2004;121: 246-253.
32. Wilde GE, Moore DJ, Bellah RD. Posttransplantation lymphoproliferative disorder in pediatric recipients of solid organ transplants: timing and location of disease. AJR Am J Roentgenol. 2005 Nov;185(5):1335-41.
33. Dotti G, Fiocchi R, Motta T et al. Lymphoma occurring late after solid organ transplantation: influence of treatment on the clinical outcome. Transplantation, 2002: 74: 1095.
34. Smets F, Vajro P, Cornu G, Reding R, Otte JB, Sokal E. transplant lymphoproliferative disease after liver transplantation. Transplantation 2000;69:982-5.
35. Carpentier L, Tapiero B, Alvarez F, et al. Epstein-Barr virus (EBV) early-antigen serologic testing in conjunction with peripheral blood EBV DNA load as a marker for risk of posttransplantation lymphoproliferative disease. J Infect Dis 2003; 188: 1853.
36. Ifthikharuddin JJ, Mieles LA, Rosenblatt JD, Ryan CK, Sahasrabudhe DM. CD-20 expression in post-transplant lymphoproliferative disorders: treatment with rituximab. Am J Hematol. 2000 Oct;65(2):171-3.
37. 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; 103:748–55.
38. Benkerrou M, Durandy A, Fischer A. Therapy for transplant-related lymphoproliferative disease. Hematol Oncol Clin North Am 1993; 7:467–475.
39. Boscà-Robledo A, Pous-Serrano S, García-Mayor RL, Trilles-Olaso LM. Acute abdomen as the first manifestation of a post-transplant lymphoproliferative disorder. Int J Colorectal Dis. 2011 Aug;26(8):1081-2.
40. Medlicott SA, Devlin S, Helmersen DS, Yilmaz A, Mansoor A. Early post-transplant smooth muscle neoplasia of the colon presenting as diminutive polyps: a case complicating post-transplant lymphoproliferative disorder. Int J Surg Pathol. 2006 Apr;14(2):155-61.
41. Chen W, Huang Q, Zuppan CW, Rowsell EH, Cao JD, Weiss LM, Wang J. Complete absence of KSHV/HHV-8 in posttransplant lymphoproliferative disorders: an immunohistochemical and molecular study of 52 cases. Am J Clin Pathol. 2009 May;131(5):632-9.
42. Orjuela M, Gross TG, Cheung YK, Alobeid B, Morris E, Cairo MS. A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. Clin Cancer Res. 2003 Sep 1;9(10 Pt 2):3945S-52S.
43. McCormack L, Hany TI, Hübner M, Petrowsky H, Mullhaupt B, Knuth A, Stenner F, Clavien PA. How useful is PET/CT imaging in the management of post-transplant lymphoproliferative disease after liver transplantation? Am J Transplant. 2006 Jul;6(7):1731-6.
44. Morrison VA, Dunn DL, Manivel JC, Gajl Peczalska KJ, Peterson BA. Clinical characteristics of post-transplant lymphoproliferative disorders. Am J Med 1994;97:14–24.
45. Gallego S, Llort A, Gros L, Sanchez de Toledo J Jr, Bueno J, Moreno A, Nieto J, Sanchez de Toledo J. Post-transplant lymphoproliferative disorders in children: the role of chemotherapy in the era of rituximab. Pediatr Transplant. 2010 Feb;14(1):61-6.
46. Timuragaoglu A, Ugur-Bilgin A, Colak D, Tuncer M, Gölbasi I, Hazar V, Kiliçarslan B, Undar L, Demirbas A. Posttransplant lymphoproliferative disorders in transplant recipients. Transplant Proc. 2006 Mar;38(2):641-5.
47. Vakiani E, Basso K, Klein U, Mansukhani MM, Narayan G, Smith PM, et al. Genetic and pheno-

typic analysis of B-cell posttransplant lymphoproliferative disorders provides insights into disease biology. Hematol Oncol 2008;26:199–211.

48. Baldanti F, Grossi P, Furione M, Simoncini L, Sarasini A, Comoli P, Maccario R, Fiocchi R, Gerna G. High levels of Epstein-Barr virus DNA in blood of solid-organ transplant recipients and their value in predicting posttransplant lymphoproliferative disorders. J Clin Microbiol. 2000 Feb;38(2):613-9.

49. Comoli P, Labirio M, Basso S, et al. Infusion of autologous Epstein–Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant recipients with evidence of active virus replication. Blood 2002: 99: 2592–2598.

50. Poirel HA, Bernheim A, Schneider A. Characteristic Pattern of Chromosomal Imbalances in Posttransplantation Lymphoproliferative Disorders: Correlation with Histopathological Subcategories and EBV Status. Transplantation 2005; 80(2):176-184.

51. Kenagy DN, Schlesinger Y,Weck K, et al. Epstein-Barr virus DNA in peripheral blood leukocytes of patients with posttransplant lymphoproliferative disease. Transplantation 1995;60:547–54.

52. Mathur RV, Kudesia G, Suvarna K, McKane W. Fulminant post-transplant lymphoproliferative disorder presenting with lactic acidosis and acute liver failure. Nephrol Dial Transplant. 2004 Jul;19(7):1918-20.

53. Doria C, Marino IR, Scott VL, et al. Posttransplant lymphoproliferative disorders presenting at sites of previous surgical intervention. Transplantation 2003; 75: 1066.

54. Johnson LR, Nalesnik MA, Swerdlow SH. Impact of Epstein-Barr virus in monomorphic B-cell posttransplant lymphoproliferative disorders: a histogenetic study. Am J Surg Pathol. 2006 Dec;30(12):1604-12.

55. Dharnidharka VR, Sullivan EK, Stablein DM, Tejani AH, Harmon WE; North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Risk factors for posttransplant lymphoproliferative disorder (PTLD) in pediatric kidney transplantation: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Transplantation. 2001 Apr 27;71(8):1065-8.

56. Guthery SL, Heubi JE, Bucuvalas JC, Gross TG, Ryckman FC, Alonso MH, Balistreri WF, Hornung RW. Determination of risk factors for Epstein-Barr virus-associated posttransplant lymphoproliferative disorder in pediatric liver transplant recipients using objective case ascertainment. Transplantation. 2003 Apr 15;75(7):987-93.

57. Smith JM, Corey L, Healey PJ, Davis CL, McDonald RA. Adolescents are more likely to develop posttransplant lymphoproliferative disorder after primary Epstein-Barr virus infection than younger renal transplant recipients. Transplantation. 2007 Jun 15;83(11):1423-8.

58. Shapiro R, Nalesnik M, McCauley J, Fedorek S, Jordan ML, Scantlebury VP, Jain A, Vivas C, Ellis D, Lombardozzi-Lane S, Randhawa P, Johnston J, Hakala TR, Simmons RL, Fung JJ, Starzl TE. Posttransplant lymphoproliferative disorders in adult and pediatric renal transplant patients receiving tacrolimus-based immunosuppression. Transplantation. 1999 Dec 27;68(12):1851-4.

59. Hayashi RJ, Kraus MD, Patel AL, Canter C, Cohen AH, Hmiel P, Howard T, Huddleston C, Lowell JA, Mallory G Jr, Mendeloff E, Molleston J, Sweet S, DeBaun MR. Posttransplant lymphoproliferative disease in children: correlation of histology to clinical behavior. J Pediatr Hematol Oncol. 2001 Jan;23(1):14-8.