

## The clinical presentation of post-transplant lymphoproliferative disorder (PTLD) following pediatric liver transplantation

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**Abstract: Introduction:** Post-transplant lymphoproliferative disorder is a life-threatening complication of solid organ transplantation. In pediatric recipients, PTLD has been reported in 6.4%-19.5% of lung, heart and heart-lung transplants, 4-15% of liver transplants and 1.2-10.1% of kidney transplants. Although most lymphomas typically occur in lymph nodes, extranodal involvement is also common. The aim of our study was to determine the site and symptoms of PTLD in children who underwent liver transplantation during 2009-2012 in Liver Transplantation Center of Nemazee Hospital. **Material and methods:** This study is a cohort study on existing data of children who received liver transplant between January 2009 and December 2012 at Liver Transplant Center of Nemazee Hospital in Shiraz. During the study period, the PTLD occurrence was assessed in follow up visits, if the diagnosis of PTLD was confirmed the affected patient was entered the study and additional information was obtained. The diagnosis of PTLD was considered in patients with fever of undetermined origin, lymphadenopathy, allograft dysfunction, and pulmonary infiltrates. The data was analyzed using SPSS software ver.18. Statistical descriptive methods, Chi square test, and independent t-test, were used for analyzing the data. P value smaller than 0.05 were considered significant. **Results:** Totally, 203 children undergoing liver transplant surgery were evaluated. The age range of patients was 8 months to 18 years with mean of 8.8±5.6 years old. In our study 17 (8.4%) patients developed PTLD. The mean interval between transplantation and PTLD diagnosis was 8.4 ±5.61 months ranging from 4 to 24 months. A total of five patients (2.5%) died during the follow-up period and all of them were PTLD affected children (29.4% of PTLD patients). Lymph nodes were the most predominant site involved (64.7%), while liver and GI involved in 35.2%. **Conclusion:** The results of this study emphasize the relatively high incidence of PTLD after liver transplantation in children. Because of its impact on patient's outcome and reducing recipient's survival, it is important to minimize this problem by early diagnosis and providing effective treatment.

[Karam-Ali Kasiri, Mohsen Dehghani, Mahmood Haghghat, Mohammad-Hadi Imanieh, Soheila Zareifar, Afsaneh Malekpour Tehrani. **The clinical presentation of post-transplant lymphoproliferative disorder (PTLD) following pediatric liver transplantation.** *Life Sci J* 2014;11(8s):8-11] (ISSN:1097-8135). <http://www.lifesciencesite.com>, 2

**Keywords:** Post-transplant lymphoproliferative disorder, liver transplant, children, clinical presentation.

### Introduction:

Post-transplant lymphoproliferative disorder refers to an uncontrolled proliferation of lymphocytes within the context of immunosuppression after solid organ or bone marrow transplantation (1, 2). PTLD is a major graft and also life-threatening complication of solid organ transplantation that includes a spectrum of disorders ranging from benign hyperplasia to invasive lymphoma(2, 3). Epstein-Barr virus (EBV) is an important factor in the pathogenesis of PTLD. The risk for EBV is thought to result from community contact or transmission of EBV from the donor organ and blood products. Different factors affects the risk of PTLD for an individual recipient: the organ

transplanted, cumulative dose of immunosuppression, and age of recipient(4). PTLD is seen in up to 10% of all solid organ transplant recipients(5). Its incidence is higher in children ranging from 1.2% to 30% depending on the immunosuppressive regimen used and the type of transplanted organ (6). In paediatric recipients, PTLD has been reported in 6.4%-19.5% of lung, heart and heart-lung transplants, 4-15% of liver transplants and 1.2-10.1% of kidney transplants (3). In children PTLD is the most common malignancy after organ transplantation and in adults it is the second most common malignancy after skin cancer (7). In both children and adults PTLD is the most common cause of mortality due to cancer after solid

organ transplantation and its reported overall mortality exceeds 50% (3). According to World Health Organization Classification of Tumors, there are several distinct categories of PTLT: early lesion (Plastic hyperplasia, infectious mononucleosis-like PTLT), polymorphic PTLT, monomorphic PTLT (B and T/NK cell types), and classical Hodgkin lymphoma (1). The clinical presentation of PTLT is very variable. Some patients stay symptomless, in others non specific symptoms such as malaise, fever and weight loss might be appeared. Sometimes the clinical presentation of PTLT can resemble infectious mononucleosis, especially in children (1). Although most lymphomas typically occur in lymph nodes, extranodal involvement is also common. Although any site can be involved, gastrointestinal and CNS involvement are more common (8). PTLT can also involve the allograft itself and rarely can be presented as fever without any localizing features (2). The aim of our study was to determine the site and symptoms of PTLT in children who underwent liver transplantation during 2009-2012 in Liver Transplantation Center of Nemazee Hospital.

#### Material and methods:

This study is a cohort study on existing data of children who received liver transplant between January 2009 and December 2012 at Liver Transplant Center of Nemazee Hospital in Shiraz, the only pediatric liver transplantation in Iran. The proposal of this study was approved in vice chancellor for Research and Technology of Medical University of Shiraz. Written and informed consent was obtained from all patients's parents. Also the confidentiality of information managed carefully by researchers. All the patients who have been referred to this hospital during this three year were entered the study. The Inclusion criteria were the age of less than 18 years and conduction of liver transplantation. The exclusion criteria was death due to post-surgical complications within the first week after transplantation. The patients were referred to this center after necessary examinations by pediatric gastroenterologists. Before transplantation surgery all of the children were evaluated for infections like hepatitis A, B And C, HIV, EBV and CMV. Other evaluations such as ultrasound or computed tomography were done if the child had any related sign or symptoms. During the study period, the PTLT occurrence was assessed in follow up visits, if the diagnosis of PTLT was confirmed the affected patient was entered the study and additional information was obtained. The diagnosis of PTLT was considered in patients with fever of undetermined origin, lymphadenopathy, allograft dysfunction, and pulmonary infiltrates. The diagnosis of PTLT was confirmed by tissue biopsy

according to published criteria (9). The data was analyzed using SPSS software ver.18. Statistical descriptive methods, Chi square test, and independent t-test, were used for analyzing the data, P value smaller than 0.05 were considered significant.

#### Results:

Totally, 203 children undergoing liver transplant surgery were evaluated. The age range of patients was 8 months to 18 years with mean of  $8.8 \pm 5.6$  years old. Eighty-two (40%) patients were female and 121 (60%) were male. The most prevalent underlying diseases that led to liver transplantation were biliary atresia in 29 (14.3%), tyrosinemia in 25 (12.3%), cryptogenic cirrhosis in 25 (12.3%), Crigler-Najjar in 24 (11.8%), PFIC (Progressive Familial Intrahepatic Cholestasis) in 22 (10.8%) and Wilson's disease in 21 (10.3%) children. In our study 17 (8.4%) patients developed PTLT. The mean interval between transplantation and PTLT diagnosis was  $8.4 \pm 5.61$  months ranging from 4 to 24 months. The time of PTLT diagnosis in these seventeen patients were shown in figure 1. Eight PTLT patients (41.7%) were male and nine patients (52.9%) were female, this difference was not statistically significant ( $p$  value = 0.38). A total of five patients (2.5%) died during the follow-up period and all of them were PTLT affected children (29.4% of PTLT patients). Of these five children three (60%) were male and two (40%) were female and the difference between two genders was not significant ( $p$  value: 0.49). The mean time to PTLT diagnosis in expired and alive patients were  $11.40 \pm 7.9$  and  $7.25 \pm 4.1$  months, respectively ( $p$  value: 0.17). The location of PTLT are shown in Table 1. Lymph nodes were the most predominant site involved (64.7%), while liver and GI involved in 35.2%. Of those patients who had expired two (40%) had liver involvement and three other patients (60%) had submandibular lymph node involvement.

#### Discussion:

In our study the incidence of PTLT in liver transplant recipients was 8.4%. The incidence of PTLT has been reported in various studies and its risk depends on the type of organ transplant and the age of recipients. In adult recipients PTLT has been reported to occur in 1-2.8% of liver transplant while the incidence of PTLT is significantly higher in children (10-12). The rate of PTLT in our study is similar to PTLT incidence from other studies ranging from 3.8% to 10.7% in paediatric recipients (3, 13, 14). The incidence of PTLT would be expected to increase with the duration of observation. Although PTLT may happen at any time after transplantation, the risk of PTLT development is highest within the first year and reduces over time

thereafter(3, 15).Our findings is concordant with other studie (12, 13, 16) as most of the PTLT cases (88%) occurred during the first year after liver transplantation, but in one study only one-third of PTLT patients were diagnosed during the first year after transplantation, although it has been reported that this lower rate can be as a cause of underreporting bias especially in early-stage PTLT(6).The mortality rate of PTLT patients in our study was 29.4% that is lower than some other studies that has reported 60% mortality in child recipients.This difference may be as a consequence of improvement in patients care over time and differences in immunosuppressive drugs(13), but our findings is consistent with more recent studies

that has reported the death rate about 25% within the first year after diagnosis of PTLT(17).The majority of PTLT patients in our study had lymph node involvement, liver and GI were the second frequent site involved.In other studies the lymph node and liver were the most affected sites and other organs included bowel, lung, kidney, mediastinum, bone marrow and CNS(3, 12, 13).The results of this study emphasizes the relatively high incidence of PTLT after liver transplantation in children.Because of its impact on patients outcome and reducing recipients survival, it is important to minimize this problem by early diagnosis and providing effective treatment.

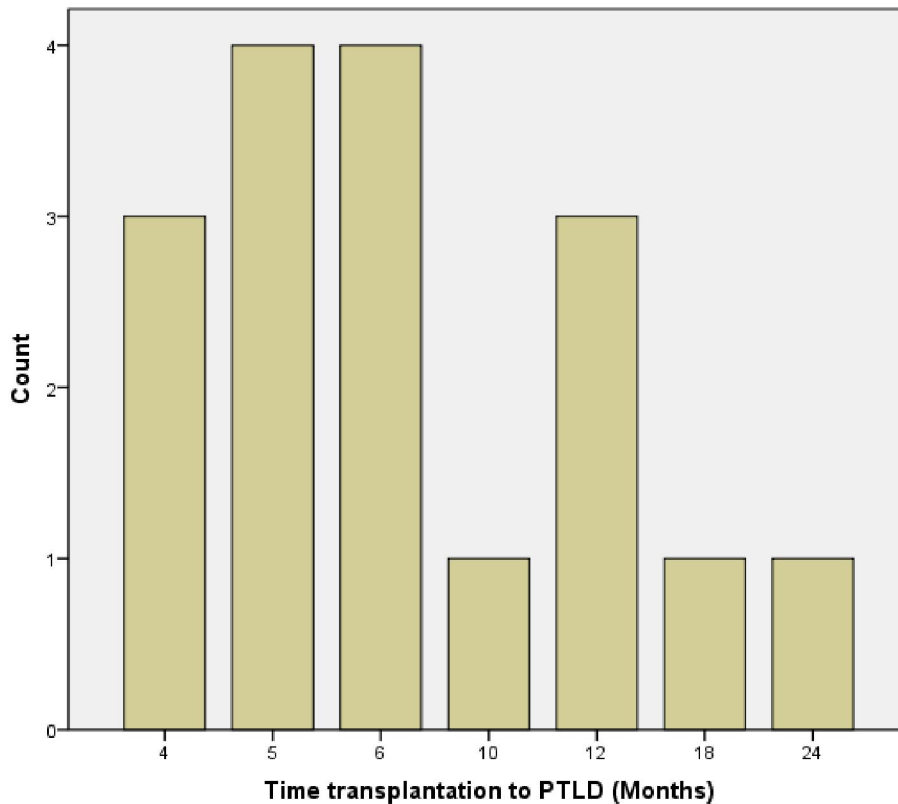


Figure 1. Interval between transplantation and PTLT diagnosis.

Table1. Location of PTLT involvement.

Location	Frequency	Percent
Lymph node:		
Submandibular	9	52.9
Para aortic	1	5.9
Auxillary	1	5.9
Liver	3	17.6
GI	3	17.6
Total	17	100

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4/24/2014