

A single-center experience of post-transplant lymphoproliferative disorder (PTLD) cases after pediatric liver transplantation: Incidence, outcomes, and association with food allergy

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ABSTRACT

Background/Aims: We evaluated our 16-year single-center experience of pediatric post-transplant lymphoproliferative disorder (PTLD) cases who underwent liver transplantation between 2001 and 2017.

Materials and Methods: Of the 236 pediatric patients who underwent liver transplantation between 2001 and 2017, the clinical and laboratory data of eight patients diagnosed with PTLD were reviewed. The pre-transplant Epstein-Barr virus (EBV) status of 172 patients was also recorded.

Results: The total incidence of PTLD was 3.4%. The incidence of PTLD was 10% in pre-transplant EBV immunoglobulin G (IgG)-seronegative patients and 0.8% in pre-transplant EBV IgG-seropositive patients. The mean age of the patients at liver transplantation was 2.71±3.21 years, and four patients were aged below 1 year at the time of transplantation. PTLD was diagnosed at 21.81±18.1 months after transplantation. The primary site of involvement was variable among patients: peripheral and mediastinal lymph nodes, stomach and intestine, transplanted graft, bone marrow, and nasopharynx. The eosinophil count varied greatly among patients, with a mean value of 524.62±679/mm³. Three patients had a food allergy and were administered an elimination diet at the time of PTLD diagnosis. Six patients had PTLD of B-cell origin. One patient died due to neutropenic sepsis during chemotherapy, whereas seven patients were followed up in full remission for 7.75±4 years.

Conclusion: PTLD is a life-threatening complication of solid-organ transplantation with a heterogeneous clinical spectrum. Food allergy had a close association with PTLD. A close follow-up of patients with risk factors and an early diagnosis with appropriate treatment may lead to a better outcome.

Keywords: Post-transplant lymphoproliferative disease, liver transplantation, EBV, food allergy

INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) is a significant complication of pediatric solid-organ transplantation, with a reported incidence of 6%-20% and a mortality rate of 12%-60% (1-3). The development of PTLD is associated with discordance between immunosuppression and immune reaction. The risk of graft rejection has decreased with the use of potent immunosuppressants; however, the impairment of T-cell functions can increase the risk for PTLD (4). Most pediatric PTLD cases are associated with

Epstein-Barr virus (EBV) infection, and EBV-related PTLD tends to occur in the first 1 to 2 years after transplantation (5,6). The disease has a wide clinical spectrum changing from polyclonal PTLD to lymphoma (5). In this study, we present our 16-year single-center experience of pediatric PTLD cases after liver transplantation.

MATERIALS AND METHODS

Of the 236 pediatric patients who underwent liver transplantation between 2001 and 2017, the clinical and lab-

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oratory data of eight patients diagnosed with PTLD were reviewed. The patient age, gender, primary diagnosis before transplantation, age at transplantation, donor type, and time of PTLD emergence after transplantation were recorded.

PTLD was diagnosed when there was a histopathological confirmation of the lymph node or the involved organ. PTLD was histopathologically classified according to the World Health Organization classification into four groups: early type, polymorphic, monomorphic PTLD, and classical Hodgkin lymphoma. The B- or T-cell origin of the lesions was noted. The EBV association was defined according to EBV-encoded RNA (EBER) in situ hybridization in tissue samples. The EBV viral loads, which were measured by real-time polymerase chain reaction (PCR) of EBV DNA from peripheral blood, were also recorded. The pre-transplant EBV serology was available for 172 of 236 patients. Pediatric patients with negative EBV IgM and IgG levels were recorded as EBV-naïve. Patients were clinically classified as early and late PTLD and as early PTLD occurring within 1 year after transplantation. The primary site of PTLD was also recorded.

Laboratory values at the time of PTLD diagnosis were investigated: serum albumin, lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels, and eosinophil count, and the immunosuppressive drug levels before PTLD diagnosis were noted. Upper gastrointestinal endoscopy and colonoscopy were performed for patients with gastrointestinal symptoms. Postoperative complications like rejection, infection, food allergy, or recurrent surgery after liver transplantation were evaluated. Patients diagnosed with a food allergy were recorded.

All patients, except one, were administered tacrolimus for immunosuppression. Our center's protocol for immunosuppression was as follows: 10 mg/kg prednisolone was administered in theater, then tapered to 1 mg/kg in 1 month, and gradually weaned off in 6 months. Mycophenolate mofetil was administered to all patients at a dose of 20 mg/kg/day for 6 months. Tacrolimus was the main immunosuppressive agent, and our study protocol targeted trough levels of tacrolimus from 10 to 12 ng/mL in the immediate postoperative period, then 6 to 8 ng/mL at 1 month after liver transplantation, and 4 to 6 ng/mL at 1 year after liver transplantation. The treatment for PTLD and prognosis after PTLD were also recorded.

Informed consent was obtained from all patients and their parents; the study was approved by the Ethics Committee of Başkent University.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp.; Armonk, NY, USA).

RESULTS

Of the 236 pediatric patients who underwent liver transplantation between 2001 and 2017, eight patients were diagnosed with PTLD, with an incidence of 3.4%, among which six were male. The mean age of the patients at liver transplantation was 2.71 ± 3.21 years (min-max: 0.5-10 years), and four patients were aged below 1 year at the time of transplantation. All patients received a liver transplant from living related donors. Three patients were diagnosed with biliary atresia, three patients had progressive familial intrahepatic cholestasis (PFIC), one patient had hepatoblastoma, and one patient had cryptogenic cirrhosis. PTLD was diagnosed at 21.81 ± 18.1 months after transplantation (min-max: 4-57 months). Since 2010, only two cases have been diagnosed with PTLD. The primary diagnosis and demographic characteristics of the patients are shown in Table 1.

The presenting symptoms were cervical lymph node enlargement in three patients, abdominal pain and diarrhea in two patients, cough in one patient, and treatment-resistant nasal stuffiness in one patient. Two patients were diagnosed during routine abdominal ultrasonography screening. Some patients had multiple symptoms. The primary site of involvement was variable among patients: two patients had peripheral lymph node involvement; two patients had gastrointestinal PTLD; two patients had graft PTLD, one of whom also had bone marrow involvement; one patient had a nasopharyngeal tumor; and the remaining patient had a mediastinal mass.

The laboratory values of the patients at the time of presentation were as follows: The mean CRP level was 52.98 ± 32.52 mg/dL (min-max: 0.8-86 mg/dL), and the mean albumin level was 2.95 ± 0.75 g/dL (min-max: 2.1-4 g/dL). Patients with gastrointestinal and peripheral lymph node involvements had initial albumin levels <3 g/dL, whereas other patients had initial albumin levels >3 g/dL. The eosinophil count varied greatly among patients, with a mean value of $524.62 \pm 679/\text{mm}^3$ (min-max: 22-1800/ mm^3), and the highest values occurred in two patients with peripheral lymph node involvement and one patient with gastrointestinal involvement. Three patients had a food allergy and were administered an elimination diet around the time of PTLD diagnosis. Patients were diagnosed according to the positivity of specific IgEs in blood or skin prick test or eosinophilia in the gastrointestinal

Table 1. Univariate analysis for risk factors of mortality in cirrhotic patients with UGIB

Case No.	Primary diagnosis	Gender	Age at transplantation (years)	Donor	Time of PTLD diagnosis after liver transplantation (months)
1	Biliary atresia	F	0.5	Father	4.5
2	Biliary atresia	M	0.75	Mother	11
3	PFIC	F	10	Elder sister	39
4	Hepatoblastoma	M	3	Grandfather	22
5	Cryptogenic cirrhosis	M	4	Mother	4
6	PFIC	M	0.8	Uncle	57
7	PFIC	M	2.16	Uncle	17
8	Biliary atresia	M	0.5	Mother	20

PFIC: progressive familial intrahepatic cholestasis

epithelium and cessation of symptoms after receiving the elimination diet. Patient no.2 had a milk protein and wheat allergy; patient no.6 had an egg allergy; and patient no.8 had multiple food allergies including milk, egg, red meat, poultry, wheat, and lentil.

Tacrolimus levels vary among patients due to patient compliance and drug interactions. The highest tacrolimus levels occurred in two patients who underwent transplantation in 2006 and one noncompliant patient who underwent transplantation in 2014. The mean trough level of tacrolimus in our patients was 12.42 ± 6.48 ng/mL (min-max: 5.1-22 ng/mL). One patient was on sirolimus and mycophenolate mofetil treatment at the time of PTLD diagnosis, with a trough level of sirolimus as 4.6 ng/mL. This patient had intractable epilepsy and was intolerant to calcineurin inhibitors.

The pre-transplant EBV status of 236 patients who underwent liver transplantation between 2001 and 2017 was evaluated; 172 patients had a pre-transplant EBV serology. Fifty-five patients (32%) were reported as EBV-naïve, whereas 117 (68%) patients were negative for EBV IgM and positive for EBV IgG. Seven patients with PTLD had a pre-transplant EBV serology. Six patients were EBV-naïve before liver transplantation and negative for EBV IgM and EBV IgG. One patient with PTLD occurring in the graft (liver) was negative for EBV IgM and positive for EBV IgG before transplantation. The incidence of PTLD among EBV-naïve patients was 10% (6 of 55 patients), whereas the incidence of PTLD among patients who had positive pre-transplant EBV IgG was 0.8% (1 of 117 patients) ($p < 0.001$).

The EBV PCR status of seven patients at the time of PTLD diagnosis was evaluated. Two patients were EBV PCR-negative, whereas five patients were EBV PCR-positive. The mean EBV PCR viral load values were $283, 900 \pm 219, 886$ copy/mL (min-max: 11,500-560 000 copy/mL). The EBV PCR value was unavailable for one patient who was serologically EBV-naïve at the time of PTLD diagnosis. The laboratory values and PTLD type of our patients are given in Table 2.

Immunosuppressive drug doses were tapered in all patients as a part of the PTLD treatment. Four patients with B-cell PTLD were administered intravenous ganciclovir for 2 to 3 weeks or oral valganciclovir for 3 months.

Six patients had lymphoproliferative disease of B-cell origin (B-cell PTLD), with a positive CD20 expression on lymphocytes. In all of these patients, the EBV viral load was high, and EBER was positive at histopathological examination. Three patients with B-cell disease had been accepted in the polyclonal lymphoproliferation phase and treated with two to four doses of rituximab. The other three patients showed monoclonal proliferation and were in the lymphoma phase. In these patients, a modified OEPA-C chemotherapy regimen (prednisolone, etoposide, vincristine, doxorubicin, and cyclophosphamide) for immunosuppressed patients was used in three to six courses. Patient no.3 and no. 4 had T-cell PTLD; one was in a polyclonal phase and the other was in a monoclonal phase. Modified BFM-90 (prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, 6-mercaptopurine, and methotrexate) and modified OEPA-C regimens were administered to each patient re-

Table 2. Laboratory values and post-transplant lymphoproliferative disease (PTLD) type of our patients

Case No.	Involved site	PTLD type	Preoperative EBV status	EBV PCR at the time of PTLD diagnosis (copy/mL)	Albumin level (g/dL)	Eosinophil count (%) (/mm ³)	Tacrolimus level (ng/mL)	PTLD treatment	Prognosis	Follow-up period after PTLD (year)
1	Peripheral lymph node	B cell, monoclonal, EBER+	Naive	440 000	2.3	1380 (14.4%)	14.7	Rituximab (4 doses) IVIg (2 doses) Gancyclovir IV, 3 weeks	Remission	10
2	Stomach and intestine	B cell, monoclonal, EBER+	Naive	560 000	2.42	240 (2.33%)	22	Modified OEPA-C chemotherapy (3 courses) Valgancyclovir, po, 3 months	Remission	10.75
3	Liver + solid mass at portal hilus	T cell, polyclonal, EBER-	EBV IgM-, IgG+	150 000	4	22 (0.39%)	4.6 (sirolimus level, ng/mL)	Modified OEPA-C chemotherapy (4 courses) Radiotherapy	Remission	10.75
4	Mediastinal lymph nodes	T cell, monoclonal, EBER unavailable	Unavailable	negative	3.57	50 (1%)	8 BFM-90 modified	BFM-90 modified chemotherapy	Exitus due to neutropenic sepsis	0.16
5	Nasopharynx	B cell, monoclonal, EBER+	Naive	Unavailable	3	78 (1.26%)	8.8	Rituximab (4 doses) Modified OEPA-C chemotherapy (4 courses)	Remission	6.5
6	Stomach and intestine (colon)	B cell, polyclonal, EBER+	Naive	11 500	2.4	1800 (34%)	8.6	Rituximab (2 doses) Gancyclovir IV, 2 weeks	Remission	4
7	Liver + bone marrow	B cell, monoclonal, EBER+	Naive	negative	3.82	210 (1.49%)	5.1	Modified OEPA-C chemotherapy (6 courses)	Remission	11.3
8	Peripheric lymph node	B cell, polyclonal, EBER+	Naive	258 000	2.1	417 (12%)	19.8	Rituximab (3 doses) Gancyclovir IV, 3 weeks	Remission	1

EBV: Epstein-Barr virus; PTLD: post-transplant lymphoproliferative disease; EBV Naive: EBV IgM-, IgG-; EBER: EBV-encoded RNA; Modified OEPA-C: Prednisolone, Etoposide, Vincristine, Doxorubicin, Cyclophosphamide; BFM-90 modified: Prednisone, Vincristine, Daunorubicin, L-Asparaginase, Cyclophosphamide, Cytarabine, 6-Mercaptopurine, Methotrexate; IV: intravenous; IVIG: intravenous immunoglobulin

spectively. Conformal 3D radiotherapy was also administered to the latter patient who partially responded to chemotherapy.

One patient with B-cell gastrointestinal PTLD developed an inflammatory myofibroblastic tumor in the lung tissue during follow-up and underwent lung surgery.

The patient who underwent liver transplantation due to hepatoblastoma and had polyclonal T-cell disease in his mediastinum had died due to neutropenic sepsis during chemotherapy in the second month of the PTLD treatment. The other seven patients were followed up in full remission for 7.75±4 years (min-max: 1-11.3 years). There was no graft loss due to PTLD treatment. The PTLD type,

treatment, and the prognosis of the patients are shown in Table 2.

Postoperative complications other than PTLD after liver transplantation in these seven patients were as follows: acute rejection (1), food allergy (3), hepatic artery and portal vein thrombosis with bile duct stenosis (1), tacrolimus-associated cardiac hypertrophy (1), and diaphragmatic hernia (1).

DISCUSSION

In our study, the first pediatric PTLD case was experienced in 2005, with a total incidence of PTLD after liver transplantation as 3.4%, which is lower than the incidence of PTLD reported in the literature (1). Six of the eight patients with PTLD underwent transplantation before 2010. We observed a further reduction in PTLD cases in subsequent years. A decrease in the incidence of PTLD in recent years was also reported by different transplant centers (1-3). A preference of lower trough levels of tacrolimus in the recent years, full awareness of PTLD signs and symptoms, close monitoring of the EBV viral load, and adjustment of immunosuppressant blood levels accordingly may lead to a decrease in the incidence of PTLD worldwide and also at our center (1,7).

In our PTLD case series, three patients had biliary atresia and three had PFIC, all of whom (except one) underwent liver transplantation at <2.5 years of age confirming that younger age at the time of solid-organ transplantation is a significant risk factor for PTLD. One of the reasons for young age being a risk factor is that most young patients are EBV-naïve at the time of liver transplantation, and they usually receive a graft from an EBV seropositive donor (8). Six patients in our PTLD case series were EBV-naïve at the time of liver transplantation, and these patients (except one) were aged below 2.5 years.

Older donor age increases the risk of PTLD (1). Because liver transplants and partial grafts from living donors were used in all of our patients, the donor age was older than that for cadaveric transplants, leading to a higher risk of EBV-positive donors for younger EBV-naïve recipients.

Approximately 70% to 80% of PTLD cases are EBV-related (4,5,8). PTLD related to EBV infection is most common within the first 2 years after liver transplantation, and non-EBV-related PTLD tends to occur later (6). Similarly, in our series, the incidence of PTLD was 10% in pre-transplant EBV-naïve patients and 0.8% in pre-transplant EBV seropositive patients. Additionally, most of our patients

were diagnosed with EBV-driven B-cell PTLD. PTLD of T-cell origin (T-cell PTLD) constitutes 10% of the cases in the literature (3,9). However, in our series, 25% of patients had T-cell PTLD, which may be biased due to a low patient number.

Hypoalbuminemia and eosinophilia are important laboratory findings that may indicate PTLD (2). In our series particularly patients with lymph node and gastrointestinal involvement presented with these features.

Monitoring the EBV viral loads for early detection of PTLD is controversial (1,7,10,11). Some centers experience a decrease in the incidence of PTLD after monitoring the EBV viral load and reducing immunosuppression upon recognition of high-titer EBV of over 10,000 copies/mL (7). At our center, we did not perform routine EBV PCR screening in EBV-negative patients at the post-transplantation period. Instead of using this technique, we preferred observing patients at risk for PTLD such as recipient EBV-negative and donor EBV-positive cases, young infants, and patients who had clinical and laboratory signs indicating the development of PTLD. We hardly attempted to avoid very high tacrolimus levels and also closely monitored the immunosuppressive drug levels in patients and families with drug adjustment and noncompliance problems.

Extranodal disease is commonly prevalent (75%-80%), but solid-organ grafts may also be involved in 15%-30% of PTLD cases (1,4). Consistent with the literature, our two patients had liver graft involvement at our center. Patients with organ involvement required more intense treatment compared with those with peripheral lymph node involvement. This may be related to early diagnosis in nodal disease, as peripheral lymph nodes can be easily recognized with physical examination. Symptoms like chronic cough or nasal obstruction and difficulty in breathing necessitate prompt and early evaluation to exclude lymph node enlargement in the mediastinum or nasopharynx. Many studies have shown that early diagnosis and early intervention with appropriate treatment leads to a better outcome (1,7,12). Similarly, Jeong et al. (7) have reported that rituximab therapy and reduction of immunosuppressive drug treatment were sufficient to induce remission in early recognized, localized, and polyclonal benign lesions. Nevertheless, in our series, three monoclonal B-cell and two T-cell originated cases had received chemotherapy and experienced its complications. In fact, one patient was lost to follow-up due to death because of neutropenic sepsis during the chemotherapy

course. As a result, careful examination of patients, close follow-up of patients particularly with risk factors, and detection of eosinophilia or hypoalbuminemia and inconsistent calcineurin drug levels may lead to early diagnosis of PTLD and enable us to take some precautions.

Giraldi et al. (9) applied a risk protocol in which FCD-R blocks (fludarabine, cyclophosphamide, doxorubicin, and rituximab) were used for polymorphic and non-Burkitt-like lymphomas, and a BFM-based program was used for Burkitt-like lymphomas; they also suggested to include rituximab as an initial therapy, decreasing immunosuppression together with surgical resection in case of fully resectable masses in children. They also recommended discontinuation of immunosuppressive drugs together with rituximab and chemotherapy in high-risk patients. In this study, the disease-free survival was 94% and 75% in 1 and 5 years, respectively.

In our study, approximately 50% of patients with PTLD could be treated with immunosuppressive drug reduction and rituximab therapy. In resistant cases, a low-dose cyclophosphamide with prednisolone and rituximab may result in high response rates. Radiotherapy and a more intensive chemotherapy were restricted to patients with refractory or recurrent cases. Although ganciclovir does not have any inhibitory effect in vivo, it has a theoretical advantage on EBV replication, and thus an oral or intravenous ganciclovir/acyclovir was administered in more than half of our patients. Interestingly, three of eight PTLD cases (37.5%) had a food allergy. Food allergies are commonly observed in young patients, particularly those aged below 3 years after liver transplantation, possibly due to immature gastrointestinal and immune systems (13-15). Additionally, tacrolimus plays an important role in gastrointestinal immunotolerance by increasing the intestinal permeability and exposing the body to more allergens (16). The incidence of food allergy was 19.2% in pediatric patients who underwent liver transplantation at our center (unpublished data). Although the incidence of food allergy was higher in our patients who received liver transplants than in the general population, we observed a further increase in the frequency of food allergy in patients with EBV viremia in this study (17). We further observed that the incidence of food allergy was high as 37.5% in PTLD cases. This may be explained by several reasons. First, most of our patients with PTLD are aged below 3 years, which may lead to a relative increase in food allergy. Second, high tacrolimus levels might lead to the formation of both PTLD and disturbance in immunotolerance. Third, increased eosinophilia may further sup-

port the coexistence of immune dysregulation and food intolerance in patients with PTLD.

The limitations of our study are due to its retrospective design and small patient cohort. Further large-scale multi-center studies are required for proper investigation of the association between PTLD, EBV, and food allergy.

PTLD is a life-threatening complication of solid-organ transplantation with a heterogeneous clinical spectrum. Transplant clinicians should be aware of the subtle or overt symptoms of this disease and take precautions in early phases. A close follow-up of patients with risk factors and an early diagnosis with appropriate treatment may lead to a good outcome. In summary, we emphasized the strong association between PTLD and food allergies after liver transplantation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Başkent University.

Informed Consent: Written informed consent was obtained from all patients and their parents who participated in this study.

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