Post-Transplant Lymphoproliferative Disorder – Case Reports of Three Children with Kidney Transplant

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SUMMARY

Introduction Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous group of diseases, characterized by abnormal lymphoid proliferation following transplantation. It is a disease of the immunosuppressed state, and its occurrence is mostly associated with the use of T-cell depleting agents, and also intensification of immunosuppressive regimens. In the majority of cases, PTLD is a consequence of Epstein-Barr virus (EBV) infection and is a B-cell hyperplasia with CD-20 positive lymphocytes. The 2008 World Health Organization classification for lymphoid malignancies divides PTLD into four major categories: early lesions, polymorphic PTLD, monomorphic PTLD and Hodgkin PTLD. The treatment and prognosis depend on histology. The cornerstone of PTLD therapy includes reduction/withdrawal of immunosuppression, monoclonal anti CD-20 antibody (rituximab) and chemotherapy.

Outline of Cases We reported here our experiences with three patients, two girls aged 7.5 and 15 and a 16-year old boy. They had different organ involvement: brain, combined spleen-liver and intestines, respectively. Even though EBV was a trigger of lymphoid proliferation as it was confirmed by histopathology or in cerebrospinal fluid, qualitative EBV-PCR was positive only in one patient at disease presentation. Reduction of immunosuppression therapy was applied in treatment of all three patients, while two of them received rituximab and ganciclovir. They had an excellent outcome besides many difficulties in diagnosis and management of disease.

Conclusion Qualitative EBV-PCR is not useful marker in pediatric transplant recipients. Our suggestion is that patients with the risk factors like T-cell depleting agents, immunosuppressant protocol or increasing immunosuppressive therapy and EBV miss-match with donor must be more accurately monitored with quantitative EBV PCR.

Keywords: post-transplant lymphoproliferative disorder; Epstein-Barr virus; PCR; pediatric renal transplantation

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is the most-common neoplasm amongst pediatric transplant recipients, accounting for 52% of all malignancies in this group [1].The incidence of PTLD varies depending on the type of organ transplanted and have been reported in 2.6-9% of all pediatric renal transplant recipients, with malignancy developed in 1.5% [2, 3]. The majority of PTLD is B-cell derived and frequently associated with the Epstein-Barr virus (EBV) infection [4], although some T-cell derived cases have been reported [5]. The risk varies by the intensity and duration of immunosuppressive therapy and is 30-70 times higher in the EBV-naive recipient [6]. The spectrum of PTLD ranges from lymphoid hyperplasia and infective mononucleosis-like disease to highly malignant lymphoma. The 2008 World Health Organization classification for lymphoid malignancies [7] divides PTLD into four major categories: early lesions, polymorphic PTLD, monomorphic PTLD and Hodgkin PTLD. The usual treatment for this condition includes reduction or withdrawal of immunosuppression therapy, antiviral treatment, anti-CD20 monoclonal antibody (rituximab) and in resistant cases chemotherapy [8]. This report has presented the outcome of various PTLD organ involvement in 3 children, after kidney transplantation, during period of 10 years (June 2001 – June 2010).

CASE REPORTS

Patients' characteristics, applied immunosuppression treatment, imaging and histopathology findings were shown in Table 1. Applied therapy and patient's outcome were shown in Table 2.

Patient 1

A girl with primary diagnosis of congenital nephrotic syndrome underwent a living related renal transplantation from her father when she was 3 years old. Since she had transplantation in another Center, her and donor's EBV sero status were unknown. Her initial immuno-

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Table 1. Patient's characteristics, pre-PTLD immunosuppression, presentation of PTLD, imagining and histopathology findings

Parameter	Patient		
	1	2	3
Age (years)	7.5	15	16
Gender	Female	Female	Male
Primary disease	Congenital nephrotic Sy	Sy Frasier	Polycystic kidney disease
PTLD onset post tx (months)	48	9	12
EBV mismatch (D-/R+)	NA	Yes	Yes
HCV infection	No	No	Yes
ATG induction	No	Yes	No
Immunosuppression	MMF, CSA	MMF, CSA	MMF, TAC, SRL
High CNI levels	No	No	Yes
Immunosuppression intensifications/ acute rejection episodes	Yes/No	No/No	Yes/Yes
Initial presentation	Right-sided hemiparesis	Liver and spleen ultrasound changes	Fever, weight loss, melena, ileus
PCR EBV (at onset/follow up)	-/+	+/+	-/+
Imaging	CNS multifocal lesions	Liver and spleen multifocal lesions	Liver multifocal changes, hilum spleen lymphadenopathy
Intraoperative findings and PH	/	PH: Diffuse non-Hodgkin lymphoma of large, CD20+ cells	Multiple small bowel perforation PH: diffuse non-Hodgkin lymphoma of large cells, CD20+, CD79a +, Ki67 + (70% of tumor cells nuclei)

PTLD – post-transplant lymphoproliferative disorder; EBV – Epstein-Barr virus; D – donor; R – recipient; NA – not available; HCV – hepatitis C virus; ATG – anti thymocyte globulin; MMF – mycophenolate mofetil; CSA – cyclosporine A; TAC – tacrolimus; SRL – sirolimus/rapamycin; CNI – calcineurin inhibitors; PCR – polymerase chain reaction; CNS – central nervous system; PH – histopathology findings

Table 2. Applied therapy and outcome

Parameter	Patient		
	1	2	3
Ganciclovir	Yes	Yes	No
IVIG	No	Yes	Yes
Immunosuppresion withdrawal (except prednisone)	No, only reduction	Yes	Yes
Rituximab	No	Yes, V cycles	Yes, VI cycles
Therapy response	After 1 year almost complete remission	After 8 months complete remission	After 4 months complete regression with mild hilum spleen lymphadenopathy
Current therapy	Prednisone, AZA, SRL	Prednisone, SRL (after 1 year and 9 months)	Prednisone, SRL (after 1 year)
Outcome (year)	Remission (7)	Remission (6.5)	Remission (5)
Creatinine (μmol/l)	550	128	121
GFR (ml/min/1.73m2)	15	56	84

IVIG – intravenous immunoglobulin; AZA – azathioprine; SRL – sirolimus/rapamicin; GFR – glomerular filtration rate

suppression included prednisone, cyclosporine A (CSA) and azathioprine (AZA). NV did well almost 4 years after transplant, aside from reflux at her ureterocystoneostomy and subsequent repeated urinary tract infection with mild graft dysfunction. Three years after transplantation, AZA was replaced by MMF (mycophenolate mofetil). Four years after transplantation, she presented with sudden onset of right-sided hemiparesis. Endocranial MRI showed multiple lesions in white matter (left parietal-temporal lobe, cerebellar peduncles, pons, Figure 1). Cerebrospinal fluid (CSF) cytology revealed 2% of blasts in 36 leukocytes/ mm^3. Oligoclonal IgG bounds were also found in CSF with EBV IgG 1:1280 positivity. An EBV-PCR in CSF and serum were obtained and no virus was detectable with this qualitative method. Brain biopsy was refused by parents. The following infections were excluded: HIV, mycobacterium tuberculosis, toxoplasmosis, rubella, morbilli, and mycoplasma. Since no precise diagnosis was made, and

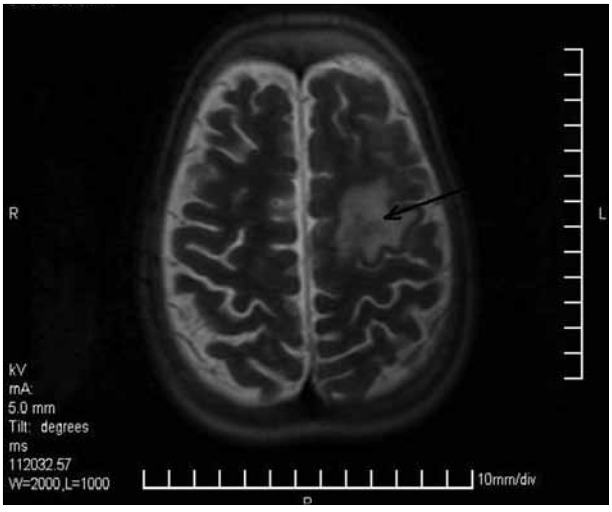

Figure 1. Endocranial lesion in the white matter marked with an arrow (patient 1)

PTLD was highly suspected, MMF and CSA were reduced and ganciclovir and dexamethasone were administered for a month. After 1 month of Ganciclovir, it was replaced by Acyclovir given orally for 6 months. Following 4.5 months, CSA was switched to sirolimus (SRL), and MMF to AZA. Two weeks later, endocranial lesions were in significant regression with normal neurological status. In a year period, almost complete regression was noted, apart from only mild linear lesions in pons. It has been 11 years after the transplantation and 7 years after high suspicion on PTLD. There is no evidence of disease recurrence, but she has advanced graft failure.

Patient 2

A girl was referred to our clinic for kidney transplant evaluation at the age of 14.5. At the age of 3.5, she was diagnosed with nephrotic syndrome (focal segmental glomerulosclerosis). Karyotype was 46 XY and genetic analyses revealed WT1 mutation in intron 9 (T->C at position +2), which confirmed diagnosis of syndrome Frasier. Eight months of hemodialysis treatment was finalized with the kidney transplantation (donor - mother) at the age of 15. The induction therapy included antithymocyte globulin, corticosteroids, MMF and CSA. There were EBV missmatch findings (recipient-negative and donor positive). Eight months upon transplantation, the patient had only one episode of fever, lasting for two days. Physical examination and laboratory findings were completely normal. Abdominal ultrasound revealed multifocal hypoechogenic changes in liver and spleen. Computed tomography (CT scan) showed diffuse focuses of changed liver and spleen tissue in length up to 4.5 cm (Figure 2). After liver biopsy, histopathological examination confirmed diffuse large cell B lymphoma (CD 20 positive, moderate risk). Qualitative PCR for EBV was positive. The patient was treated with intravenous ganciclovir for two months. CSA and MMF were reduced gradually within two weeks, up to their complete discontinuation. At the same time, prednisone was increased up to 0.3 mg/kg per day. Seven weeks from initiating ganciclovir therapy, the patient was treated with rituximab (375 mg/m^2 per dose) weekly for five courses. Eight months after the initiation of rituximab, CT scan revealed normal findings. Therapy with sirolimus was introduced for 1 year and 9 months after diagnosing PTLD. After 6 years and 10 months from diagnosing PTLD, the patient is without evidence of B-cell lymphoma and her graft function is stable.

Patient 3

A boy with primary diagnosis of polycystic kidney disease was transplanted at his age of 15 (graft donor was his mother). At the time of transplantation, the recipient was Epstein-Barr virus (EBV-) sero-negative and the donor was sero-positive (EBV+). Induction immunosuppressive therapy included steroids, CSA and MMF.

Eleven months after transplantation, the patient presented with fever, dehydration, leucopenia, anemia and worsening of graft function. The etiology for his fever was unknown. Two months later he developed significant gastrointestinal symptomatology: epigastric pain, dysphagia and melena. Esophagogastroduodenoscopy revealed gastroesophageal reflux, grade II. Due to increasing abdominal pain, the patient underwent exploratory laparotomy, and multiple perforations of distal ileum were identified. Pathological examination demonstrated a diffuse large B-cell lymphoma (CD 20 positive). Initial qualitative EBV PCR method was negative and became positive in the further course of disease. Following PTLD diagnosis, the patient's immunosuppression therapy was withdrawn and he was treated with six cycles of rituximab (375 mg/m^2 per dose). First dose of rituximab cycle was administered two weeks after the surgery. Seven days after the first dose, he developed profuse intestinal hemorrhage, which progressed to hypovolemic shock. Abdominal ultrasound showed multiple small hypoechogenic focuses (up to 3 mm) in liver, and massive splenic hilum lymphadenopathy (up to 64 mm, Figure 3). Six weeks after the surgery, the patient developed pseudomonas aeruginosa septic shock, with multi organ system failure (MOSF). He was treated with broad-spec-

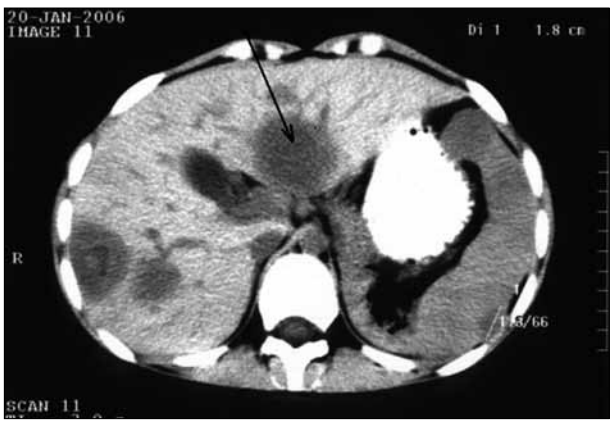

Figure 2. Multiple liver lesions, the largest one marked with an arrow (patient 2)

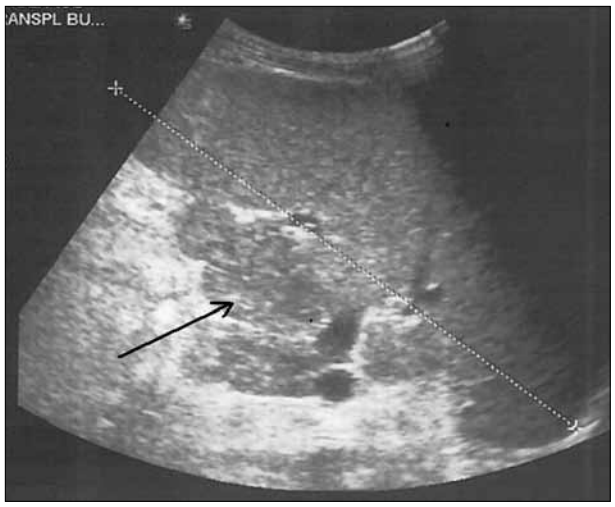

Figure 3. Spleen ultrasound: hilum lymphadenopathy marked with an arrow (patient 3)

trum antibiotics, dopamine and other supportive therapy. The patient was on mechanical ventilation for additional seven days, and due to anuric renal failure, continuous hemodiafiltration was performed during this period. He also underwent successful resuscitation due to cardiac arrest. Total parenteral nutrition was applied for two months. After completing VI cycles of rituximab, abdominal ultrasound showed disappearance of previous spleen lesions as well as significant regression of lymphadenopathy (up to 15 mm). Sirolimus was introduced after 1.5 year from PTLD diagnosis. At the time of the patient's latest control, it was 6 years after transplantation and 5 years after PTLD diagnosis. The patient was in complete remission with stable graft function.

DISCUSSION

The development of PTLD is one of the most lethal complications of solid organ transplantation. The variability of incidence of PTLD is related to the type of solid organ transplanted, adult versus pediatric recipients and the immunosuppressant protocol. The highest incidence of PTLD has been reported after intestinal transplant (20%), followed by lung transplant (15%), liver transplants (5%-10%) and heart transplants (6%). The lowest incidence is found in 2%-3% of kidney transplant recipients [9]. Previous studies (in 1990s) from pediatric kidney transplant centers reported the mortality rate of 48%. More recent single center series and prospective trials data suggested better prognosis. In a recent large study of 92 patients with PTLD, the survival rate was 84.7% at 5 years [10]. Clinically, PTLD most commonly involves lymphoid tissue such as cervical or mesenteric lymph nodes, tonsils and adenoids [11]. Like in our patients' series, PTLD can involve other organs including lungs, central nervous system, gastrointestinal tract, liver and spleen. Great majority of PTLD cases are associated with EBV infection (80%-90%), but this is not the only risk factor of PTLD development. In addition, CMV seronegativity increases the PTLD risk due to cross-reactivity of the EBV and CMV antibodies. Younger children are usually considered to be at higher risk than adolescents [9] which may be attributed to EBV serostatus at transplantation. In a large pediatric cohort, complete HLA-DR miss-match between graft and recipient was significantly associated with more frequent PTLD development [12]. Moreover, the immunosuppressive regimen with tacrolimus (TAC) vs CSA and induction therapy with anti-T-cell antibodies were associated with an increased risk of PTLD [13]. Additional risk factors have been suggested including: male sex, white race, and simultaneous hepatitis C infection (like in patient 3 from our data). Histological evaluation of the tissue involved is necessary to differentiate PTLD from the acute cellular rejection as well as for prognosis and therapy. Early lesions and polymorphic PTLD (WHO 2008) are not classical malignant lymphoma. Most monomorphic PTLD are of B cell origin with diffuse large B cell lymphoma being the most frequent subtype in children [9]. CD 20 expression (patients 2 and 3 in our series) is associated with good prognosis. Monomorphic T cell-PTLD and Burkitt or Burkitt-like PTLD are markers of poor prognosis. Other inferior prognostic markers are: age (older children), patients with late PTLD onset (>1 year after transplantation), patients with elevated LDH, with bone marrow or CNS involvement and those that are non-responders to first line therapy [9]. Elevated levels of EBV DNA were correlated with PTLD in several quantitative assays [14, 15]. In our case series, only one patient had initially positive qualitative EBV-PCR (Table 1). The development of quantitative PCR technique has significantly improved the specificity for PTLD and may serve as an early marker in high-risk patients. Frequent monitoring with this technique and treatment with reduction of immunosuppression therapy, coupled with anti-viral therapy have been reported to reduce the incidence of PTLD in pediatric liver transplant patients from 10% to 5% when compared with the historical controls [16]. It is very important to note that one of our patients (patient 2) was almost asymptomatic, no other symptoms were manifested except two days of moderate fever. This underlines that transplanted patient need very careful and detailed clinical, laboratory and imaging examination. To date, there has been no standard evidence-based treatment of PTLD. The universal first maneuver in over 90% of cases is reduction of immunosuppression. This alone can lead to complete remission in subfraction of cases [17], like in patients with early lesions and polymorphic proliferations. In PTLD cases with overt malignant transformation/lymphoma, rituximab alone or in combination with chemotherapy should also be administrated [6]. Our two patients with histology findings of diffuse large B cell lymphoma (monomorphic) and CD20 + cells were treated successfully with rituximab, despite late diagnosis and severe septic shock in case 3. Considering transplanted children with abdominal pain, like in our third case, intestinal biopsies should be thoroughly investigated in order to exclude initial PTLD. Although the reduction of immunosuppression, immunotherapy (rituximab) and surgery, well described as first line therapy regimen [18] led to tumor elimination, the clinical course with ileum perforation in our patient was a life-threatening event. Similar to Green et al. [19], new perforation of the intestine in our patient was associated with the onset of septic shock as PTLD lesions resolved on this site. It is very interesting to note that the acute clinical deterioration may be sequel of improvement as well as of progression. Besides two confirmed PTLD cases, a girl with highly suspected CNS PTLD has been in stable remission over 7 years. Very important finding in her CSF which is consistent with the most probable PTLD diagnosis is high EBV IgG titer (1:1280). We suppose that she had benign lymphoproliferation, since she was successfully treated only with ganciclovir and reduction of immunosuppression. Before kidney transplantation, all our patients presented here received T-cell depleting agents or immunosuppression intensification, and two of them had confirmed EBV miss match. So, they were in a very high risk group where their EBV status had to be checked regularly with more precise method-quantitative EBV PCR. With this method

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we could reduce on time their immunosuppression and prevent EBV replication.

In conclusion, our cases with confirmed PTLD and follow-up data suggested that combination of immunosuppression reduction and rituximab without chemotherapy results in a high rate of long term remission. This therapy is safe and effective for EBV related PTLD, taking into consideration that early recognition of disease is very important. Qualitative EBV-PCR method is not proved as a reliable marker for diagnosis and follow-up of patients with PTLD. Besides positive outcomes in described patients/cases, we would like to stress the following: the attending physician must pay attention to more accurate PTLD diagnosis, which implies monitoring of high risk patients with quantitative PCR EBV methods.

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Посттрансплантациона лимфопролиферативна болест – приказ три детета са пресађеним бубрегом

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КРАТАК САДРЖАЈ

Увод Посттрансплантациона лимфопролиферативна болест (енгл. *post-transplant lymphoproliferative disorder – PTLD*) је хетерогена група болести коју одликује поремећена лимфоидна пролиферација после трансплантације. Ова болест се јавља у стањима имуносупресије, а њена појава је углавном удружена с применом анти-Т-лимфоцитних лекова и интензивирањем имуносупресивне терапије. Код већине болесника *PTLD* је последица инфекције Епстин–Бар вирусом (*Epstein–Barr virus – EBV*) и хиперплазије Б-лимфоцита позитивних на *CD-20*. Према новој класификацији малигнитета лимфног ткива, Светска здравствена организација је 2008. године поделила *PTLD* у четири главне групе: ране лезије, полиморфни, мономорфни и *PTLD* типа Хочкиновог лимфома. Лечење ових болесника и даља прогноза битно зависе од хистолошке слике. Лечење укључује смањење или потпуно обустављање примене имуносупресивне терапије, затим примену моноклонских анти-*CD-20* антитела (ритуксимаб) и хемиотерапије.

Прикази болесника Приказујемо три болесника са дијагнозом *PTLD*: две девојчице узраста од седам и по и петнаест година и шеснаестогодишњег дечака. Они су имали различите локализације болести: млађа девојчица вишеструке лезије мождане масе, старија истовремену лезију јетре и слезине, а дечак лезију танког црева. Иако је *EBV* окидач лимфоидне пролиферације, која је потврђена било патохистолошки, било у цереброспиналном ликвору, налаз квалитативне *EBV-PCR* методе је био позитиван само код једног болесника на почетку обољења. У лечењу сва три болесника примењивано је смањење имуносупресивне терапије, а код два детета ритуксимаб и ганцикловир. Болесници су имали одличан исход и поред бројних потешкоћа како у дијагностици, тако и у лечењу.

Закључак Квалитативна *EBV-PCR* метода није поуздан показатељ у клиничком праћењу деце с пресађеним бубрегом. Сматрамо да се болесници код којих се установе фактори ризика за развој *PTLD* морају много чешће надгледати применом квантитативне *EBV-PCR* методе.

Кључне речи: посттрансплантациона лимфопролиферативна болест; Епстин–Бар (*Epstein–Barr*) вирус; *PCR*; трансплантација бубрега код деце

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