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Early Detection of Post-transplant Lymphoproliferative Disorder by Head and Neck Manifestations

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Abstract:

Introduction: Post-transplant lymphoproliferative disease (PTLD) is a collection of conditions associated with abnormal proliferation of lymphoid tissues in patients after solid organ transplants (SOT). Its clinical presentations are quite variable and non-specific. Otolaryngological signs and symptoms, manifested as adenotonsillar hypertrophy or cervical lymphadenopathy, may guide to early detection and treatment.

Methods: We conducted a retrospective review of all pediatric SOT recipients with the diagnosis of PTLD, age 0 -18, between 2005 and 2014 at the Loma Linda University Children's Hospital. The patient's age, type of organ transplant, immunosuppression, head and neck signs and symptoms, imaging modality, EBV status, histology as well as treatment regimen information were recorded.

Results: A total of 21 pediatric patients were included in this retrospective review with a history of solid organ transplant and a diagnosis of PTLD. The most commonly associated type of transplanted organ is heart (57.1%), followed by kidneys (33.3%) and liver (9.5%). Neck swelling (28.6%) was the main head and neck complaint while one patient developed upper airway obstruction with respiratory distress. Cervical lymphadenopathy was found in 66.7% and tonsillar hypertrophy in 9.5% of the patients. Monomorphic PTLD (46.2%) was the most common pathological diagnosis, followed by reactive hyperplasia (30.8%), Hodgkin lymphoma (15.4%) and polymorphic PTLD (7.7%). Majority of the PTLD patients were treated with rituximab and cyclophosphamide combination therapy with and without prednisone.

Conclusion: Adenotonsillectomy and cervical lymph node biopsies are easy to perform with low complication rates. They serve an important role in the armamentarium in the early detection of PTLD in its early stage, allowing prompt treatment and prevention of further progression.

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Introduction:

As the success of solid organ transplantation (SOT) has increased over the years, more chronic diseases as a result of vigorous post-transplant immunosuppression have emerged. It has been noted that post SOT transplant pediatric patients carry up to 45-fold increase in malignancy compared to general population without SOT as a result of the decreased immunological function and surveillance[1].

Post-transplant lymphoproliferative disease (PTLD) is a collection of conditions associated with abnormal proliferation of lymphoid tissues in this particular population. PTLD-related mortality has been reported up to 60%[2]. Primary Epstein-Barr Virus (EBV) infection has been identified as a significant risk factor in the development in PTLD[3]. Approximately 90% of adult population worldwide has been infected with the ubiquitous EBV virus[4-5]. In an immune-competent host, the initial infection in childhood with the EBV virus leads a T cell predominant response to prevent proliferation of the EBV infected B cells. Patients may present with asymptomatic sero-conversion or with infectious mononucleosis syndrome with fever, sore throat, lymphadenopathy and hepatosplenomegaly[6]. However, in the case of an immunosuppressed host, such as in the post-transplant patients, the proliferation of EBV infected B cells becomes unhindered, leading to a spectrum of lymphoproliferative disorders[6].

The incidence of PTLD varies from 1% to 20%, depending on the type of transplanted organ, age of patient, pre-transplant EBV status, type and dose of immunosuppression used[2]. In a large transplant registry, PTLD incidence in children was found to be twice to an adult cohort[7]. The pediatric population is more susceptible to PTLD due to multitude of factors[6-8]. First, due to younger age, they are more likely to be sero-negative at the time of transplantation with a greater risk of acquiring primary EBV infection afterward[6]. Second, they have a higher T cell levels and require more powerful post-transplant immunosuppression to prevent rejection[6]. As a result, the T cell response needed to fight EBV infection becomes more dampened[6].

The manifestations of PTLD are quite non-specific, such as fever, poor appetite, weight loss, irritability, and diarrhea[9]. In the head and neck region, PTLD often presents from asymptomatic enlargement of the adenoids and tonsils in the Waldeyer ring to upper airway obstruction[9]. Diffuse cervical lymphadenopathy is also a common otolaryngological presentation. Early recognition of such manifestations may lead to earlier treatment and prevention of further progression of PTLD.

Our objective is to share our retrospective investigation for PTLD in the pediatric population in the past 10 years, focusing on otolarygological manifestations and evaluating the relationship between SOT and pathohistology of PTLD for this potentially fatal disease.

Methods:

We conducted a retrospective review of all pediatric SOT recipients with the diagnosis of PTLD, age 0-18, between 2005 and 2014 at the Loma Linda University Children's Hospital. These patients were diagnosed based on clinical presentations as well as either in-house or outside pathologies. After obtaining medical institutional review board approval, data used in this study was collected from patient's charts and electronic medical databases. The patient's age, sex, types of organ transplant, immunosuppression, head and neck signs and symptoms, EBV status, pathology as well as treatment regimen information were recorded.

Results:

A total of 21 pediatric patients were included in this retrospective investigation with a history of solid organ transplant and a diagnosis of PTLD (Table 1). The age

at presentation range from 1 to 17 with the average age being 10 years old. Two-thirds of these patients were male. The most commonly associated type of transplanted organ was heart (61.9%), followed by kidney (23.8%) and liver (9.5%). EBV serology was recorded in 19 of the 21 patients. Among those tested, EBV was 100% positive. Neck swelling (28.6%) was the main head and neck complaint while one patient developed upper airway obstruction with respiratory distress. Other otolaryngological symptoms included high fevers, nasal congestion, rhinorrhea, fatigue, and bifrontal headaches (Table 2). On physical examination, 18 out of 21 patients presented with cervical lymphadenopathy and 4 with tonsillar hypertrophy. One patient had both neck and tonsillar manifestations. Positron emission tomography with CT was the most commonly used imaging modality while many patients also underwent CT scan of neck, chest and/or abdomen to evaluate for other lesions of PTLD. Tonsillectomy and cervical lymph node biopsy were performed for histopathological examination in 15 of the 21 patients while the remaining 6 patients received pathological confirmation from an outside institution. Lymphoma was the predominant pathology (80%), only 3 patients had reactive lymphocytic hyperplasia. Among the lymphoma subgroup, monomorphic PTLD was most common (83.3%). At our institution, immunosuppression was withheld in all patients. Majority was treated with cyclophosphamide, rituximab and prednisone combination therapy. One patient received R-CHOP combination (rituximab, cyclophosphamide, doxorubixin, vincristine, and prednisone). One patient underwent chemotherapy with procarbazine, bleomycin, vincristine, and prednisone. Three patients were put on prolonged antiviral therapy, either gancyclovir or valcyclovir. Two patients underwent intravenous immunoglobulin therapy to boost the immune response.

Table 1: Patient characteristics with pathological classification

Case #	Age	Sex	SOT	PTLD site	Pathology
1	2	M	Heart	Neck	lymphoma
2	3	M	Heart	Neck	lymphoma (Burkitt)
3	5	M	Heart	Neck	lymphoma (monomorphic B cell)
4	10	M	Heart	Neck	lymphoma(monomorhpinic B cell, Hodgekin's)
5	12	M	Heart	Neck	lymphoma (malignant anaplastic)
6	13	M	Heart	Neck	lymphoma (Burkitt)
7	15	M	Heart	Neck	lymphoma (TNK cell)
8	17	M	Heart	Neck	reactive hyperplasia (B cell)
9	17	M	Heart	Neck	lymphoma (diffuse large B cell)
10	5	M	Renal	Neck	lymphoma (monomorphic B cell/Burkitt)
11	15	M	Renal	Neck	outside pathology
12	16	M	Renal	Neck	reactive hyperplasia
13	17	M	Renal	Neck	lymphoma (diffused large B cell)
14	2	M	Liver	tonsil	reactive hyperplasia
15	1	F	Liver	Neck	outside pathology
16	3	F	Heart	tonsil	outside pathology
17	12	F	Heart	Neck	lymphoma (pre-B cell hodgkin's)
18	13	F	Heart	Neck	lymphoma (polymorphic B cell, low grade)
19	14	F	Heart	Neck and Tonsil	PTLD from right neck biopsy (outside path unavailable)
20	9	F	Renal	tonsil	outside pathology
21	10	F	Renal	Neck	PTLD outside path

Discussion:

PTLD is a well-known serious complication of immunosuppression in the SOT recipients. It is defined by the World Health Organization (WHO) as " a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in a recipient of a solid organ or bone marrow allograft[10]." Primary EBV infection in the post-transplant population was thought to be one of the main risk factors as well as the inciting event in the development of PTLD[4, 11]. In PTLD patients

Table 2: Otolaryngological signs and symptoms of PTLD

Otolaryngological Symptoms of PTLD
Neck swelling
Respiratory distress
High fevers
Nasal congestion
Rhinorrhea
Fatigue
Bifrontal headaches
Otolaryngological Signs of PTLD
Cervical lymphadenopathy
Tonsillar hypertrophy

in the first year after transplant, Docetti et al. has reported more than 90% of these patients with positive EBV genome[12]. In our study, all 19 patients whose EBV viral loads were recorded had elevated levels at the time of presentation.

The type of organ transplant is also a risk factor in development of PTLD. The incidence of PTLD has been reported to vary between 5% and 15% in the cardiac and liver transplants and even higher in intestinal transplants while representing only about 1-3% in the renal transplant recipients[8]. In our study, the higher incidence of PTLD in cardiac transplants may be related to the higher doses of immunosuppressive drugs that are used to prevent rejection in cardiac and pulmonary transplant patients. The aggressive T cell suppression needed in this group more would lead to decreased T cell mediated response against B cells infected with EBV, resulting in uncontrolled EBV-infected lymphocyte proliferation[9].

Generally, head and neck manifestations of PTLD occur at an earlier stage of the disease progression; routine close monitoring of the lymphoid tissues in this region may lead to earlier diagnosis and therefore treatment of PTLD as demonstrated in the Lones et al experience[13]. In another study, Herrman el al found that 39% of heart transplant patients and 25% of lung transplant patients developed PTLD presenting in the head and neck. Adenotonsillar hypertrophy or cervical lymphadenopathy are the most often seen presentation in the cardiac transplant group with sinonasal cavity as the most common site of head and neck PTLD in pulmonary transplant patients[14]. These otolaryngological manifestations are very similar to those of pediatric Hodgkin's lymphoma patients, namely asymptomatic cervical and supraclavicular lymphadenopathy with or without systemic constitutional symptoms (i.e. fever, night sweat, and weight loss)[15].

In the current study, many of our patients complained of snoring, neck swelling, sleep apnea, and/or airway obstruction. Upon comprehensive head and neck examination, majority of the patients were found to have cervical lymphadenopathy (85.7%) with only 4 patients with tonsillar hypertrophy compared to other reports with tonsillar hypertrophy being the most common manifestation[6, 13-14].

Nonetheless, we suggest that thorough examination of cervical lymph nodes and lingual tonsils on routine follow up visits may lead to early diagnosis of lymphoid hypertrophy in post-SOT patients.

WHO classifies PTLD into four categories: early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgekin's lymphoma-type PTLD[10]. PTLD is hypothesized to progress along a clinic-pathological spectrum based on cytogenetic alterations[10, 16]. In the

initial stage, benign B cell hyperplasia with intact follicular architecture is the predominant pathological finding[10]. These early lesions are more likely to spontaneously regress or regress with reduction in immunosuppression only[10]. They also more frequently involve tonsils, adenoids or cervical lymph nodes[10]. If the disease is allowed to progress, multiple organs may be involved with diffuse polyclonal B cell proliferation and changes of the microscopic lymphoid architecture[6, 10].

It is crucial to start aggressive treatment at this stage due to the rapid progression with potential mortality. Reduction of the immunosuppression is needed to restore T cell response against EBV infected B cell proliferation as much as the patient can tolerate without fulminant rejection. Surgical excision of the proliferating lymphoid tissues is also part of the treatment. Continued, uncontrolled EBV-infected B cell proliferation will eventually lead to the final stage of PTLD. At this stage, genetic mutations of the oncogenes cause irreversible changes of the B cell clone with malignant transformation of monoclonal B cell lymphoma, requiring systemic chemotherapy[6].

In our study, only 20% of the patients were diagnosed with early lesions of PTLD while the majority presented with later stages of lymphoma PTLD. Therefore, most patients required systemic chemotherapy.

One of the limitations of our study is its retrospective nature. Without prospective data collection and categorization, some of the patient charts were incomplete and follow-up was variable. The overall number of included patients was also low due to the low incidence of PTLD. Future prospective, randomized control studies comparing clinical otolaryngological manifestation of PTLD with surveillance imaging studies in pediatric SOT patients will further assist in earlier detection and management of this disease.

5. **Conclusion**:

PTLD is a recognized complication of immunosuppression in the post-transplant pediatric population. Head and neck PTLD with adenotonsillar hypertrophy and cervical lymphadenopathy help early detection of the disease in its early stage, allowing prompt treatment and prevention of further progression.

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