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Post-transplant lymphoproliferative disorder with supraglottic involvement

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Abstract. *Post-transplant lymphoproliferative disorder with supraglottic involvement. Objective*: Transplant patients with primary Epstein-Barr virus (EBV) infection may develop post-transplant lymphoproliferative disorder (PTLD). Since many infants are seronegative at the time of transplantation, PTLD is a major concern for paediatric transplant centres. First manifestations of PTLD are frequently observed in the ENT area with adenoidal and/or tonsillar involvement.
Design: Retrospective study of two cases of PTLD with confirmed supraglottic involvement, their management and outcome. Only patients with pathologically and immunologically demonstrated B-cell proliferation were diagnosed as PTLD.
Result: Two infants developed an acute stridor during PTLD respectively 8 and 10 months after orthotopic liver transplantation (OLT). These infants were seronegative for EBV at the time of transplantation. IgM anti-EBV and/or detection of EBV genome by polymerase chain reaction were positive. Laryngeal examination revealed hypopharyngeal and/or supraglottic mucosal hyperplasia. Immunostaining of laryngeal biopsy was positive for latent membrane protein-1 (LMP1). Patients were treated by a reduction in immunosuppression as far as tolerated with the intent to recover natural immune response by the patient over the proliferation of EBV-infected cells.
Complete remission of PTLD was observed in these two cases.
Conclusion: Tonsillar hypertrophy and adenoid enlargement are the most encountered features of PTLD in OLT occurring in the ENT area. Acute stridor with supraglottic involvement may also be observed in PTLD and must be promptly diagnosed as the prognosis of this disorder is related to rapid reduction in immunosuppression and consequently to the recovering of a natural immune response against the EBV infection.

Introduction

With the growing number of powerful immunosuppressive medications available, it is important to recognize that these drugs predispose transplant patients to the risk of opportunistic infections. The most common post-transplant viral infection is herpesvirus, including cytomegalovirus and Epstein-Barr virus.[1]

Although EBV infections are often asymptomatic after transplantation, it can cause a potentially lethal post-transplant lymphoproliferative disorder (PTLD), which ranges from uncomplicated post-transplant infectious mononucleosis, benign polyclonal polymorphic B-cell hyperplasia, early malignant transformation in polyclonal polymorphic B-cell lymphoma and, finally, to monoclonal polymorphic B-cell lymphoma.[2]

EBV seronegativity prior to transplantation may lead to a primary infection afterwards and is thus considered as a risk factor for PTLD development. Younger age at the time of transplantation and liver vs. renal transplant are also risk factors for PTLD.[3] Since many infants are EBV seronegative at the moment of transplantation; PTLD is a major concern for paediatric transplant centres.

The first manifestation of PTLD in children is most frequently observed in the ENT area, in which Waldeyer's ring is the most common site of involvement.[4-7]

We will present 2 cases of PTLD in children following orthotopic liver transplantation (OLT) with supraglottic involvement.

Their symptomatology, diagnosis and therapeutical approach will be discussed emphasizing the importance of rapid diagnosis and management in order to reduce morbidity and mortality of PTLD.

Materials and methods

This study is a retrospective analysis of two patients treated for PTLD with supraglottic involvement after OLT. The transplantation and PTLD were treated at Saint-Luc University Hospital, Brussels, Belgium at which approximately 600 OLT were already performed until now.

The charts were reviewed for gender of the patient, age at time

of transplantation, reason for transplantation, immunosuppressive therapy, EBV-status before OLT and at PTLD, delay between OLT and PTLD, localisation and additional sites of PTLD, pathological classification, treatment and outcome.

Post transplant immunosuppressive agents included cyclosporine, prednisolone and azathioprine and, most recently, tacrolimus used instead of cyclosporine.

Serum anti-EBV IgG and IgM levels were obtained before OLT, every two weeks during the first three months after OLT and then monthly for nine months. A real-time polymerase chain reaction test to quantitatively detect EBV genome viral sequences in circulating lymphocytes was performed according to the same follow-up. A specific enzyme-linked immunospot assay to quantify the anti-EBV specific T-cell immunity was performed as often as possible and according to the clinic.[8]

Diagnosis of primary EBV infection included detection of IgM anti- EBV and or detection of EBV genome by polymerase chain reaction. When PTLD was suspected clinically, these tests were repeated and further biochemical and histologic investigation were performed. Biochemical investigations included assessment of monoclonal or oligoclonal IgG or IgM production and absolute B-cell count. Bone marrow aspiration was performed in case of an abnormal peripheral blood cell count.

All patients underwent direct laryngoscopy with biopsies taken of the suspected lymphoid tissue. Also one cervical palpable lymph node was taken for biopsy (case report 2). Immunostaining was performed for EBV latent membrane protein-1 (LMP-1) and lymphocyte B CD20 marker. Only patients with pathologically and immunologically demonstrated B-cell proliferation were diagnosed as PTLD. Classification was made according to the recommendations of the Society for Hepatopathology Workshop[9] published in 1999.

Patients were treated by a reduction in immunosuppression as far as tolerated.

Patients with positive immunostaining for CD20 received anti-CD20 antibodies.

Complete remission was established when all signs of lymphoproliferation had disappeared and when liver function tests were normal. Remission was considered partial whenever persistent lymphoid masses were detected.

Results

Retrospective review revealed that two patients showed supraglottic involvement with PTLD after OLT. The first patient (G.N.) presented a congenital biliary atresia and underwent liver transplantation at the age of 8 months. EBV status before OLT was negative. She had an asymptomatic primary EBV infection 2 months after transplantation which was serologically confirmed. Acute stridor was diagnosed 8 months after OLT and fiberoptic examination revealed hypopharyngeal and supraglottic mucosal hypertrophy. Direct laryngeal examination under general anaesthesia was performed and laryngeal biopsy was immunohistologically positive for LMP1. Vocal cords and trachea were preserved. High EBV viral load with low anti-EBV cellular immunity was confirmed by blood examination.

Immunosuppressive agents were reduced with partial resolution. Four months later, an episode of acute tonsillitis was diagnosed which led to rapid tonsillectomy (and adenotomy) under general anaesthesia. Immunochemistry performed on tonsils samples was positive for LMP1.

Pathological classification of the PTLD was polymorphic lymphoproliferative syndrome.

The immunosuppression was decreased and, four months later, a direct laryngeal examination with laryngeal biopsy revealed complete remission of the PTLD (Table 1).

The second patient (B.S.) presented congenital biliary atresia and was transplanted at the age of 10 months. EBV status before OLT was negative. He developed 12 months post-transplant an acute stridor which led to a rapid fiberoptic examination. Laryngeal examination revealed mucosal hypertrophy located in the aryepiglottic folds, in the laryngeal side of the epiglottis and in the ventricular folds. Vocal cords and trachea were preserved. Direct laryngoscopy under general anaesthesia was performed in order to take a biopsy and perform immunochemistry on the tissue sample (Figure 1).

A palpable cervical node was resected for immunochemistry (node level V).

This examination confirmed the extension of PTLD revealed by fiberoptic examination.

Pathological classification of PTLD was a mononucleosis-like syndrome. Immunochemistry for LMP1 and for CD20 was positive. PTLD diagnosis led to a decrease in immunosuppressive agent.

Table 1

Case reports summary

	G.N.	B.S.
Sex	Female	Male
Reason for OLT	Biliary atresia	Biliary atresia
OLT number at institution	1108	1161
Age at OLT	8 months	10 months
Localization of PTLD	Supraglottic area Tonsils (4 months later)	Supraglottic area
Pathological classification	Polymorphic syndrome	Mononucleosis-like syndrome
OLT to PTLD	8 months	12 months
EBV before OLT	Negative	Negative
EBV at PTLD	Seroconversion	Seroconversion
CD20	Not available	Positive
LMP1 in biopsy	Positive	Positive
Treatment	Tonsillectomy Reduction of Immunosuppression	Reduction of Immunosuppression
Evolution	Complete remission	Complete remission

Legend: OLT: Orthotopic Liver Transplantation; EBV: Epstein-Barr Virus; PTLD: Post-Transplant Lymphoproliferative Disorder; LMP1: Latent Membrane Protein-1.

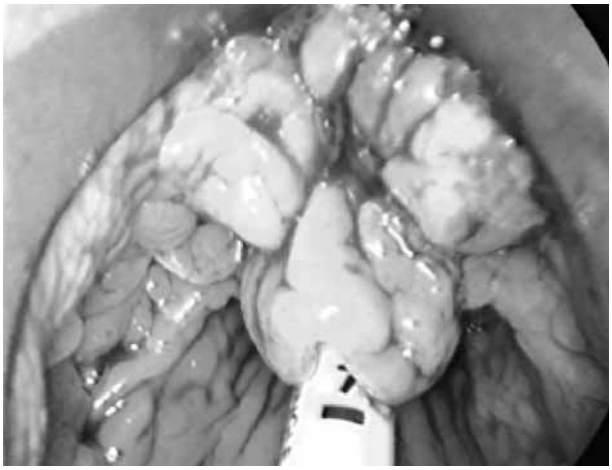

Figure 1

Endoscopic view under general anaesthesia showing supraglottic and hypopharyngeal involvement with PTLD (Case report 2).

Complete remission of PTLD was achieved in this patient with a negative direct laryngeal examination performed 6 months later (Table 1).

Discussion

Post-transplant lymphoproliferative disorder represents a group of abnormal lymphoid proliferations that follow pharmacologic immunosuppression after organ transplantation.

PTLD is associated with primary EBV infection resulting in B-cell proliferation and inadequate T-cell response.[1,8] Early recognition of PTLD is important since mortality of this disease is between 40 and 90% and decreases with rapidity of diagnosis.[1]

PTLD may encompass many different symptoms such as fever, adenopathy, weight loss and nodal hypertrophy. The first symptoms in children with PTLD are often localised in the ENT area and pharyngitis, tonsillitis and cervical adenopathy were frequently observed.[10]

Laryngeal involvement is rare. In our department, only two patients with PTLD experienced an acute stridor due to mucosal hypertrophy located in the supraglottic area. In the literature, only two similar cases have been described.[11,12]

Despite the increased understanding of EBV-related PTLD in solid organ transplant recipients, the optimal management of this potential fatal complication remains controversial.

Reduction of immunosuppressive therapy is now widely accepted as the initial strategy for the treatment of most categories of EBV-related PTLD. The goal of this approach is to allow the host to recover natural immune surveillance and subsequently gain control over the proliferation of EBV–infected cells. Antiviral therapy with Acyclovir is of little interest.

Complete surgical resection is another option. The goal of surgical resection is to reduce the EBV viral load by removing the tonsils for instance. When laryngeal involvement is suspected or demonstrated, this option is of course not suitable. Therefore, PTLD patients with laryngeal involvement and incomplete response to the immunosuppressive agents reduction require an obligatory systemic approach. Immunotherapy with anti-CD20 antibody (Rituximab) has been recently proposed.[13] This monoclonal antibody binds

specifically to the CD20 antigen of normal and malignant B cells and results in antibody- and complement-dependent cytotoxity. Rituximab also induces apoptosis. It has been used with success in adults with PTLD after solid organ transplantation, but only in a few paediatric cases. Before using this agent, antigen expression on tumoral B-cells must be demonstrated. In case of high histopathological classification of PTLD (malignant lesion), chemotherapy and cytotoxic agents must be discussed.

It should also been pointed out that laryngeal involvement in our two patients did not lead to cardiopulmonary resuscitation manoeuvres. Stridor was present at the time of PTLD diagnosis without severe respiratory problems and the airway was not significantly compromised. Mucosal hypertrophy secondary to EBV-related PTLD was mainly demonstrated in the supraglottic area without vocal cords and tracheal involvement. This can be explained by the relative paucity of lymphatic tissue in these two areas compared to the supraglottic area.

Conclusion

Early suspicion and tissue diagnosis remain critical for early therapeutic intervention in PTLD after OLT. As two thirds of PTLD in children present clinical symptoms in the ENT area and facing the increasing number of paediatric transplants, the otorhinolaryngologist should be aware of this complication and should be familiar with its clinical presentation.

Tonsillar hypertrophy and adenoid enlargement are the most frequently encountered features but laryngeal involvement with acute stridor may be present in some cases and represent the first manifestation of PTLD.

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