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Post-transplant lymphoproliferative disease following liver transplantation

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Abstract

Purpose of review—Despite contemporary immunosuppressive regimens, post-transplant lymphoproliferative disease (PTLD) remains a major complication after liver transplantation. This review highlights advances in the understanding of the pathophysiology, diagnosis, and management of PTLD in liver transplant recipients.

Recent findings—The spectrum of PTLD after liver transplant ranges from polymorphic lymphoproliferation to high grade monoclonal lymphoma and is usually related to outgrowth of lymphocytes infected with Epstein-Barr virus (EBV). Risk factors for PTLD include EBV-seronegativity of the recipient, young age, intensity of immunosuppression, and the first year post-transplant. Measurement of EBV load by quantitative polymerase chain reaction assays is an important aid in the surveillance and diagnosis of PTLD although the specificity for PTLD is only about 50% (specificity for EBV is ~100%). In patients diagnosed with PTLD, management options include reduction of immunosuppression, rituximab, combination chemotherapy, and adoptive immunotherapy. Outcomes have improved since rituximab has been incorporated into treatment regimens, and immunotherapy approaches show promise.

Summary—PTLD is a significant complication after liver transplantation, particularly in children. Advances in early detection approaches have aided in the diagnosis and management of PTLD, but further research to identify better predictive biomarkers is needed to improve risk-based treatment strategies.

Keywords

post-transplant lymphoproliferative disease; liver transplantation; Epstein-Barr virus

Introduction

Post-transplant lymphoproliferative disease (PTLD) occurs in immunosuppressed liver transplant recipients due to uncontrolled lymphoproliferation, which is prevented in

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immunocompetent individuals by an Epstein-Barr virus (EBV) specific immune response. The PTLT spectrum ranges from reactive, polyclonal hyperplasia to high-grade monoclonal lymphoma and is usually related to outgrowth of EBV-infected lymphocytes [1]. The incidence of PTLT is increased in individuals receiving intensive immunosuppression. The incidence is also higher in organs with many B-cells, such as small bowel [2]. In liver transplant recipients, PTLT is reported in up to 2.8% of adults and up to 15% of children [3]. Mortality has been reported as high as 50%, although current management strategies appear to result in improved outcomes [4–7]. Here we will review the pathophysiology, risk factors, clinical presentation, and management of PTLT after liver transplantation.

Pathophysiology of PTLT

Although PTLT is heterogeneous, EBV has a critical role in its pathogenesis. Approximately 85% of PTLT is of B-cell origin, and more than 80% of these are associated with EBV [8]. Of the 15% that is of T-cell origin, 30% are associated with EBV [9].

EBV-positive PTLT

EBV is a γ -herpesvirus with the ability to stimulate B-cell proliferation and transformation. In normal individuals, primary lytic EBV infection occurs in the oropharynx and triggers a robust humoral and cellular immune response. After clearance of the primary infection, EBV persists in infected B-lymphocytes, establishing latent infection. Four types of latency exist, differentiated by the EBV antigen expression pattern in infected B-cells. In type 3 latency, six nuclear proteins (EBNA 1-6), two membrane proteins (LMP 1-2), and two EBV-encoded RNAs (EBER 1-2) are expressed, driving B-cell proliferation and memory B-cell expansion. Type 3 latency is highly immunogenic and rarely detected in immunocompetent individuals. In type 2 latency, EBNA 1 and LMP 1-2 are expressed and drive B-cell differentiation into the memory compartments in germinal centers. Upon entering the peripheral circulation, infected memory B-cells downregulate viral proteins. Type 1 latency is associated with expression of only EBNA 1 and is seen in proliferating B-cells. Most infected circulating B-cells express no viral antigens, type 0 latency, and remain invisible to the host immune system. Reactivation to type 3 latency likely occurs periodically but is rapidly controlled by the EBV-specific cytotoxic T-lymphocyte (CTL) response [10–13]. Pharmacologic immunosuppression after transplantation leads to decreased frequency and functional impairment of EBV-specific CTLs [14]. In this setting, EBV-driven lymphoproliferation with type 3 latency may occur and is labeled PTLT, with PTLT depending on the virus to inhibit apoptosis and drive proliferation [12;15*]. However, the progression to PTLT may also require molecular alterations, such as microsatellite instability, DNA hypermethylation, aberrant somatic hypermutation, or alterations of *c-myc*, *bcl-6*, and *p53* [16–18].

EBV-negative PTLT

The mechanism behind the development of EBV-negative PTLT is unclear, but it is usually associated with later onset, monomorphic histology, and aggressive clinical behavior [17;19–21**]. EBV-negative PTLT may be associated with as yet unidentified viral agents or loss of EBV. In the latter hit-and-run scenario, lymphoproliferation initially stimulated by EBV may lead to new mutations over time, including alterations that result in EBV-independent cell replication [22].

Risk Factors for PTLT

Risk factors for PTLT after liver transplant include EBV-seronegativity in the recipient, age ≥ 18 years, degree of immunosuppression, and first year post-transplant [3;4;23–26]. EBV-seronegative patients who receive a transplant from an EBV-seropositive donor are at

particularly high risk, because EBV-infected B-cells in the transplanted organ are invariably introduced into the recipient. The recipient has neither virus-specific antibodies to neutralize infectious virions released by infected B-cells nor virus-specific T-cells to control the outgrowth of subsequently infected recipient B-cells. An increased incidence of PTLD is also seen with intensive immunosuppressive regimens using anti T-cell antibodies such as OKT3 and ATG [4]. It has been suggested that mTOR inhibitors may be associated with decreased incidence of PTLD [27], but clinical studies have been inconclusive, partly due to lack of widespread use [28–30]. Recipients who receive steroids pre-transplant due to immunological disorders may have an increased risk of PTLD [31].

Clinical Presentation of PTLD

The 2008 World Health Organization classification of PTLD includes four categories (Table 1). Early lesions usually occur within one year of transplantation and may have features of reactive plasmacytic hyperplasia or infectious mononucleosis [1]. These EBV-driven lesions are frequently polyclonal, and they are more common in patients who were EBV-seronegative pre-transplant and in younger patients. Polymorphic PTLD, monomorphic PTLD, and classic Hodgkin lymphoma-type PTLD are more likely to be monoclonal and have variable onset after transplantation. Monomorphic B-cell PTLD, particularly diffuse large B-cell lymphoma, is the most common. [1;32;33*]. Monomorphic and monoclonal PTLD may be more aggressive, but histology and clonality do not consistently predict outcome [1].

Post-transplant lymphomas are more likely than general lymphomas to have extranodal involvement, high grade, aggressive clinical behavior, and poor outcomes. Poor prognostic factors for PTLD include high grade, poor performance status, EBV-negativity, and graft involvement [5**]. Symptoms may include fever, lymphadenopathy, weight loss, or splenomegaly. Disease may be localized to one site or to the allograft, or it may present as diffuse disease with multi-organ failure. Bone marrow and central nervous system (CNS) involvement may also occur [21**;24;32;34].

Post-transplant lymphomas in liver transplant recipients have preference for localization to the liver. The Collaborative Transplant Study includes 165 liver transplant recipients with PTLD. Of these, 21.8% had disease localized to the liver, whereas 13.3% demonstrated multifocal disease [4].

Diagnosis of PTLD

Early diagnosis of PTLD is important to facilitate prompt initiation of treatment and prevent evolution to a more aggressive variant. Guidelines for the diagnosis and management of PTLD in adult solid organ transplant recipients were developed by the British Committee for Standards in Haematology and the British Transplantation Society and published in the last year [5**;21**]. Similar guidelines for children have not yet been developed, but the benefits of early diagnosis are illustrated by a recent comparison of PTLD in liver transplant recipients at a single institution during 1993–1997 and 2001–2005. In the latter period, patients had less advanced histological disease at presentation and no deaths, compared to advanced disease and 3 deaths in the earlier era. The difference was ascribed to implementation of molecular EBV monitoring and preemptive reduction in immunosuppression [7].

A high index of suspicion is essential to early detection of PTLD. Measurement of EBV load by quantitative polymerase chain reaction assays is an important aid in surveillance and diagnosis of PTLD. A number of assays that use whole blood, serum, or peripheral blood mononuclear cells (PBMCs) are available but require different interpretation [35]. A virus

load in PBMCs reflects the frequency of virus-infected cells, while a virus load in serum can reflect free virus DNA released by killed infected cells or infectious virions released by productively infected cells. The latter two possibilities can be distinguished by treatment of serum with DNase, which destroys free viral DNA while DNA in virions is protected by the capsid [36]. A high virus load in whole blood may result from any of the three possibilities. Although the frequency of testing EBV load post-transplant has not been established, close monitoring in pediatric transplant recipients during the first year post-transplant is recommended [13^{**};37]. While EBV load is highly sensitive for predicting PTLD, the specificity in liver transplant recipients is only around 50% [5^{**};21^{**}], which may reflect increased numbers of EBV-infected cells with restricted latency in some recipients [38]. Nevertheless, longitudinal monitoring of EBV DNA can help differentiate patients with a persistently elevated but stable EBV load from those with an increasing EBV load. Because of the low specificity of EBV load, there is interest in identifying additional biomarkers for PTLD risk. Alternatives, such as soluble CD30, are being evaluated [39]. Combining assays of T-cell function with viral load may also improve predictive power [40].

A progressively rising EBV DNA load should prompt further investigation for PTLD by physical examination and imaging [13^{**};41]. If clinical suspicion is raised, a low threshold should be used for pursuing tissue biopsy. Excisional biopsy is strongly preferred over needle core biopsy, and fine needle aspiration is inadequate for diagnosis. Tissue should be submitted for EBV analysis (usually EBER in situ hybridization or immunohistochemistry for the LMP1 antigen) and determination of CD20 expression, which are useful in determining treatment options. If PTLD is diagnosed, a comprehensive staging and pre-treatment workup is necessary, including: CT of neck, chest, abdomen/pelvis; evaluation of the transplanted liver; echocardiogram and glomerular filtration rate. Fluorodeoxyglucose-positron emission tomography, particularly when combined with CT, can identify areas infiltrated by lymphoma that have not yet increased in size [24]. Some patients may need bone marrow evaluation, CNS imaging, or lumbar puncture.

Preemptive Therapy for PTLD

The clinical context and the risk of PTLD are important in deciding when to institute preemptive therapy. The intensity of immunosuppression is a modifiable risk factor for PTLD, so reduction of immunosuppression may be considered if a rising EBV load is seen early after transplantation in the setting of high immunosuppression. In 73 pediatric liver transplant patients treated during 2001–2004, the incidence of PTLD was reduced from 16% to 2% by reducing immunosuppression in individuals with a high EBV load. Only one patient developed graft rejection [42]. Clearly, the risk of graft rejection must be considered before reduction in immunosuppression. The liver is a tolerogenic organ, with a low incidence of graft losses from acute or chronic rejection. Reduction of immunosuppression is tolerated better after liver transplant than other solid organ transplants, with withdrawal of immunosuppression possible in selected patients [43].

Antiviral therapy may help prevent PTLD in EBV-seronegative solid organ transplant recipients. These agents can block EBV replication in donor B-cells and infection of recipient B-cells [44–46]. Indeed, prophylactic intravenous ganciclovir after liver transplant in children has been associated with decreased incidence of PTLD [44], perhaps due to reduction in the number of latently-infected B-lymphocytes [10;45]. However, antiviral agents have no effect on the growth of established PTLD when the cells are already transformed.

Treatment of PTLT

Treatment options for established PTLT include reduction of immunosuppression, targeting of B-cells with monoclonal antibodies, or chemotherapy. Surgery may be an option for localized disease. Treatment decisions are based on histology, stage, location, clinical status, graft status, and time after transplant.

Reduction in Immunosuppression

Reduction of immunosuppression can lead to regression of PTLT due to restoration of T-cell functions. Immunosuppression should be decreased to the lowest tolerated levels, which are often 25–50% of the starting dose, depending on concerns for graft rejection. In some patients, reducing immunosuppression alone is sufficient to produce remission, while in others it is used as adjunct treatment. Risk factors for failure of immunosuppression reduction include high lactate dehydrogenase (LDH), organ dysfunction, and multiorgan involvement at diagnosis. In individuals without any of these risk factors, a 90% response rate has been seen with reduction of immunosuppression [47].

The response to reduction in immunosuppression is usually seen within 2–4 weeks and should be assessed by evaluating the change in tumor size, LDH, and EBV load [47]. When immunosuppression cannot be reduced or reduction is inadequate, alternative therapies should be considered early. Early lesions and polymorphic lymphomas often respond well to immunosuppression reduction. Late-onset, monomorphic PTLT is less responsive to immunosuppression reduction and may need rituximab and/or chemotherapy.

Rituximab

Rituximab is a monoclonal antibody against CD20, a B-lymphocyte specific antigen frequently expressed on PTLT. Rituximab monotherapy appears to be effective in the management of selected B-cell, CD20-positive PTLT cases, with remission rates of 44%–65% [48–51]. A multicenter, retrospective analysis suggests that both progression-free and overall survival are significantly improved with early rituximab-based treatment in PTLT [6*]. However, some patients may progress on or after rituximab, necessitating chemotherapy [52].

Chemotherapy

Anthracycline-based chemotherapy for PTLT is effective in achieving long-term disease-free survival, although the benefits must be weighed against potential toxicities. The use of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), with or without rituximab, has response rates of 65–100% with very low rates of graft loss [50;53–55]. Prompt institution of CHOP-based therapy should be used for patients with high-grade lymphoma, inadequate response or progression despite other therapy, or critical organ compromise. Late-onset PTLT outcomes may be better with CHOP-based regimens. A less intensive chemotherapy regimen with cyclophosphamide and prednisone also has excellent response rates, up to 83% in children, and might be considered as an alternative [56;57].

Local Control

In the minority of liver PTLTs that are localized at presentation, surgical resection or radiotherapy may be useful in conjunction with immunosuppression reduction. However, the utility of local control in front-line therapy has not been clearly demonstrated [5**;20]. Surgery and radiation may be helpful in the management of local complications from PTLT, and radiation may be considered for certain disease locations such as orbit or CNS [5**;56]. Primary CNS lymphoma after transplant is very difficult to treat, with mortality up to 88%

[58]. High-dose methotrexate chemotherapy has also shown activity in children with CNS PTLT after liver transplant [59].

Adoptive Immunotherapy

Adoptive immunotherapy with EBV-specific CTLs to restore a cellular immune response to EBV is theoretically an attractive treatment option. Infusions of autologous EBV-specific CTLs generated from peripheral blood of the recipient have been associated with a marked decrease in EBV DNA [60] and have been given without significant toxicity [61]. However, long-term EBV-specific immunity is not sustained in patients, such as solid organ transplant recipients, who continue to receive immunosuppression. The generation of autologous EBV-specific CTLs is also time- and labor-intensive, requires specialized facilities, and is currently available only through investigational trials.

Infusion of partially human leukocyte antigen-matched CTLs derived from a bank of EBV-seropositive donors may allow timely administration of immunotherapy to more patients [62;63]. This approach resulted in a 52% response rate at 6 months in patients who had received solid organ transplant or hematopoietic stem cell transplant [64]. A recent update 4–9 years after CTL infusion showed increased survival among recipients who attained a partial or complete response. Of the 14 patients who achieved an initial complete response, only 1 subsequently died of relapse [65*].

Conclusion

A general strategy for monitoring and treating PTLT is shown in Figure 1. We recommend monitoring of EBV DNA in high-risk liver transplant recipients at 1–2 week intervals. Patients with rising EBV DNA but no signs of PTLT may be considered for preemptive therapy, particularly reduction in immunosuppression. Indeed, a high virus load may be used as a marker of overimmunosuppression [42]. In patients with clinical findings suggestive of PTLT, biopsy should be obtained and staging/pre-treatment studies should be performed. Immunosuppression should be reduced if possible, and further management should be based on histology, stage, location, and performance status. Surgical resection and/or radiotherapy may be considered for localized stage I disease. Patients with clinically low risk B-cell disease may be treated with rituximab monotherapy. Patients with failure to respond to the above measures, high risk disease, or critical organ compromise should urgently be considered for chemotherapy. Clinical trials using EBV-specific CTLs may be considered for these patients if available. Prospective studies are needed to develop prediction models for PTLT risk and improve risk-stratified treatment algorithms for PTLT.

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Key points

- Risk factors for PTLT include EBV-seronegativity of the recipient, young age at transplantation, intensity of immunosuppression, and first year after transplant.
- Measurement of EBV load by quantitative polymerase chain reaction assays is an important aid in the surveillance and diagnosis of PTLT.
- Preemptive therapy, including reduction in immunosuppression and/or antiviral therapy, should be considered in patients at high risk for PTLT.
- PTLT management should be based on the clinical context and the risk profile of the patient and may include reduction in immunosuppression, rituximab, chemotherapy, and/or adoptive immunotherapy

Figure 1.
Monitoring and treatment strategy for PTLD

Table I

WHO classification of PTLD 2008 [1]

Category	Clonality	EBV status
Early lesions (plasmacytic hyperplasia, infectious mononucleosis)	Polyclonal	Always EBV+
Polymorphic PTLD	Monoclonal	Always EBV+
Monomorphic PTLD		
B-cell lymphomas	Monoclonal	Frequently EBV+
T-cell lymphomas	Monoclonal	Rarely EBV+
Classic Hodgkin lymphoma-like PTLD	Monoclonal	Frequently EBV+