REVIEW

Rokshana Shroff · Lesley Rees

The post-transplant lymphoproliferative disorder—a literature review

Abstract The Epstein-Barr virus (EBV)-induced post-transplant lymphoproliferative disorder (PTLD) affects 1%–10% of all paediatric renal transplant recipients. This is a heterogeneous group of conditions characterised by EBV-driven proliferation of B-lymphocytes in the face of impaired T-cell immune surveillance. The risk factors predisposing to PTLD are becoming better understood, but its pathogenesis and myriad of clinical and histological features remain poorly defined. While new treatment modalities are being tried with variable success, regular EBV surveillance and carefully monitored reduction of immunosuppression remain the mainstay of treatment. In this review, we have presented the current knowledge of this increasingly common complication in renal transplant recipients.

Keywords Post-transplant lymphoproliferative disorder · Epstein-Barr virus

Introduction

With the expansion of solid organ transplantation programmes and the use of more-aggressive immunosuppressive drug regimens, there has been an increasing awareness of the risk of post-transplant lymphoproliferative disorder (PTLD). The term PTLD describes a heterogeneous group of lymphoproliferative disorders, and is often loosely used to describe all Epstein-Barr virus (EBV)-related post-transplant problems. The lack of a standard definition, including both clinical and histological parameters, has resulted in a wide variation in its

R. Shroff · L. Rees (✉)
Department of Nephrourology,
Great Ormond Street Hospital for Children,
London, WC1 N 3JH, UK
e-mail: Reesl@gosh.nhs.uk
Tel.: +44-0207-8138346
Fax: +44-0207-8298841

reported incidence. Although the risk factors that predispose a patient to developing PTLD are now better understood, there are several gaps in our understanding of its pathogenesis and clinical course. This review summarizes the current knowledge of post-transplant EBV-related disorders, including the accepted diagnostic and management strategies.

Incidence

PTLD complicates 1%–10% of all renal transplantations [1]. In the paediatric renal transplant population, two large series have reported an incidence of 1.2% [2] and 4.5% [3], respectively. It is the most-common neoplasm amongst paediatric transplant recipients [4], accounting for 52% of all malignancies in this group [5].

The incidence of PTLD varies with the type of solid organ transplanted, with adult versus paediatric transplant recipients, and the immunosuppression regimen used.

Adult versus paediatric transplantation programmes

The incidence of PTLD is 4 times higher in paediatric than adult transplant recipients [6]—presumably because a larger proportion of children are EBV naïve pre transplant. The pre-transplant EBV status is the single most-important, although possibly not the only factor explaining this.

Type of solid organ transplanted

The incidence of PTLD varies with the type of allograft [7], with the highest incidence following intestinal transplant (19%) [8]. PTLD has been reported in 2%–10% of heart transplants [9], 5%–9% of heart-lung transplants [10], and 2%–8% of liver transplants [11]. The reasons for these differences in incidence are not clear, but possibly vary depending on the amount of lymphoid tissue present

in each organ and the immunosuppression regimen used [12].

Risk factors

A seronegative recipient status and the use of potent immunosuppressive agents are the two most-important risk factors that have been implicated in the development of PTLD [2, 3, 13, 14, 15, 16]. The North American Pediatric Renal Transplant Co-operative Study (NAPRTCS), being both multi-centred and longitudinal, provides some very useful epidemiological data on PTLD.

Seronegative recipient status

This is the single most-important risk factor in the development of PTLD. It was first reported in 1988 [13] and has been consistently found in all studies [2, 3, 13, 14, 15, 16]. In one paediatric series, the incidence of PTLD was found to be 25–50 times higher in the EBV-naïve recipient [17]. The relative risk of PTLD in the 1st post-transplant year is about 20-fold higher in EBV-seronegative recipients than in seropositive recipients, and is 200-fold higher than in seronegative healthy individuals [18]. The acquisition of donor EBV is a risk factor for PTLD development in a previously seronegative transplant recipient [19]. In a large series of renal transplant recipients, 86% of paediatric patients who were EBV negative received a kidney from an EBV-positive donor, compared with only 50% of EBV-negative adults who received a seropositive graft [20]. Also, it has been shown that in the transplant recipient primary EBV disease develops later, is more likely to be clinically symptomatic, and is associated with a greater rise in serum creatinine and risk of graft loss than reactivation disease [16]. In one study a pre-transplant EBV-seronegative status was also found to be a significant risk factor for the development of late-onset PTLD [21].

Immunosuppression regimens

PTLD is a disease of the immunosuppressed state. With the use of newer, more-potent immunosuppression, the incidence of PTLD is on the increase [2, 6, 12, 22, 23]. Longitudinal studies evaluating the incidence of PTLD through various immunosuppressive eras have found that there is a trend towards increasing incidence and earlier occurrence of PTLD [2, 15, 24]. Also, PTLD is more often fatal in the setting of intensive immunosuppression [15, 25].

Earlier reports suggested a higher incidence of PTLD with the use of tacrolimus- (13%–20%) compared with cyclosporin- (2%–3%) based immunosuppressive regimens [26, 27]. However, a more-recent report from NAPRTCS has not shown any increased risk with tacrolimus use [28]—increasing experience with the use of this drug and lower targeted therapeutic drug levels possibly account for this improvement [29]. Also, there was no increased risk with the use of mycophenolate mofetil (MMF) or the combined use of tacrolimus and MMF [30]. Currently a large prospective multi-centre case-control study is in progress in the United States, aiming to provide further information on the effects of specific immunosuppressive agents on PTLD development and progress [3].

Simultaneous cytomegalovirus disease

In a group of patients with primary cytomegalovirus (CMV) disease, the post-transplant risk of PTLD was found to be 4- to 6-fold higher [31]. CMV disease can modify EBV replication through the modification of inflammatory cytokines such as tumor necrosis factor-α [13]. In one small study, children with simultaneous CMV and EBV infection had an earlier onset, worse symptoms, and a greater rise in serum creatinine than was seen with primary CMV or primary EBV disease alone [16].

Other factors

A younger age at transplantation, male sex, white race, and simultaneous hepatitis C infection are also potential risk factors described in some studies [2, 29, 32, 33]. The development of PTLD does not appear to have any association with the underlying disease state [2].

Pathogenesis

EBV affects the majority of individuals, but causes little significant disease in a healthy immunocompetent person. In the immunocompromised transplant recipient, the fragile balance between EBV replication and EBV-specific immune surveillance is tipped in favour of uncontrolled viral replication, so that this relatively innocuous infection can progress to a hyperplastic or neoplastic state with significant morbidity and graft loss.

The virus

EBV is a lymphotropic herpes virus that is associated with a number of lymphoid and epithelial cell malignancies [34, 35]. EBV affects the majority of individuals, so that more than 90% of adults have some serological evidence of EBV infection [36]. During initial infection, the major envelope glycoprotein gp350 of the virus interacts with CD21 molecules on the surface of the B-lymphocytes and thus enters the cell [37]. Once the virus has established itself in the host cell nucleus, it will remain in the body in a state of latency for that individual's lifetime [35]. A small number of B-lymphocytes carry the virus in a non-replicative form, with intermittent low-grade viral repli-

cation occurring in the oropharyngeal epithelium from time to time [38]. This latent state is associated with the production of viral proteins, EBNA (Epstein-Barr nuclear antigen) and LMP (latent membrane proteins) [39], which protect the B-cell from apoptosis and allow for ongoing viral replication. In healthy individuals the viral replication is kept in check by a cytotoxic T-cell (CD8+ T-cells) driven EBV-specific immune surveillance [40].

Pathogenesis of PTLD

In the immunosuppressed state, there is an impaired EBV-specific cytotoxic T-cell immune response that allows viral replication [41]. This is manifested by an increased number of virus-carrying B-cells in the circulation and antibodies to the virus lytic cycle antigens [41]. Thus the latently affected cells now undergo lytic replication and ultimately B-cell transformation. In the immunosuppressed state, the cytokine responses are T_H-2 like, allowing an uncontrolled proliferation of the EBV-transformed B-cell clone [42, 43]. This can ultimately lead to hyperplastic or neoplastic PTLD. With solid organ transplants the abnormal B-cells are usually of recipient origin, while with bone marrow transplants the abnormal B-cells are more likely to be of donor origin [12, 44].

Classification of PTLD

Despite two international meetings—the EBV-PTLD Task Force Meeting and the Mayo Clinic International Consensus Development Meeting on EBV-PTLD—no standard classification system has been proposed, with ensuing confusion in reporting and comparing incidence, management strategies, and outcome. In most reports all post-transplant EBV-related events are included under PTLD. These have been grouped into three main categories [12, 13, 45, 46] based on their clinical and histological features as follows:

1. Infectious mononucleosis or benign hyperplasia—the mildest form manifesting clinically with fever, tonsillar and/or adenoidal hypertrophy, and cervical lymphadenopathy. On histology the nodal architecture is maintained [47].
2. Polymorphic PTLD—an intermediate stage with polyclonal proliferation and local invasion with destruction of the nodal architecture. T-cells and macrophages are often found within these polymorphic masses, possibly representing an abortive host response.
3. Monomorphic PTLD—neoplastic transformation of the tissue occurs.

The first two stages are relatively benign [16, 48] and depend on continued viral replication. They can resolve with a reduction of immunosuppression [49]—by allowing anti-EBV immune surveillance to improve and curtail viral replication. The use of anti-viral therapy that acts by interrupting the EBV replicative cycle may be of benefit at this stage [50, 51].

EBV-negative PTLD

These are more often seen in late-onset PTLDs and may simply represent sporadic lymphomas arising in immunocompromised patients [52, 53]. A "hit and run" hypothesis for EBV has also been proposed [54]. EBV induces pre-neoplastic cell injury, but once rapid neoplastic cell division starts the virus becomes a liability by slowing down tumour growth or by attracting CD8+ T-cells that attack the tumour, and it is therefore disposed of.

T-cell PTLD

Only 16 cases of EBV-associated T-cell PTLDs have been reported in the literature to date [55]. The pathogenesis of T-cell PTLDs is unclear–it has been suggested that the EBV may infect a sub-set of T-cells that express the CD21 receptor [56, 57]. The prognosis is significantly worse than that for B-cell PTLDs, with a 1-year patient survival of 50% [4].

Clinical features

The clinical features of post-transplant EBV-related illnesses are multiple and varied [16, 48, 58] and can range from an asymptomatic seroconversion to monoclonal B-cell proliferation with nodal and extra-nodal tumours or a fulminant and disseminated disease with sepsis. The early symptoms can be non-specific, such as fever, malaise, and weight loss [16, 48, 58]. In children with primary EBV infection, infectious mononucleosis is the most-common presentation [16], often occurring in the early post-transplant weeks [59, 60]. A histological diagnosis is required to differentiate infectious mononucleosis from a more-severe hyperplastic or neoplastic process [12]. In two small series describing paediatric renal transplant recipients, the most-common presenting features were fever, tonsillar and adenoid hypertrophy, cervical lymphadenopathy, and hepatomegaly with raised liver enzymes [16, 48]. The central nervous system and gut are involved in approximately 25% of cases [5, 61, 62], with pressure effects or secondary manifestations such as seizures, abdominal pain, diarrhoea, and gastrointestinal bleeding or perforation.

The incidence of PTLD affecting the allograft itself varies with the organ transplanted [63, 64]. With lung and intestinal transplants, organs that have a large indigenous lymphoid supply, PTLD occurs in up to 80% of allografts [1]. In renal transplant recipients, the allograft is affected in approximately one-third of all cases [62].

Post-transplant time to onset

PTLD is remarkable for a short post-transplant time to onset—47% of cases occur within 6 months, 62% within 1 year, and 90% within 5 years of the transplant [65].

Investigations

Serology and polymerase chain reaction

Traditionally, serological investigations for EBV looked for IgG and IgM against the virus capsid antigen (VCA), early antigen (EBV-EA), and the Epstein-Barr nuclear antigen (EBNA). A primary infection was defined as the appearance of IgM antibodies to the VCA, while reactivation was defined as a fourfold or greater increase in anti-VCA IgM [66]. A chronic infection is denoted by a combination of an increased titre of anti-VCA IgG and the lack of EBNA antibodies [67]—these patients should be closely monitored as they are at a particularly high risk of developing PTLD.

Since the mid-1990s, polymerase chain reaction (PCR) for EBV-DNA has replaced serological testing, which is both unreliable in the face of immunosuppression and can have a variable lag period after acute infection [68]. Also, patients can have a passive transfer of antibodies from blood transfusions given in the peri-transplant period. In an individual who has previously encountered the virus, in the post-transplant immunosuppressed state intermittent low-grade viraemia with circulating EBV-DNA may be detected in whole blood at all times. The presence of EBV-DNA in plasma implies a higher viral load and is more suggestive of ongoing viral replication [69, 70]. All studies have shown a significantly higher viral load in primary than reactivation disease [70, 71, 72, 73]. Several studies have attempted to correlate viral load with clinically significant EBV-related events [71, 73, 74]. Viral loads are variably reported as copies per microlitre of blood or plasma, per number of peripheral blood lymphocytes, or genomes per microgram of DNA, depending on the technique used. Figure 1 shows a suggested schema for the use of EBV viral load as a screening tool.

Radiology

As part of the clinical evaluation, based on history and examination, detailed radiological investigations (including X-ray, ultrasound and computed tomographic scans of the chest and/or abdomen), endoscopy, lumbar puncture, and pleural or ascitic taps may be included.

Histology

The use of the term "PTLD" as a final histological diagnosis can only be made on biopsy of the affected
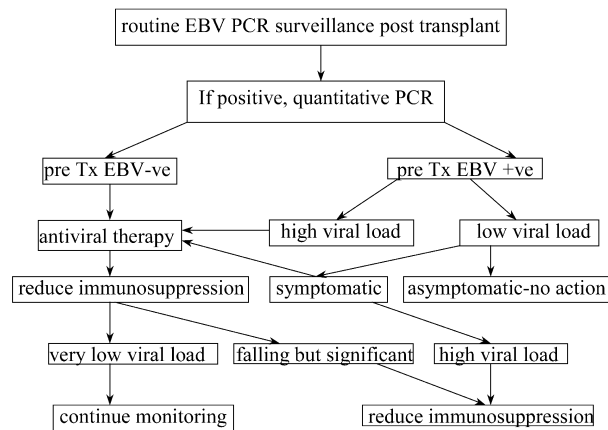

Fig. 1 Epstein-Barr virus (EBV) monitoring post transplant

tissue [12]. In EBV-positive neoplastic PTLD, a B-cell lymphoproliferative process, mono- or oligoclonal cell populations and the presence of EBV in the cells [as demonstrated by in-situ hybridisation for EB-ER (Epstein Barr early RNA)] replace the underlying tissue structure [75]. Also, EBV LMPs can be found on immunostaining [76]. PTLD can be confused with transplant rejection unless the cells are identified as B-cells by B-cell markers such as CD19, CD20, CD21, or CD22 [75].

Clonality is based on the expression of kappa or lambda chains on the surface of immunoglobulin molecules. The United Kingdom Children's Cancer Study Group (UKCCSG) has collected data on lymphoproliferative diseases in 42 children with primary immunodeficiency or post-transplant immunosuppression. In their report, monoclonal PTLD was the most-common subtype in children after solid organ transplants [4]. Neither clonality nor any specific pathological subtype predicted response to a reduction in immunosuppression or clinical outcome [4].

PTLD can co-exist with acute rejection. This has been particularly linked with T-cell PTLDs [57]. When the allograft itself is affected, histological features such as plasmacytoid infiltrates, immunoblastic cells, nodular infiltrates, and serpinginous necrosis, notably with an absence of neutrophils, suggest PTLD [75].

Markers of disease activity

In a search for markers of early disease, monoclonal proteins, particularly IgM, have been found in the urine of patients with PTLD at a greater frequency than in otherwise healthy post-transplant patients (72% vs. 27%) [77]. Also, provided anti-viral prophylaxis has not been used, CD19+ B-cells have been demonstrated in the peripheral blood of patients with PTLD [77]. The β2-microglobulin/cystatin C ratio was shown to be a sensitive and highly specific marker of lymphoproliferation in a small group of children with lymphoproliferative disease [78].

Prevention of PTLD

Three risk factors have been consistently identified in several large epidemiological studies: seronegative recipient status, use of potent immunosuppression, and active CMV disease [2, 3, 13, 14, 15, 16]. While some of these risk factors may be inevitable, careful surveillance for EBV seroconversion and anti-viral therapy has been tried as prophylactic strategies, with varying degrees of success [16, 48, 49, 58, 79, 80]. The use of an EBV vaccine in seronegative recipients is also thought to be of benefit.

EBV surveillance

It is difficult to predict when EBV-driven lymphoproliferation will become truly malignant or behave in an aggressive, potentially fatal manner. The myriad of clinical presentations, as well as a significant number of asymptomatic infections, calls for routine EBV screening in this highly susceptible population, especially in the early post-transplant period [16, 48, 80]. With a decrease in immunosuppression, especially in the early stages of EBV infection, it is hoped that the host immune system will recover sufficiently to halt the EBV lytic-replicative cycle. Some small series have shown that careful EBV surveillance post transplant, followed by a prompt reduction in immunosuppression, can prevent further morbidity while preserving graft function [16].

EBV vaccine

As EBV-naïve recipients are at the greatest risk of PTLD, vaccination of all seronegative transplant recipients should lead to a significant decrease in the incidence of PTLD. The viral protein gp350 is found in the EBV envelope [35] and in the membrane of lytically infected B-cells [81]. It is a major EBV membrane antigen that binds to the C3d receptor (CD21) on B-cells to initiate the first stage of infection. Studies conducted in healthy adult volunteers using EBV gp350 vaccine have shown good immunogenic responses and no significant adverse effects [82]. However, the level of anti-gp350 antibody required to prevent EBV infection is unknown [82]. A pilot study in seronegative children awaiting solid organ transplants is due to begin in some centres in the United Kingdom in the near future. This will aim to identify the optimal dose of the vaccine. It will be followed by a larger pan-European controlled study.

Anti-viral agents

The use of anti-viral agents remains controversial with conflicting data on their benefit in reducing the burden of EBV-PTLD [50, 51]. The currently available anti-virals, aciclovir and ganciclovir, inhibit the lytic-replicative cycle of EBV, but have no effect on the latent or oncogenic virus [50, 83, 84]. Thus, for these agents to be of any benefit, they would have to be started pre transplant and continued throughout life. Nevertheless, many centres use prophylactic anti-viral agents for the first 3–6 months post transplant when maximum immunosuppression is used and the risk of PTLD is highest.

Treatment of established PTLD

The treatment for EBV-driven lymphoproliferative and neoplastic states continues to remain a controversial subject, with no standard evidence-based treatment or multi-centred trials to support any particular treatment modality. However, a reduction in immunosuppression is the most-common management strategy and is used in over 90% of cases [3]. Studies have shown that a judicious decrease in immunosuppression alone will reverse the EBV-driven lymphoproliferation in one-third to one-half of all cases [85]. Indeed, there are anecdotal reports of the disappearance of EBV-positive tumours on reduction of immunosuppression alone [48].

Immunosuppressive drug reduction

While there are no standard algorithms for immunosuppressive drug reduction, this will clearly depend on a serial evaluation of the patient's clinical status, tumour size, clonality, and graft function. The Karnofsky scale, used for the standard evaluation of lymphomas, helps to identify clinical severity and therefore the urgency of treatment.

In our centre we use prednisolone, tacrolimus, and azathioprine as standard immunosuppression, and start with halving the azathioprine dose when primary EBV infection occurs. The patient is carefully monitored for any clinical deterioration and weekly EBV PCRs are performed to monitor viral load. The azathioprine is stopped if viral loads continue to increase. The patient's response to reduction of immunosuppression is monitored by immunophenotyping studies. If clinical deterioration or tumour activity continues, the calcineurin inhibitor is reduced in a step-wise fashion, usually with the introduction of adjunctive treatment at this stage. As reduction or temporary withdrawal of immunosuppression carries with it a very real risk of allograft rejection, serial monitoring of graft function, often with biopsies, is necessary to differentiate PTLD from acute rejection.

Monitoring the host immune response to reduction of immunosuppression

The host immune response that leads to a remission of PTLD can be monitored through a lymphocyte activation phenotype characteristic of an anti-viral response [86]—when a response is seen, it may be possible to delay further reduction of immunosuppression. This centres on

CD8+ cytotoxic T-cells directed against the EBV-transformed B-cell. The CD8+ cytotoxic T-cell, in association with CD57+ cells and NK cells, is the principal EBV effector cell in the normal host. During active PTLD these cell counts are low [87]. They rise with recovery of the immune response and a "switching off" of the lymphoproliferative process. Also, CD69+ T-cell numbers are high during active PTLD, indicating an abortive attempt at activation [87]. Thus, a sustained expansion of CD8+ T-cells is necessary for PTLD clearance [88].

Second-line treatment

Anti-CD20 antibodies

In patients who are refractory to a reduction of immunosuppression, the anti-CD20 monoclonal antibody, rituximab, has been used with varying success [89]. Rituximab neutralises the B-cells expressing CD20 and thus aborts the lytic-replicative phase of EBV-driven lymphoproliferation [90]. Similarly, anti-CD21 and anti-CD24 antibodies have also been tried in a prospective multi-centre trial, with remission rates of 80% and 46% in polyclonal and monoclonal disorders [89]. Major drawbacks of treatment included a high rate of secondary infections, tumour lysis syndrome, and impaired immunoglobulin synthesis [91].

Interferon alfa

There have been anecdotal reports of success with the use of the cytokine interferon alfa; this stimulates the host immune system to reject PTLD, but carries with it a high risk of rejection [92].

Chemotherapy

In one small series of patients with monoclonal PTLD and frank malignant changes, anthracycline-based chemotherapy (CHOP or ProMACE-CytaBOM) resulted in a high remission rate, with 70% of patients being disease free at 20 months of follow-up [93]. No patient with T-cell PTLD has achieved remission with chemotherapy [4].

Cytotoxic T-cells

Passive immunisation using in vitro expanded EBV-specific cytotoxic T-lymphocytes (CTL) has been used to successfully treat EBV-driven lymphoproliferation following bone marrow transplant [94]. EBV-specific CTLs are the body's principal defence against PTLD—they recognise and destroy the EBV modulated B-cells and thus prevent viral replication. Infusions of donor-derived EBV-specific CTLs have been used with encouraging results in allogenic bone marrow transplants [95]. The
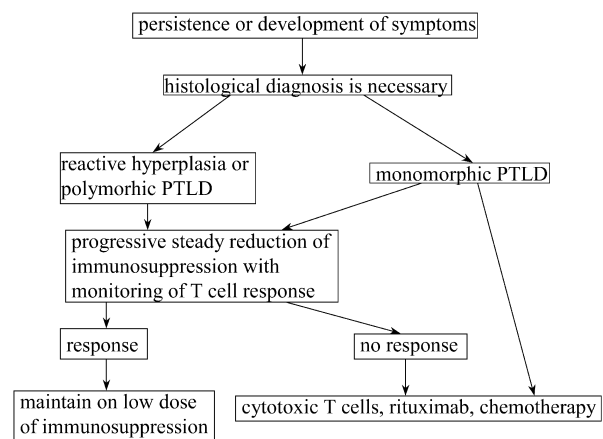

Fig. 2 The management of PTLD using EBV PCR screening

situation is more complex in solid organ transplants when it is not possible to use donor lymphocytes, but a recent phase I/II trial in liver or renal transplant recipients in the United Kingdom has shown variable results [96].

A suggested schema for the management of PTLD using EBV PCR screening when reduction of immunosuppression has failed is shown in Fig. 2.

Re-transplantation after PTLD

There are anecdotal reports of successful re-transplantation after PTLD in a previous renal allograft with no evidence of PTLD recurrence [97].

Prognosis

Prognosis and survival rates are difficult to compare given the wide spectrum of clinical and histological features seen with EBV-driven post-transplant conditions. The United Kingdom Children's Cancer Study Group reported eight cases of neoplastic PTLD in renal transplant recipients; three of these cases died [4]. In a separate series, it was found that 44% of PTLD survivors had only one organ involvement, whereas involvement of three or more organs was seen in 57% of fatal cases [98].

Conclusion

This literature review shows that there are several lacunae in our current understanding of EBV pathogenesis and its myriad manifestations in the immunosuppressed transplant recipient. Multi-centre randomised trials and standardised clinical, diagnostic, and treatment strategies are required to improve our understanding and management of this condition.

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