CHAPTER 7.2 Epstein-Barr virus infection and post-transplant lymphoproliferative disorder (PTLD)

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1 Epstein-Barr virus

Epstein-Barr virus (EBV) infection is typically caused by salivary transmission ("kissing disease"). After productive infection of epithelial cells and B cells of the oropharynx (lytic phase), naïve circulating B cells are infected and progress from latently infected proliferating blasts to long-lived memory B cells (latent phase). In the context of solid organ transplantation (SOT), EBV is also transmissible through the transplant, and reactivation of virus-producing cells is possible at any time, especially under immunosuppressive medication [1]. Primary EBV infection and viral reactivation in the course of subsequent latent virus persistence may be asymptomatic, oligosymptomatic or cause severe systemic disease, including infectious mononucleosis and post-transplant lymphoproliferative disorder (PLTD, see below).

In paediatric kidney transplant (KTx) recipients, the 5-year incidence of EBV-associated PTLD is 1–10%. Risk factors for the development of PTLD include the recipient's EBV seronegativity prior to KTx, which is found in approximately 41% of paediatric KTx patients, and the type and intensity of immunosuppression [2, 3]. As EBV-specific antiviral drugs and effective EBV vaccines are lacking, early diagnosis of EBV infection or reactivation and surveillance are necessary in paediatric KTx patients.

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2 EBV diagnostics

Prior to kidney transplantation, both donor and recipient should be serologically tested for EBV. Patients with an EBV D+/R– serostatus are at highest risk of primary EBV infection. After transplantation, EBV infection/reactivation is diagnosed by determining the virus load in whole blood, plasma or serum by quantitative PCR (qPCR) [4]. Viral load in cell-containing material reflects the abundance of virus-infected cells, whereas in plasma or serum it reflects free viral nucleic acid from productively infected or dead cells. Quantitative EBV DNA testing can also be performed on cerebrospinal fluid, biopsy material, bronchoalveolar lavage (BAL), etc., where the viral load of all non-liquid materials should be related to a cellular genome. Where possible, virus concentrations should be reported in international units/ml, using the WHO EBV standard (www.nibsc.org/documents/ifu/09-260.pdf).

Because there is no absolute viral load threshold for predicting EBV-associated PTLD, longitudinal monitoring of EBV viral loads should be performed using the same specimen and laboratory [4, 1]. This helps to distinguish patients with increasing viral loads from those with elevated but stable viral loads. Transplanted patients can have persistent high viral loads without developing PTLD. In contrast, an undetectable or low viral load does not rule out the development of PTLD, including EBV-associated PTLD. An increasing viral load should prompt a physical examination with imaging, tissue biopsy, immunophenotyping, and preemptive therapy as appropriate. Where possible, mutational analysis may also be helpful in estimating the risk of PTLD, as mutations in the EBV LMP1 gene (positions 212 and 366) have been associated with an almost 12-fold increased risk of EBV-positive PTLD [1].

Table 1 Viral diagnostics

	EBV VC IgG[1]	EBV qPCR[2]	LMP1 mutation analysis[3]
Donor	Before Tx[4]		
All KTx recipients	Before Tx[5]	In case of clinical signs of EBV disease (e.g. infectious mononucleosis, PTLD) or transplant dysfunction	Consider in case of chronic high EBV viral load
D+/R– recipients		Month 0, 1, 2, 3, 4, 5, 6, 9, 12 post-transplant	
D–/R– recipients		Surveillance until primary EBV infection (community-acquired infection)	
R+ recipients		Surveillance in case of additional risk factors (e.g. T-cell depletion, recent EBV primary infection, re-transplantation, etc.)	

[1] in serum
[2] usually in whole blood (if necessary, in plasma or serum). Use same specimen type and laboratory, assay calibrated according to WHO standard. In case of PTLD, additional monitoring in other specimens (e.g. cerebrospinal fluid, BAL, biopsy specimens, etc.) is recommended.
[3] specific LMP1 mutations associated with increased risk of PTLD
[4] consider donors < 3 months of age EBV-positive in the case of positive EBV VC IgM result
[5] consider recipients < 12 months of age EBV-negative (regardless of EBV VC IgG result) due to maternal antibodies

3 Prophylaxis and treatment of EBV infection

Despite many efforts, the development of a vaccine to provide reliable, long-term protection against EBV infection has not been successful. There are no specific antiviral drugs. Acyclovir and ganciclovir inhibit EBV in the lytic phase *in vitro* and *in vivo,* and therefore theoretically have prophylactic potential to prevent primary EBV infection. However, in a systematic review with meta-analysis, their benefit could not be proven. Therefore, their use is not recommended, but at the same time the available data are not sufficient to reject their use [5].

Although rituximab is often used to pre-emptively treat EBV replication in haematopoietic stem cell transplant (HSCT) patients, its beneficial effect as a preemptive therapy to prevent manifest PTLD in SOT recipients has not been proven. It is therefore not generally recommended for paediatric KTx recipients, but may be considered on a case-by-case basis.

For prophylaxis and treatment of EBV infection, immunosuppressive medication can be reduced in order to strengthen the patient's cellular defence against EBV. However, the patient's individual risk-benefit ratio needs always be taken into account to avoid transplant rejection [1, 5, 6].

4 Diagnosis of PTLD

Symptoms of PTLD can be variable with either classic symptoms (lymphadenopathy, hepato-/splenomegaly, blood count abnormalities, fever, night sweats, weight loss) or atypical symptoms (failure to thrive, abdominal pain, diarrhoea, chronic fatigue, unexplained cough). Biopsy is mandatory to confirm the diagnosis, and pathological workup should include immunohistochemistry (CD20, CD30), evaluation of c-myc translocations and EBV association (EBER in situ hybridisation; staining for LMP or EBNA). PTLD is classified according to the WHO classification with polymorphic or monomorphic B-cell disease being the most frequent subtypes [7].

Table 2 The WHO classification of PTLD (2017)

Category	Examples
Non-destructive PTLD	Reactive plasmacytic hyperplasia Infectious mononucleosis Florid follicular hyperplasia
Polymorphic PTLD	
Monomorphic PTLD	Diffuse large B-cell lymphoma Burkitt lymphoma Plasma cell myeloma, plasmacytoma EBV-positive Marginal Zone lymphoma Peripheral T-cell lymphoma, not otherwise specified Hepatosplenic T cell lymphoma
Classical Hodgkin lymphoma PTLD	

5 Diagnostic workup and staging

Diagnosis and treatment should be carried out by an interdisciplinary team of paediatric oncologists and transplant physicians. Except for non-destructive PTLD of the tonsils or adenoid tissue all other patients require complete staging. Imaging should include ultrasound and/or MRI of the abdomen and cervical lymph nodes, and chest CT. A ^{18}FDG-PET CT/MRI should be performed to secure all active lesions. Bone marrow histology and lumbar puncture are performed to evaluate bone marrow or central nervous system (CNS) involvement. Peripheral blood EBV qPCR and measurement of lactate dehydrogenase should be performed as baseline for follow-up investigations.

Staging is performed according to the International Paediatric Non-Hodgkin Lymphoma staging system [8] or the St. Jude staging system [9]. Both systems identify 4 stages based on the number and location of lymph node regions involved, extralymphatic disease, and bone marrow or CNS involvement. Stages I to IV are associated with the absence (a) or presence (b) of general symptoms such as fever, night sweats and weight loss.

6 Treatment of PTLD

Treatment of PTLD has been extensively reviewed in a recent IPTA report and should be carried out in multi-disciplinary teams [6]. Reduction of immunosuppressive medication without risk of graft rejection is the cornerstone of PTLD treatment. Preclinical data suggest that cessation of calcineurin inhibitors and/or a switching to an mTOR inhibitor-based regimen may be beneficial, but clinical evidence is lacking. In CD20+ PTLD, rituximab is the first-line treatment of choice. In the Ped-PTLD trial, 3-weekly doses of rituximab (375 mg/m^2) were administered and, if a complete or partial remission was achieved, were followed by 3 further rituximab infusions on a 3-weekly schedule. In patients who do not respond to rituximab alone, low-dose chemotherapy (modified COMP, cyclophosphamide, vincristine, methotrexate, prednisolone) should be added [7]. Alternatively, 6 cycles of rituximab + low-dose chemotherapy (cyclophosphamide + prednisolone) resulted in similar survival rates [10]. In patients who progress on this regimen, more intensive chemotherapy regimens have been used according to NHL-BFM, DA-EPOCH, FAB/LMB or COG schemes. Supportive measures should include antifungal and *Pneumocystis jirovecii* prophylaxis. Recently, EBV-specific T cells have been approved by the EMA for second-line treatment of relapsed or refractory EBV+ PTLD (tabelecleucel, Ebvallo® [11]). Alternatively, EBV+ T cells freshly isolated from partially HLA-matched donors have been used with similar success rates [12]. These cells have also been used successfully in patients with CNS involvement, who otherwise have a poor prognosis [13].

In a retrospective analysis of Hodgkin-like PTLD treated with conventional Hodgkin's disease chemotherapy, 81% of patients achieved and maintained complete remission at 5 years [14]; therefore, Hodgkin-like PTLDs should be treated according to protocols developed for *de novo* Hodgkin's disease. For rare types of PTLD (e.g. monomorphic T-cell PTLD, plasmacytoma-like PTLD), no standardised recommendations have been evaluated and treatment should be individualised.

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