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REVIEW

Lymphoproliferative Disorders After Solid Organ Transplantation—Classification, Incidence, Risk Factors, Early Detection and Treatment Options

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Abstract Posttransplant lymphoproliferative disorder (PTLD) is a heterogeneous disease group of benign and malignant entities. The new World Health Organisation classification introduced in 2008 distinguishes early lesions, polymorphic, monomorphic and classical Hodgkin lymphoma-type PTLD. Based on the time of appearance, early and late forms can be identified.

PTLDs are the second most frequent posttransplantation tumors in adulthood, and the most frequent ones in childhood. The incidence varies with the transplanted organ—from 1%–2% following kidney transplantation to as high as 10% following thoracic organ transplantation—due to different intensities in immunosuppression. Immunocompromised state and Epstein-Barr virus (EBV) infection are the two major risk factors.

In Europe and the US approximately 85% of PTLDs are of B-cell origin, and the majority are EBV-associated. Symptoms are often unspecific; extranodal, organ manifestations and central nervous system involvement is common. Early lesions respond well to a decrease in immunosuppression. Malignant entities are treated with rituximab, chemotherapy, radiotherapy and surgical therapy. Adoptive T-cell transfer represents a promising therapeutic approach. The prognosis is favorable in early PTLD, and poor in late PTLD. Five-year survival is 30% for high-grade lymphomas. The prognosis of EBV-negative lymphomas is worse.

Lowering the risk of PTLD may be achieved by low dose maintenance immunosuppression, immunosuppressive drugs inhibiting cell proliferation, and special immunotherapy (e.g. interleukin-2 inhibitors). Early detection is especially important for high risk—e.g. EBV-negative—patients, where the appearance of EBV-DNA and the increase in its titer may help.

Keywords Adoptive T-cell therapy · Early detection · Epstein-Barr virus · Immunosuppression · Lymphoma · Posttransplant lymphoproliferative disorders · Rituximab · Risk factors · Solid organ transplantation · Therapy

Abbreviations

ATG	Anti-thymocyte globulin
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
CTL	Cytotoxic T-lymphocyte
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
FDG-PET	Fluorodeoxyglucose positron emission tomography
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
HTLV	Human T-cell leukemia virus
IL	Interleukin
LMP	Latent membrane protein
mTOR	Mammalian target of rapamycin
NK	Natural killer

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PCR	Polymerase chain reaction
PSI	Proliferation signal inhibitor
PTLD	Posttransplant lymphoproliferative disorders
SOT	Solid organ transplantation
UNOS	United Network for Organ Sharing
WHO	World Health Organisation

Introduction

Organ transplantation has become a successful treatment method, and transplanted patients live longer due to modern immunosuppression. As the length of the immunocompromised period is longer now, the risk of malignant tumor formation is increasing [1, 2]. Prognosis is different in each tumor type. Skin cancers, although frequent and may be aggressive, are rarely lethal. However, other tumors such as high-grade lymphomas, visceral Kaposi's sarcoma, hepatic, lung and colorectal cancers have a poor prognosis [3–5].

Due to their frequency and poor prognosis, lymphomas have long been in the focus of attention. Posttransplantation lymphomas were first described in 1968 [6, 7]. Based on 75 cases in 1971, lymphomas, skin tumors and sarcomas were the most frequent posttransplantation tumors [8]. Based on 241 tumor cases following nearly 15 000 transplantations, lymphomas—occurring in 26%—developed earlier than other tumors; lymphoma patients received anti-lymphocyte globulin treatment more often, and their prognosis was worse than that of other tumors [9]. Lymphoproliferative lesions and lymphomas were summarized as posttransplant lymphoproliferative disease (PTLD) in 1984 [10]. Our knowledge about PTLD has since enormously increased—the aim of this paper is to summarize the most important aspects.

Histopathological Classification of PTLD

PTLD is a unifying name for several benign and malignant lymphoproliferative lesions. Due to their frequence and poor prognosis, an emphasis is given to lymphomas; nevertheless, PTLD is not a synonym for posttransplantation lymphoma. The previous, widely used WHO classification of PTLD was modified in 2008. (The current WHO classification can be seen in Table 1) [11–13]. The differences between the previous and the new WHO classification are few. There are two important changes: 1. many Burkitt-like lymphomas (according to the previous WHO classification) now fall into the new category of unclassifiable B-cell lymphoma, with intermediate features between DLBCL and Burkitt lymphoma. 2. Hodgkin lymphoma-like PTLD (according to the previous WHO classification), based on its immunophenotype is currently considered DLBCL and belongs to the monomorphic PTLD group. These changes have an impact on the choice of treatment, which is different for each type of lymphoma [14].

Table 1 Current WHO classification of PTLD (2008)

I. Early lesions
Plasmacytic hyperplasia
Infectious mononucleosis-like
II. Polymorphic PTLD
III. Monomorphic PTLD (classify according to lymphoma they resemble)
B-cell neoplasms
Diffuse large B-cell lymphoma (DLBCL)
Burkitt lymphoma
Plasma cell myeloma
Plasmocytoma-like lesion
Other
T-cell neoplasms
Peripheral T-cell lymphoma, not otherwise specified
Hepato-splenic lymphoma
Other
IV. Classical Hodgkin lymphoma-type PTLD

The four subtypes of PTLD can be characterized as follows:

I. Early lesions

Two histological patterns are described. 1. Plasmacytic hyperplasia: the architecture of the involved tissue is generally retained. The lymphoid tissue shows sheets of plasma cells with scattered EBV-positive large immunoblasts. 2. Infectious mononucleosis (IM)-like PTLD: morphology is similar to IM; there is an expansion of the T-cell zone by immunoblasts and plasma cells. Cytologic atypia of early lesions is minimal [14, 15].

II. Polymorphic PTLD

Histology shows effacement of underlying tissue architecture and a mixed infiltrate with small and medium-sized lymphocytes, immunoblasts and plasma cells. High mitotic rate and atypical lymphoid cells may be observed (Fig. 1). Early lesions and polymorphic PTLD are specific for transplanted patients. They mostly occur in childhood and are usually related to primary EBV infection. The other types of PTLD (see below) can also be diagnosed in immunocompetent individuals [14–16].

III. Monomorphic PTLD

B-cell PTLD is the most common form of PTLD. Histology shows the destruction of underlying tissue architecture and malignant cytological features. There are four main categories: diffuse large

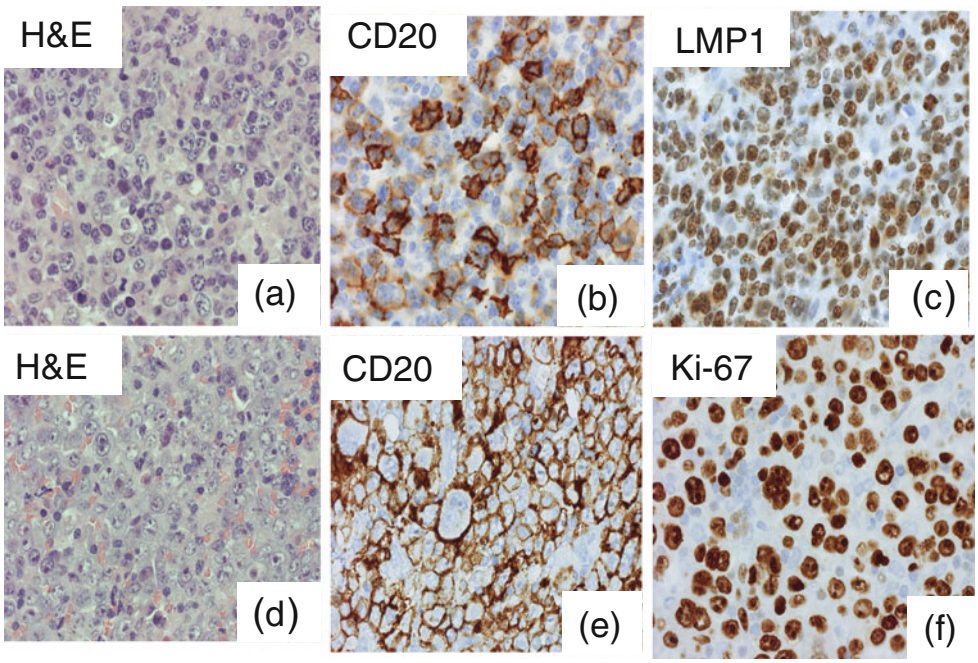

Fig. 1 Histopathology of PTLD. Polymorphic PTLD. Morphology is polymorphic; histology shows a diffuse infiltrate of lymphocytes, immunoblasts and plasma cells, mitotic and apoptotic activity is relatively high (**a**). Most of the large cells are CD20-positive B-cells (**b**), lymphocytes are polyclonal (not shown) and EBV infection in lymphoid cells is confirmed by LMP1 positivity (**c**). Monomorphic PTLD. Diffuse large B-cell lymphoma with large atypical lymphocytes (anaplastic variant) (**d**). Almost all cells show positive immunoreactivity with the B-cell marker CD20 (**e**), and Ki-67 immunoreactivity shows high proliferative activity (**f**)

B-cell lymphoma shows immunoblastic, centroblastic or pleomorphic morphology (Fig. 1). Burkitt lymphoma shows monomorphic cells with prominent apoptosis. Plasma cell myeloma and plasmocytoma-like lesions contain sheets of mature plasma cells. The *T-cell* PTLD group includes T/NK-cell lesions. Histology shows a wide range of morphological appearances depending upon the type of T-cell lymphoma [14–16].

IV. Classical Hodgkin lymphoma-type PTLD

This rare form of PTLD shows the histology of Hodgkin lymphoma in immunocompetent patients. The mixed cellularity form is most frequent [14, 15].

PTLD is almost always of recipient origin following solid organ transplantation (SOT), whereas it may be donor-derived following hematopoietic stem cell transplantation (HSCT). In Europe and in the USA approximately 85% of PTLDs are of B-cell origin, 80% of which is associated with EBV. The proportion of T-cell PTLD is 10%–15%, however, it may be as high as 40% in the Far East, due to the presence of human T-cell leukemia virus (HTLV-1). Natural killer cell derived forms are extremely rare [17, 18].

Incidence

The incidence of PTLD varies according to the age of the patient and the type of the transplanted organ. The risk is lowest following renal transplantation, moderate after heart transplantation, and highest after lung, small intestine and multivisceral transplantation [16]. The incidence is 1%–2.3% following kidney transplantation, 1%–2.8% after liver transplantation, 1%–6.3% after heart transplantation, 2.4%–5.8% after combined heart and lung transplantation, 4.2%–10% after lung transplantation, and may be as high as 20% after small bowel transplantation [13]. Tsao published lower incidences (1%–4.3%), with an overall incidence of less than 2%, perhaps as a result of better immunosuppressive management [16]. Differences according to transplanted organs are primarily due to the varying level of immunosuppression. The higher incidence of PTLD following lung and small intestine transplantation can be attributed to aggressive immunosuppression and the presence of preexisting lymphoid tissue in these organs, which is transferred to the recipient, increasing the probability of EBV infection [16, 17].

The frequency of PTLD is higher in childhood, regardless of the transplanted organ: the incidence is 2 to 3-fold, compared to adults. Pediatric patients are often EBV-seronegative, and PTLD is usually induced by primary EBV infection [16, 19].

PTLD may develop at any time following organ transplantation, however, its risk is highest during the first year. Accordingly, early and late forms can be distinguished, with different therapeutic response and prognosis. The incidence decreases with time after the first year [20]. Early development of PTLD is characteristic for heart and lung transplantation, with nearly half of the cases appearing in the first year. However, only 20% of PTLD cases have an early manifestation in kidney transplanted patients. This difference is due to higher dose immunosuppression and induction treatment following heart and lung transplantation [17, 21].

Etiological and Risk Factors

The two most important risk factors are the immunosuppressed state and EBV infection, which are closely related to each other. EBV-infected lymphocytes are normally killed by EBV-specific cytotoxic T-lymphocytes (CTLs). However, this function is damaged by immunosuppression, and a dysfunctional growth program may be initiated in EBV-infected lymphocytes, leading to PTLD [16, 17].

Further risk factors are: young age of the recipient (<10 years), adults over 60 years of age, malignant tumor in the anamnesis, the degree of HLA-compatibility and the occurrence and severity of acute rejection, the type of the transplanted organ, and the immunosuppressive drugs used [16, 17, 22, 23]. An important factor is the EBV status of the donor and the recipient: the risk of PTLD increases 10 to 50-fold if the recipient is EBV-seronegative and the donor is EBV-seropositive [16, 24].

Other viruses such as HTLV, human herpesvirus 8, cytomegalovirus, simian virus 40 and hepatitis C virus may also increase the incidence of PTLD [16, 25, 26].

Transplantation due to autoimmune hepatitis, primary biliary cirrhosis, cystic fibrosis and Langerhans-cell histiocytosis carries a higher risk [16, 27, 28].

Cytokine gene polymorphisms may also influence the frequency of PTLD via cytokine production. Low interferon-γ production may increase the risk in liver and kidney transplanted patients [16, 29].

An EBV-driven lymphoproliferative disorder is polyclonal in the beginning. However, cells may acquire genetic alterations with a higher probability in the immunocompromised state, which promotes monoclonal lymphoma formation [17]. Chromosomal translocations and mutations of several oncogenes and tumor suppressor genes have been described in monomorphic PTLD. Alterations of c-MYC, N-RAS and p53 are infrequent—they occur in monomorphic PTLD and multiple myeloma, but not in polymorphic PTLD. Rearrangement of BCL-6 is also rare, however, its mutation is more frequent and carries a poor prognosis. Epigenetic alterations may also occur, such as the hypermethylation of O6-methylguanine-DNA methyltransferase, a DNA repair gene, in 60% of monomorphic PTLD cases [30]. Microsatellite instability and the defects of DNA mismatch repair occur more often in PTLD than in non-Hodgkin lymphomas of non-immunodeficient patients [16, 31, 32]. The etiological and risk factors of PTLD are summarized in Table 2.

Table 2 Etiological and risk factors of PTLD

Immunosuppression:
type of immunosuppressive drug (CNI, OKT3, ATG, etc.)
degrees of immunosuppression (aggressive treatment)
cumulative immunosuppressive dose
Epstein-Barr virus:
EBV-seronegative recipient
mismatch of EBV status in the recipient and donor (seronegative recipient/seropositive donor)
EBV infection (primary and EBV reactivation)
Other viruses:
human T-cell leukemia virus, cytomegalovirus, human herpesvirus 8, hepatitis C virus, simian virus 40
Type of transplanted organ:
kidney<liver<heart<heart/lung<lung<small bowel<multivisceral
Age: <10 years, >60 years
HLA matching: HLA-B, HLA-DR mismatches
Acute rejection episodes
Underlying host disease
Cytokine gene polymorphisms: low interferon-gamma production
Chromosomal abnormality: c-MYC, N-RAS, p53, BCL-6

Immunosuppression

Immunosuppressed state is a major causal factor in PTLD, however, the risk depends on the composition of immunosuppression. Certain drugs may modify the risk of PTLD. Retrospective studies suggest that calcineurin inhibitors increase the risk. Cyclosporine increases the risk mainly in higher doses (>6,6 mg/kg per day) [33, 34]. Tacrolimus increases the incidence of PTLD two to fivefold, compared to cyclosporine [20, 35, 36]. Several studies show that OKT3 (anti-CD3 monoclonal antibody), Thymoglobulin and ATG (anti-thymocyte globulin) increases the incidence [17, 20, 37]. IL-2 receptor inhibitor antibodies (daclizumab, basiliximab) and alemtuzumab (anti-CD52 antibody) did not increase the risk [20, 38, 39]. A number of studies have reported that rapamycin and its derivates—a proliferation signal inhibitor (PSI)/mammalian target of rapamycin (mTOR) inhibitor immunosuppressant—decrease the incidence of posttransplantation lymphomas [17, 40–42]. However, conflicting data has been derived from recent observations, which suggests that mTOR inhibitors may also carry an increased risk. The UNOS study reported a twofold increase in PTLD in transplant recipients treated with sirolimus after renal transplantation [14, 39, 43]. Antimetabolites such as azathioprine and mycophenolate mofetil are associated with a lower or not increased risk [38, 44–46]. Betalacept, a new immunosuppressive agent (a selective costimulation inhibitor) had an increased incidence of PTLD versus cyclosporine-treated patients in a phase III study [47].

In addition to the type of the immunosuppressive drugs, the dosage and combinations (triple, quadruple therapy), i.e. the intensity of immunosuppression and the length of aggressive treatment also influence the risk [20, 34, 48].

Epstein-Barr Virus

EBV is closely involved in the pathogenesis of PTLD. It is an oncogenic DNA-virus belonging to the γ-herpesvirus family. EBV is acquired by the vast majority of the population: 90%–95% of adult individuals are seropositive worldwide. The infection is transmitted primarily by saliva, but also by other body fluids (such as blood) and transplanted organs. The virus replicates in the mucosal epithelium of the pharynx, is partly excreted into the saliva, or reaches the lymph nodes or tonsils through lymphatic vessels, infecting B-lymphocytes. Expressed viral proteins induce polyclonal proliferation in infected B-cells. Some B-lymphocytes differentiate into memory cells, which carry the virus in a latent form, whereas other cells are killed by EBV-specific CTLs. Primary infection is usually asymptomatic, occurring in the first life years in persons living under poor socio-hygienic conditions. Individuals living under better social conditions acquire the infection later, at the age of 15–25 years, and may develop a benign lymphoproliferative disorder termed infectious mononucleosis [17, 49].

EBV is also strongly associated with several malignancies. One of the two "classical" EBV-related tumors is Burkitt lymphoma, which is frequent in the regions of Africa endemic for malaria. The other one is nasopharyngeal carcinoma, which occurs more frequently in the Far East. Other EBV-associated tumors are Hodgkin lymphoma and several non-Hodgkin lymphomas. EBV is also an etiological factor for lymphomas in acquired immunodeficiencies—such as HIV-related non-Hodgkin lymphomas—and PTLD [50–53].

Genes encoded by the EBV genome can be divided into two groups. "Lytic" genes are expressed during productive infection, whereas "latency" genes are expressed in non-productive, latent viruses. Latency genes encode for 6 nuclear (EBNA) and 3 membrane-associated proteins (latent membrane protein; LMP), which may be responsible for the defective growth program and malignant transformation in B-lymphocytes. Four gene expression programs can be distinguished in latently infected B-lymphocytes: latency 0, I, II, and III. None of the genes is expressed in latency 0, whereas all of the 9 latency genes are active in latency III. Latency I is generally associated with Burkitt lymphoma. Latency II has been associated with classical Hodgkin lymphoma and T-cell non-Hodgkin lymphoma. Latency III occurs mainly in immunocompromised individuals with PTLD, and HIV-associated lymphoproliferative disorders [17, 49, 50, 54, 55].

The role of EBV in PTLD development is supported by several observations: 1. ~60%–80% of PTLD patients are infected by EBV, including 100% of early-onset cases. 2. EBV infection is monoclonal in many cases of monomorphic PTLD, consistent with the hypothesis that the virus has been present in the tumor progenitor cell since the early phases of clonal expansion. 3. A decrease in EBV-specific CTLs and an increase in EBV viral load are strongly associated with PTLD. 4. Treatment of PTLD with autologous EBV-specific CTLs results in viral load control and tumor size reduction. 5. Several viral genes expressed during latent PTLD infection have transforming activity for B-cells [25, 50, 56, 57].

PTLD is mainly the consequence of primary EBV infection, however, it may be caused by virus reactivation. PTLD is usually associated with EBV, however, EBV cannot be detected in 15%–20% of cases. Clinical manifestation and prognosis of EBV-positive and EBV-negative PTLD are different. EBV-negative PTLD is usually a monomorphic lymphoma with late manifestation and poor prognosis. [16, 17, 58].

Clinical Manifestations

PTLD may present with variable symptoms: fever, lymphadenomegaly, weight loss, intestinal perforation and septic shock. Extranodal manifestations (liver, lung, intestines, kidney, tonsil, bone marrow and skin) are common. Central nervous system involvement may be as high as 30%, compared to only 1% among non-Hodgkin lymphomas of the non-transplanted population [17, 59]. PTLD may appear in the transplanted organ, the likelihood of which correlates with the time interval after transplantation. More than 50% of PTLD cases in the first year appear in the graft in lung-transplanted patients, whereas less than 15% of lymphomas develop in the lung after 1 year [20, 60, 61].

Early Detection and Diagnostics

The early detection and treatment of PTLD is crucial. Symptoms are often uncharacteristic, which renders early diagnosis difficult. The risk of PTLD must be assessed in each patient. Childhood age, EBV-negative status, transplantation from an EBV-positive donor into an EBV-negative recipient and aggressive immunosuppression carry an increased risk. Primary EBV-infection, less often EBV-reactivation is responsible for the majority of PTLD cases, which implies that early diagnosis may be achieved by screening regularly for EBV-DNA following transplantation: an increasing EBV-DNA load in the blood may be an early sign. This is supported by data showing differences in circulating EBV-DNA load in transplanted patients with and without PTLD [62, 63]. This possibility raises several practical questions, such as the method of choice for EBV-

DNA detection, the interpretation of the findings—e.g. do we really have to consider the probability of PTLD, and what is the cut-off level which indicates risk or unequivocal diagnosis—, and the therapeutic consequence. No clear-cut consensus has been reached; however, recommendations can be found in the literature [64]. As a starting point, the EBV serostatus of the donor and recipient must be determined. Serological tests are less informative after transplantation, therefore, quantitative, real time polymerase chain reaction (rq-PCR) based methods should be used, which have a lower limit of EBV-DNA detection (10 copies per reaction) [21, 65]. The quantity of EBV-DNA may be measured in the plasma (cell-free) and in peripheral blood mononuclear cells (cell-associated). The whole amount of EBV-DNA may be measured from whole blood. Plasma EBV-DNA load represents the cell-free fraction only, which may lead to underestimations [21, 66]; however, a plasma EBV-DNA load of more than 10 000 copies/ml gives the diagnosis of PTLD with 100% specificity and sensitivity [67]. The presence of free plasma EBV correlated with the presence of EBV-positive PTLD. Taken together, the detection of free plasma EBV is a highly specific test with a high positive predictive value (100%). Measuring intracellular EBV is considered to be less efficient, due to the high rate of false positivity [68].

The American Society of Transplantation recommends that all seronegative recipients and all children <1 year of age regardless of their pre-transplant EBV serostatus should be screened monthly for EBV viral load in the first year following transplantation. After one year, regular screening should be continued in patients with a persistently higher but stable copy number, and in patients receiving intensive immunosuppression. Selective monitoring may be recommended for seropositive patients—who have a lower risk of PTLD—, e.g. when new immunosuppressive drugs are introduced into clinical practice, especially in pediatric trials. The quantification of EBV viral load is required when PTLD symptoms are present [64].

EBV-DNA load monitoring was effective in establishing early diagnosis following pediatric liver transplantation, and the consequent modification of immunosuppression lead to a decrease in PTLD frequency and PTLD-related mortality [69]. EBV-DNA monitoring was also useful following hematopoietic stem cell transplantation (HSCT) in high-risk patients [70].

We have to keep in mind that PTLD may be non-EBV-associated, especially in late PTLD, and it may develop in the absence of an increasing EBV-DNA load.

Over-immunosuppression carries an increased risk of PTLD, which may be estimated by determining both EBV-DNA load and EBV-specific CTL response. High EBV load and the concomitant lack of CTL response indicates over-immunosuppression and an increased PTLD risk [21]. This increased risk must prompt further examination of the patient, or the modification of therapy such as reducing immunosuppression, the initiation of preemptive therapy (adoptive CTL therapy, rituximab) or tumor therapy. Measuring EBV-DNA load and CTL function together may be useful because high EBV-DNA load does not always lead to the development of PTLD, which may be explained by an increased CTL function [49, 71].

The suspect of PTLD should warrant further, thorough patient checkup, including ultrasound, computed tomography (CT), magnetic resonance imaging and endoscopic examinations (Fig. 2). Fluorodeoxyglucose positron emission tomography (FDG-PET) may be helpful in the diagnosis of atypical, extranodal manifestations—which are not uncommon—, and may be used for tumor staging and patient follow-up. Initial results with PET/CT are encouraging. Diagnosis must be confirmed by histology, and patients should be staged using the Ann Arbor staging system [15, 21, 72].

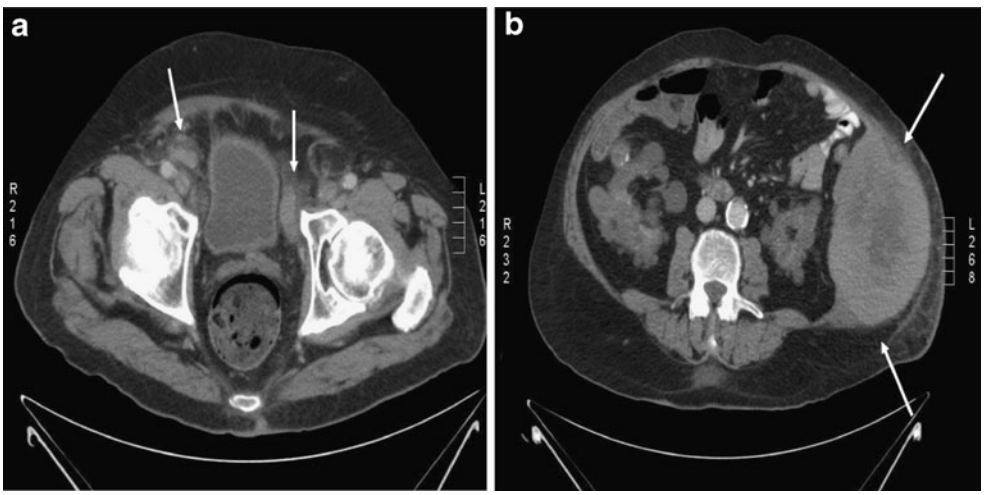

Fig 2 Computed tomography (CT) images of PTLD. Retroperitoneal lymphadenomegaly (histology: polymorphic PTLD) (**a**). Bulky abdominal mass (histology: monomorphic PTLD – diffuse large B-cell lymphoma) (**b**)

Treatment

The treatment of PTLD is a complex task requiring special considerations. Therapeutic design requires the cooperation of an onco-hematologist with experience in lymphoma therapy, a transplant specialist with experience in immunosuppression and an infectologist. Therapeutic decisions must be based on multiple factors: Ann Arbor staging and WHO classification, EBV status, patient performance, the transplanted organ and the drugs used for immunosuppressive therapy. The transplanted organ and the lymphoproliferative disease must be both considered when establishing a therapeutical plan. In the case of crucial organs (liver, lung and heart)—where the impairment of the transplanted organ can determine the fate of the patient—, the protection of the graft is of utmost importance. Therefore, PTLD therapy must be planned individually.

PTLD is a heterogeneous group of diseases, and treatment is different in each entity. Unfortunately, consensus therapeutical protocols in distinct PTLD subtypes based on prospective trials do not exist. The Haemato-oncology subgroup of the British Committee for Standards in Haematology and the British Transplantation Society has recently made recommendations for the diagnosis and management of PTLD in adult recipients of solid organ transplants, based on literature data and the experience of PTLD specialists [15, 73]. Table 3. shows the summary of treatment options and their indications based on these guidelines.

The first step is the *reduction* or discontinuation of *immunosuppression*, which might restore CTL function and elicit a favorable response in EBV-positive PTLD. The dosage of immunosuppressive drugs must be reduced to 25%–50% of the normal therapeutic whole blood trough level. A response to reduction is usually seen within 2–4 weeks. The long term remission rate of early lesions and polyclonal PTLD is 40%–86% in children and 25%–63% in adults [17, 50, 74–76]. Monoclonal and EBV-negative PTLD is usually refractory to the reduction of immunosuppression [17, 58]. The risk of acute rejection may be reduced by the administration of corticosteroids (7.5–10 mg daily), which are also important components of most chemotherapy regimens for PTLD [17].

Further therapy may include surgical resection (histological sampling, localized PTLD), irradiation (localized and CNS PTLD, complementary to systemic therapy), chemotherapy and monoclonal antibody therapy.

Chemotherapy is commonly used when the reduction in immunosuppression fails to control the disease, and as an initial therapy for aggressive, monoclonal PTLD. The most widely used cytostatic combination is CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) [17, 77, 78]. Chemotherapy can, however, cause severe toxic and septic complications, increasing lethality. Therefore, chemotherapy is often combined with hematopoietic growth factors to reduce neutropenic sepsis. Low dose chemotherapy may decrease the occurrence of toxic complications, but will lead to a higher relapse rate [79].

Rituximab—a chimeric mouse/human anti-CD20 monoclonal antibody, which binds to the surface and elicits the lysis of CD20-positive normal and malignant B-cells—has been a breakthrough in PTLD therapy. The antibody is generally well tolerated and rapidly induces the depletion of mature B-lymphocytes, reducing the compartment of EBV-infected cells, with an associated normalization of the viral load [50, 80]. Initial results with rituximab combined with reduced immunosuppression or low dose chemotherapy (in a synchronous or sequential manner) have been promising [17, 81–83]. Rituximab has become the first line treatment option for PTLD. A 70%–100% response rate and a 30%–70% complete remission rate may be achieved using rituximab as a single treatment [50, 81, 84, 85]. However, it does not restore CTL-mediated surveillance of EBV-dependent proliferation, which carries a higher risk of PTLD relapse when B-lymphocytes reappear [50, 86].

Table 3 Treatment options of PTLD

Treatment	Indication/recommendation
Reduction in immunosuppression (RIS)	should be started as soon as PTLD is suspected (restoration of recipient's immunity)
Rituximab	Rituximab monotherapy is recommended for clinically low risk[a] PTLD patients who fail to respond adequately to RIS
Rituximab+Chemotherapy	clinically intermediate and high risk* PTLD persisting post RIS, persistent or progressive PTLD after rituximab monotherapy
Surgery	histological sampling, localized PTLD (stage I.), local complication of PTLD, emergency management of gastrointestinal PTLD, graft removal
Radiotherapy	localized (stage I.) PTLD, CNS PTLD, relapse, palliation
Adoptive T-cell therapy	not recommended outwith a clinical trial (restoration of recipient's immunity)
Antiviral agents+arginine butyrate	not recommended outwith a clinical trial

[a] Risk factors: age >60 years; Eastern Cooperative Oncology Group (ECOG) performance status 2–4; increased LDH. Low risk : 0 risk factor; Intermediate risk: 1 risk factor; High risk: more than 1 risk factor

Furthermore, it may lead to the selection of CD20-negative B-cells [87]. Based on the results of prospective multicenter phase II. studies, rituximab should be used in combination with chemotherapy in patients with poor prognosis (intermediate and high risk groups, see Table 3), e.g. in the case of high tumor load, EBV-negative and late PTLD forms [50, 73, 88].

The impairment of EBV-specific cytotoxicity is an important factor in PTLD development. CTL function may be restored by discontinuing immunosuppression. This may also be achieved by *adoptive T-cell therapy*, i.e. the administration of EBV-specific CTLs. This method is applicable only in EBV-positive PTLD [17]. CTL therapy to prevent or treat PTLD was first used successfully in allogeneic HSCT recipients where the donor's peripheral blood was used as a source of EBV-specific CTLs [89, 90]. After solid organ transplantation, autologous EBV-specific CTLs may be generated from recipients who were EBV seropositive prior to transplantation, although this may take around 10–14 weeks, and long-term clinical efficacy is limited. This approach is complicated or not applicable in recipients who were EBV-seronegative prior to transplantation [17, 85, 91]. Taken together, allogeneic CTLs are more suitable for adoptive T-cell therapy. The blood of cadaver donors is no more available following SOT. CTLs may be isolated from EBV seropositive, healthy, HLA-typed blood donors. Haque, et al. established a bank of 70 different, frozen CTL cell lines. (The bank has since been expanded to contain 100 cell lines, and provides the option of choosing the most closely HLA-matched CTL cell line, in order to prevent rejection.) PTLD patients were treated by weekly intravenous CTL infusions (2×10^6 CTLs/kg body weight) for 4 weeks in a phase II. multicenter clinical trial. Initial results have been promising: no adverse effects were observed and the response rate was 64% at 5 weeks and 52% at 6 months in 33 patients [92, 93].

The efficacy of adoptive T-cell therapy is reduced by synchronous immunosuppression. Tacrolimus and cyclosporine have been shown to inhibit the proliferation and function of CTLs in vitro [94]. Therefore, the reduction of immunosuppression may be required, which carries an increased risk of graft rejection. To circumvent this problem, Brewin, et al. engineered genetically modified EBV-specific CTL cell lines, which were resistant to calcineurin inhibitors. These resistant CTLs were able to function effectively to treat PTLD in SOT patients, without requiring a reduction in immunosuppression [95].

Interferon-alpha may be effective in the treatment of PTLD by supporting the immune response and increasing CTL activity. Nevertheless, it increases the risk of graft rejection, which—along with its other, toxic side effects—limits its applicability in transplant patients [96, 97].

Interleukin-6 (IL-6) promotes the proliferation of EBV-infected B-cells, which suggests that *monoclonal antibodies directed against IL-6* may be therapeutically useful; however, current clinical results need to be confirmed by larger studies [17, 98]

Theoretically, *antiviral drugs* (ganciclovir, acyclovir and valacyclovir) may also be used in the treatment of PTLD. However, they do not increase therapeutic efficacy. Although some favorable effects have been reported, most studies suggest that profilactic antiviral therapy in EBV-seronegative patients does not prevent EBV infection, and that these drugs are not appropriate for EBV and PTLD profilaxis. The reason for ineffectiveness is that EBV-transformed cells do not express thymidine kinase, which is necessary for drug activation. *Arginine butyrate* in vitro induces the expression of thymidine kinase, rendering cells susceptible to gangiclovir. The combination of the two drugs in PTLD therapy showed promising results in a phase I/II. trial [99]. Ganciclovir is an efficient agent against cytomegalovirus (CMV) infection, which is a cofactor in PTLD [74, 100–102]. However, a multicentric, retrospective study showed that antiviral drugs did not decrease the risk of PTLD; furthermore, anti-CMV immunoglobulin was efficient only in the prevention of early non-Hodgkin lymphomas in kidney transplant patients, but not in the prevention of late types [103].

EBV vaccination may be effective in PTLD prevention, especially in seronegative pediatric transplantation candidates. Vaccination may be performed using the gp350 virus membrane protein; this vaccine triggered a favorable immune response in healthy volunteers. However, the issue of EBV vaccination in transplantation is still controversial [17, 80, 104, 105].

Organ transplanted patients with posttransplant lymphoma in remission face the controversial issue of immunosuppression, which is required for the protection of the graft, but increases the risk of lymphoma relapse. The dosage of immunosuppressive drugs should be kept low, along with a careful follow-up in order to detect any sign of acute or chronic rejection. Which immunosuppressive drug should be chosen? The ideal compound should protect the transplanted organ, but it should not interfere with oncological treatment. Immunosuppressants inhibiting cell proliferation seem to be most suitable for this task. *Rapamycin* and its analogs have been proven to inhibit lymphoma proliferation via mTOR kinase inhibition, and can be recommended for maintenance immunosuppressive therapy in transplanted patients treated for PTLD [17, 48, 80, 106]. Initial data suggests that conversion to rapamycin as an immunosuppressant has a favorable effect in kidney transplanted patients with PTLD [48, 107]. However, recent results suggest that mTOR inhibitors (in high dosage, used in maintenance therapy) may carry an increased PTLD risk; therefore, further studies

are warranted before sirolimus should be considered as a therapy for PTLD [43]. Mycophenolic acid/mycophenolate mofetil—another immunosuppressive drug—can also decrease the risk of PTLD [38, 44–46, 108]. In vitro and in vivo studies support its antiproliferative and apoptotic properties in human B-cell non-Hodgkin lymphoma and multiple myeloma cell lines [109, 110], which suggests that it may be a useful tool in the immunosuppressive therapy of PTLD patients. Further trials are required to test its favorable effects in clinical PTLD therapy.

Despite these treatments, the overall lethality of PTLD after solid organ transplantation is around 50% [93]. Different types of PTLD respond differently to treatment, and their prognosis is variable. The prognosis of early PTLD is better, whereas that of late forms is poor. 40%–50% of kidney and heart transplanted patients with high-grade lymphomas die in the first year; 5-year patient survival is around 30% for high-grade lymphomas. The prognosis of EBV-negative lymphomas is worse [17, 20].

Conclusion

PTLD is a serious complication of solid organ transplantation, contributing significantly to morbidity and mortality in this patient group. Lowering its risk is a major aim, considering its frequency and poor prognosis. Low dose maintenance immunosuppression, immunosuppressing agents inhibiting cell proliferation and immunotherapy containing interleukin-2 inhibitors may contribute to this goal. EBV-vaccination may be applied as a preventive measure in EBV-seronegative transplant candidates. Careful follow-up of high-risk patients may facilitate the early detection of PTLD. The appearance of EBV-DNA and an increase in its copy number may indicate the risk of PTLD. Early detection and timely preventive or therapeutical intervention may be key in improving outcome and patient survival.

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