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REVIEW

# Presentation and early detection of post-transplant lymphoproliferative disorder after solid organ transplantation

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## Summary

Post-transplant lymphoproliferative disorder (PTLD) is a serious and still frequently observed complication of solid organ transplantation. Despite the recent introduction of anti B-cell monoclonal antibody therapy (rituximab) for treatment of PTLD, mortality rates remain high. Because PTLD often presents in a nonspecific way in clinically unsuspected patients, it is a major challenge to diagnose PTLD at an early stage. Epstein–Barr virus (EBV)-DNA load monitoring is a promising tool for the identification of patients at risk for PTLD development. However, there are some limitations of this method, and not all patients at risk for PTLD can be identified by EBV-DNA measurements alone. Therefore, it is of major importance to recognize early clinical signs and symptoms of PTLD. In this review, risk factors for PTLD development, disease presentation, and methods for early detection will be discussed. Special attention is given to allograft and digestive tract localization and the relation with time of onset of PTLD. The value and pitfalls of EBV-DNA load monitoring are discussed. In addition, because fluorodeoxyglucose (FDG)-positron emission tomography (PET) has shown to be a powerful tool for staging and response evaluation of malignant lymphoma, the role of FDG-PET for early diagnosis and staging of PTLD is addressed.

## Introduction

Development of lymphoma after transplantation was first described by Doak *et al.* [1] in a renal transplant recipient in 1968, whereas the term post-transplant lymphoproliferative disorder or disease (PTLD) was introduced by Starzl *et al.* in 1984 [2]. PTLD is a serious complication of solid organ transplantation, contributing significantly to morbidity and mortality in this group of patients. Despite the recent introduction of anti B-cell monoclonal antibody therapy (rituximab) for treatment of PTLD [3], mortality rates of 30–60% are not uncommon [4–6].

Post-transplant lymphoproliferative disorder encompasses a heterogeneous group of lymphoproliferative diseases, ranging from Epstein–Barr virus (EBV) driven polyclonal proliferation resembling infectious mononucleosis, to highly aggressive monomorphic proliferations which may be indistinguishable from aggressive types of lymphoma, such as diffuse large B-cell lymphoma [7,8]. Generally, PTLD is considered to be an iatrogenic complication of immunosuppression after transplantation, leading to decreased function of EBV specific T-cells, which, in turn, may lead to uncontrolled proliferation of EBV infected B-cells [9,10]. PTLD is, however, not exclusively associated with EBV infection, as EBV-negative PTLD, with a preference to develop late after transplantation, is also increasingly recognized [11–13]. Most PTLD are of B-cell origin, but also T- or natural killer (NK)-cell lymphomas arising in the transplant recipient are classified as PTLD [8]. Although PTLD constitutes a continuing long-term

 

risk after transplantation, it is most frequently observed during the first year after transplantation, especially in lung transplant recipients [14].

Post-transplant lymphoproliferative disorder incidence varies significantly between different types of organ transplants, with the highest incidence (5–20%) found after lung and small bowel transplantation [14,15]. In contrast, reported incidences in kidney transplant recipients are much lower (1–3%). Differences in incidence most likely result from more aggressive immunosuppression during the early post-transplant period in the first group of patients [14]. However, as many thousands of renal transplants are performed each year, the majority of PTLD are observed in kidney transplant recipients [14,16].

Post-transplant lymphoproliferative disorder characteristically involves extranodal sites, with frequent involvement of the allograft and digestive tract [17,18], but may present at virtually any site, including for instance the skin [19] and central nervous system (CNS) [20].

Because of the heterogeneous presentation and difficulties in early diagnosis of PTLD, much attention has been focused on methods for early detection. Over the last years, monitoring of EBV-DNA load after transplantation has been increasingly used to identify the individual patient at risk for PTLD [21]. However, this method has not been standardized yet [22,23].

Treatment of PTLD always consists of reduction of immunosuppression. In addition, monoclonal antibody therapy (rituximab) is frequently applied and is now widely regarded as first line treatment [3,6]. Polychemotherapy is reserved for patients in whom other treatment options have failed or when PTLD is CD20 negative [24].

Treatment of PTLD after solid organ transplantation has been reviewed recently [3]. The present review will focus on presentation, diagnosis and early detection of PTLD after solid organ transplantation.

## Histological classification of PTLD

Histology is essential for the diagnosis of PTLD, and differentiation between rejection and PTLD involvement of the graft is necessary, because episodes suggestive of rejection may in reality present allograft involvement of PTLD [25,26]. An excision biopsy is preferred to provide adequate tissue for the evaluation of cell type, clonality, virological studies and architectural background. Needle biopsy should only be performed when larger biopsies are not possible [27]. Although cytology may be helpful in the diagnosis of PTLD [28], it has a limited role and should not be used to classify PTLD.

Post-transplant lymphoproliferative disorder comprises a variety of lymphoid tumours rather than one specific disease entity, and different classification systems have been applied to categorize PTLD [29,30]. Currently, classification is based on the Society of Hematopathology classification system [7], which identifies four major categories of PTLD (Table 1): (i) lymphoid hyperplasias or 'early' lesions; (ii) polymorphic PTLD; (iii) lymphomatous or monomorphic PTLD, including T-cell lymphoma; and (iv) other lymphoproliferative disorders, including myeloma and Hodgkin lymphoma. In addition, PTLD may also present with discordant lesions, in which different histological subtypes can be present in a single patient [31]. Apart from the routine histological examination, including immunophenotype (especially staining for CD20) and analysis for Epstein–Barr encoding RNA's, analysis of clonality may be helpful to differentiate between (sub)categories of PTLD and guide treatment [8]. Early lesions, including plasma cell hyperplasia and lesions resembling infectious mononucleosis are usually polyclonal and often regress after reduction of immunosuppression only. In contrast, monomorphic PTLD, which has a clinical course more resembling diffuse large B-cell lymphoma, should be treated more aggressively, including monoclonal antibody therapy (rituximab) and sometimes polychemotherapy [8].

**Table 1.** Current WHO classification of PTLD.

| |
|---|
| *Hyperplastic PTLD 'early lesions'* |
| Reactive plasmacytic hyperplasia |
| Infectious mononucleosis |
| Atypical lymphoid hyperplasia |
| *Polymorphic PTLD* |
| *Lymphomatous PTLD* (monomorphic PTLD) |
| B-cell lymphoma |
| Diffuse large B-cell lymphoma |
| Burkitt/Burkitt-like lymphoma |
| Maltoma |
| T-cell lymphoma |
| Peripheral T-cell lymphoma, unspecified |
| Anaplastic large cell lymphoma (T or null cell) |
| Hepatosplenic gamma–delta T-cell lymphoma |
| Other (e.g. T–NK) |
| *Other* |
| Plasmacytoma |
| Myeloma |
| T-cell rich/Hodgkin's disease-like large B-cell lymphoma |

NK, natural killer; PTLD, post-transplant lymphoproliferative disorder.

Although the association between EBV and PTLD is well established, the presence of EBV in tumour cells is not required for the diagnosis of PTLD [8]. This implicates that, according to the international classification, any lymphoma arising in the post-transplant patient is considered to be (a variant of) PTLD [8]. However, there is increasing evidence that EBV-negative PTLD is a distinct disease entity [13,32]. This type of PTLD tends to develop much later after transplantation [11] and has a

significantly worse outcome when compared with EBV-positive PTLD [12]. Whether EBV-negative lymphoma in the post-transplant host is a coincidentally arising non-Hodgkin's lymphoma or a 'true' PTLD as a result of the transplant process cannot be answered with the current knowledge and, until solved, remains a matter of semantics.

For an extensive discussion of the pathologic work-up and classification of PTLD, the reader is referred to the review by Nalesnik [8].

## Risk factors

An important risk factor for PTLD development is the intensity and the amount of immunosuppression administered to the patient. In this respect, induction [33] and the rejection treatment with anti T-cell antibodies, especially OKT3 and ATG, may lead to an increased risk of developing PTLD [14,16,34,35]. The higher incidence of early PTLD in lung and heart/lung transplant recipients supports this concept, because immunosuppressive induction therapy is more commonly applied in these patients [14]. Furthermore, rejection treatment is more aggressively applied, probably because of the lack of alternative organ replacement therapies in this category of patients. Interestingly, induction therapy with the more recently introduced interleukin (IL)2-receptor antibodies does not seem to lead to a higher incidence of PTLD [16]. However, more data are necessary to confirm these findings.

There is no conclusive evidence that development of PTLD is associated with a single immunosuppressive maintenance agent [36–38]. Although there is some discussion on the effects of tacrolimus (compared with cyclosporin A) as a risk factor for PTLD development [14,16,36,39], the more recently introduced immunosuppressive drug mycophenolate mofetil has not been associated with an increased risk of PTLD development yet [16,37,40]. The effect of mammalian target of rapamycin inhibitors (sirolimus, everolimus) on PTLD development in clinical transplantation, is not clear yet [16,41]. These drugs might theoretically be associated with a lower risk, because these inhibitors display an inhibitory effect on PTLD-derived cells *in vitro* and *in vivo* in an animal model [42]. The lack of prospective randomized trials assessing these different immunosuppressive regimens and the risk of PTLD is a major drawback and restrains any firm conclusions on PTLD risk regarding these agents.

At this moment, it may be concluded that the total amount of immunosuppression including induction and rejection therapy rather than a single immunosuppressive maintenance agent is associated with an increased risk of PTLD [14,16,40].

Until now, it is unknown whether a genetic predisposition might also play a role in the development of PTLD. It has been suggested that patients with an inherent lower immune capacity might be at an increased risk for PTLD development [43], In this respect, it has been reported that cytokine polymorphisms associated with a low cellular immune response (interleukin (IL)-2 and interferon (IFN)-$\gamma$), are associated with an increased risk of PTLD development [44].

A special category of patients at particular risk for PTLD development (10- to 50-fold increased risk) are EBV-seronegative patients receiving allografts from EBV-seropositive donors, consequently leading to primary EBV infection [45–47]. This is also the main reason for the higher incidences of PTLD observed in the early post-transplant period in paediatric transplant recipients, who more often are still EBV-seronegative at the time of transplantation.

Because of the markedly increased risk for PTLD development in EBV-seronegative patients receiving organs from EBV-seropositive donors, pretransplant immunization for EBV has been suggested. However, a vaccine against EBV is not commercially available yet, although work is in progress [48,49]. There is an anecdotic report describing the successful immunization of two patients following donor blood transfusion before living-related kidney transplantation, after which symptom-free seroconversion was observed after transplantation [50]. However, the concept of pretransplant iatrogenic EBV infection is not feasible yet, because of ethical and safety issues.

There is some discussion whether antiviral agents (aciclovir, ganciclovir), primarily used as cytomegalovirus (CMV) prophylaxis, might also prevent PTLD development. Funch *et al.* [51] retrospectively reported a strong association between freedom from PTLD and prophylactic aciclovir or ganciclovir administration in 100 PTLD patients compared with 375 matched controls. However, other reports, addressing more specifically the impact of ganciclovir on EBV viraemia, especially in EBV-seronegative transplant recipients [52], could not show any beneficial effects of these drugs on EBV-DNA load or PTLD development [53].

Whether CMV is associated with an increased risk of PTLD development, is debatable. CMV pretransplantation mismatch (i.e. a CMV naïve recipient transplanted with a CMV seropositive donor) [54] and CMV disease after transplantation (especially in EBV naïve transplant recipients) [55,56] have both been linked to an increased risk of PTLD development. However, this association could not be confirmed in recent studies [16,47,51,57,58]. Thus, although it cannot be excluded that CMV plays a role in PTLD development, at least it seems that CMV mismatch or disease are not major risk factors for PTLD development.

Whether the degree of HLA matching between donor and recipient plays a role in the development of PTLD is debatable [57,59]. In a recent study, increased total numbers of HLA mismatches were found to be associated with PTLD development [16]. In addition, we have shown that mismatches at HLA-B loci might confer greater risk for PTLD development after renal transplantation [57]. This relation was independent of immunosuppressive therapy. We have hypothesized that decreased surveillance by T cells with dual specificity for EBV, as well as for allo HLA-antigens on the allograft, might facilitate clonal expansion of B-cells latently infected with EBV. Interestingly, HLA-B mismatches were also identified as an independent risk factor for the development of skin cancer after renal transplantation [60]. This suggests that the risk of HLA-B mismatches in the context of poor immune surveillance is not restricted to PTLD. However, larger cohort studies are necessary to further study this relationship.

## Time of onset after transplantation and site of PTLD presentation

Post-transplant lymphoproliferative disorder may arise at any time after transplantation and present as early as 15 days after transplantation [61]. The risk of PTLD development is significantly higher in the early post-transplant period (<1 year after transplantation), especially in heart/lung and lung recipients. This is generally attributed to higher doses of immunosuppression and more intensive use of induction therapy with anti T-cell antibodies in these categories of patients. In a large series, comprising approximately 200 000 patients, Opelz and Dohler [14] showed that almost half of all PTLD following lung and heart/lung transplantation develop in the first year post-transplantation, after which the risk of developing PTLD levels off. This is in sharp contrast to kidney transplant recipients, in whom only 20% of all PTLD develop within the first year following transplantation after which the incidence stabilizes at lower rates in subsequent years [14]. Beyond 1 year post-transplant, the risk of PTLD development between lung and kidney transplant recipients is nearly comparable [14]. This suggests that the higher incidence of PTLD in lung transplant recipients observed in the early post-transplant period might indeed be attributed to the use of more intensive immunosuppression in the early post-transplant period.

The site of PTLD presentation seems to be closely related to the time elapsed after transplantation (Fig. 1). In lung transplant recipients, more than 50% of all PTLD during the first post-transplant year develop in the allograft [14,17,62], whereas allograft localization is rarely observed after the first post-transplant year (<15%)

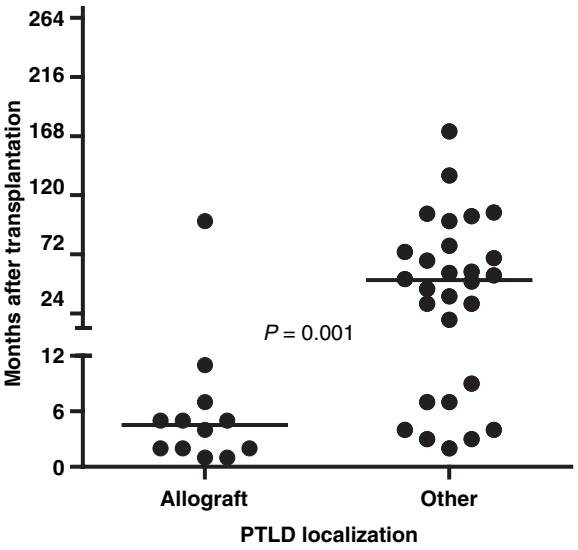


**Figure 1** Primary site of post-transplant lymphoproliferative disorder (PTLD) presentation and time after transplantation in kidney and lung transplant recipients. PTLD localized in the allograft occurred significantly earlier after transplantation when compared with PTLD localized outside the allograft (median: 4.5 months, range: 1–99 months vs. median: 51 months, range: 2–172 months, $P = 0.001$) (adapted from ref. [17], printed with the permission of Blackwell Publishing).

[17,62]. Although not as evident as in lung transplant recipients, PTLD development in the allograft is also higher (30%) in the first post-transplant year in kidney transplant recipients [17,63].

The pathophysiological mechanisms leading to this preferential allograft localization of PTLD early after transplantation have not been resolved yet. One could hypothesize that these lymphomas might be the result of EBV-infected donor B-lymphocytes transplanted with the graft, which escape host immune surveillance, ultimately leading to donor-derived PTLD [64,65]. In concordance with this hypothesis, PTLD of donor origin tends to arise early after transplantation and is more often localized in or near the allograft without dissemination as compared with recipient-derived PTLD [66]. On the other hand, the majority of early PTLD after solid organ transplantation are of recipient origin [67–69], and allograft localization of PTLD, even early after transplantation, is far from exclusively associated with donor origin [70,71]. Therefore, an alternative hypothesis would be required for the majority of PTLD localized to the allograft.

In this respect, we and others have hypothesized that continuing allogeneic stimulation of the host immune system by the allograft might be a contributory factor in the development of PTLD [17,72]. The local inflammatory processes associated with this allogeneic reaction might lead to a promiscuous microenvironment facilitating

proliferation of latently EBV-infected autologous-B lymphocytes, ultimately leading to PTLD.

The same may hold true for PTLD developing in the allograft late after transplantation, in which other factors, for example a chronic infection of the allograft, might also contribute to this promiscuous microenvironment. An interesting observation in this respect is the strong relationship between EBV-infected proximal tubular cells of the transplanted kidney (chronic EBV nephritis), even months before the onset of PTLD, and subsequent localization of PTLD in or near the graft [73]. It has been suggested that chronic EBV infection of renal proximal tubular cells may participate in evoking a cellular immune response not only resulting in a damaged renal interstitium, but also leading to a local inflammatory environment [74]. This observation suggests that chronic EBV infection of renal proximal tubular cells, even months before the onset of PTLD, is not causally associated with the development of PTLD, but acts like an inflammatory trigger, facilitating local inflammatory processes, thereby facilitating PTLD development. It is unknown whether other viruses, such as the oncogenic BK virus (frequently observed in kidney transplant recipients [75]) might also contribute to the development of PTLD as a result of providing a local inflammatory environment. It would be of interest to study this relationship in the next future.

Apart from allograft involvement, the most commonly affected extranodal sites of PTLD are observed in the gastrointestinal (GI) tract [62,76]. There seems to be no relation between the time of onset and the development of PTLD in the GI tract. However, given the high incidence of PTLD in the GI tract, one could hypothesize, in analogy with the development of PTLD in the allograft (see above), that more continuous exposure to infectious antigens (including EBV and other viruses), may trigger a local inflammatory response, ultimately leading to PTLD.

An interesting observation further supporting the hypothesis that PTLD might be facilitated by a nonspecific inflammatory microenvironment is the observation of PTLD at sites of previous surgical intervention, which has been described in 2003 by Doria *et al.* [77].

Other commonly affected sites of PTLD involvement include the sinonasal cavity [78] and the CNS. Isolated PTLD involvement of the CNS, like in other patients with impaired T-cell function such as patients with HIV infection, are more frequently observed compared with isolated CNS localization of non-Hodgkin's lymphoma in patients without apparent immune deficiency [20]. Isolated lymph nodes may also be affected in up to 25% of all PTLD cases [17]. Skin involvement is observed in approximately 5–10% of all PTLD patients [19], and must be differentiated from other cutaneous malignancies, given the fact that organ allograft recipients have an increased risk for the development of cutaneous malignancies such as squamous cell carcinoma.

## Early diagnosis

Because PTLD often presents in a nonspecific way in clinically unsuspected patients, it is a major challenge to diagnose PTLD at an early stage. Keeping in mind that PTLD often presents at extranodal sites, including the allograft and digestive tract, there may be early signs and symptoms that should at least include PTLD in the differential diagnosis. This is especially true for allograft involvement of PTLD. Kidney transplant recipients with allograft involvement of PTLD often present with renal dysfunction, hydronephrosis because of ureteral obstruction and fever [63,79]. An ultrasound scan may then quickly reveal adenopathy or an ill-defined mass [79]). Lung transplant recipients may present with organ dysfunction after which a plain chest X ray or computerized tomography (CT) scanning of the thorax may be helpful in the diagnostic process [62,80,81].

Because the GI tract is also frequently involved, GI signs and symptoms such as diarrhoea and bleeding may also lead to a diagnosis of PTLD. Other signs that should trigger awareness of PTLD may be more subtle, such as unexplained fever or lymphadenopathy, but also more localized symptoms such as headache or confusion in case of CNS involvement [20], nasal airway obstruction in case of sinonasal PTLD involvement [78], or subtle orbital symptoms in case of orbital PTLD [82].

On the other hand, PTLD may also present with a bowel perforation or with disseminated disease in asymptomatic patients. Given this myriad of nonspecific clinical signs and symptoms, often masquerading PTLD as infection or adverse drug effects or reactions, or even absence of symptoms at all, methods for early detection of PTLD in transplant recipients would be extremely valuable.

## EBV-DNA load monitoring after transplantation

Because elevation of EBV-DNA load in blood is considered to reflect aberrant EBV induced B-cell proliferation, much effort has been put in developing methods that might identify patients at risk for developing PTLD by measuring the amount of circulating EBV-DNA in the peripheral blood. After the first reports which claimed a quantitative difference in circulating EBV-DNA load and EBV nuclear antigen-1 antibodies between transplant recipients with and without PTLD [83,84], this relation has been intensively investigated to establish its significance and clinical relevance for the identification of the

patient at risk for PTLD. More recently, pre-emptive strategies to prevent PTLD, that is reduction of immunosuppression guided by EBV-DNA load, have been evaluated [85,86].

Different methods for the detection of EBV-DNA have been used. These include comparative polymerase chain reaction (PCR) assays with end point dilution, quantitative, competitive PCR assays as well as real time quantitative PCR assays. The latter is considered to be sensitive, precise, reproducible and suitable for widespread application [87–90], and is now commonly regarded as the detection method of choice.

However, the specimen in which EBV-DNA should be measured is debatable [91,92]. EBV-DNA load can be measured in plasma, peripheral blood mononuclear cells as well as in whole blood. One could argue that there may be an underestimation of EBV-DNA load in plasma, as whole blood contains all EBV-DNA (i.e. cell free and cell associated), whereas plasma contains only cell-free EBV-DNA. On the other hand, Wagner *et al.* [93] reported that an EBV-DNA load of more than 10 000 copies/ml in plasma had both a sensitivity and specificity of 100% for the diagnosis of PTLD.

Despite the consensus that PTLD patients have a significantly higher EBV-DNA load compared with healthy EBV-seropositive donors or non-PTLD transplant recipients [83,84,94], it is still unclear which threshold values are predictive for PTLD. Many different threshold values have been reported, all with different sensitivity (60–100%) and specificity (71–100%) [86,95–98]. These differences can probably be explained by the number of patients studied, differences in types of transplant recipients, immunosuppressive regimens as well as blood compartments in which EBV-DNA was measured [91].

Another limitation of EBV-DNA load monitoring may be the observation that PTLD developing late after transplantation is not necessarily associated with EBV (negative staining for EBV in the tumour), and may therefore develop without a concomitant rise in EBV-DNA load. Indeed, there are studies showing EBV-negative PTLD developing late after transplantation without a rise in EBV-DNA load [97,99]. In this respect it is very interesting that there are also EBV-negative PTLD cases developing simultaneously with a sharp increase in peripheral blood EBV-DNA load [99]. These observations suggest that, although increased EBV-DNA load is generally considered to represent an increase in circulating EBV-positive tumour cells, these high EBV-DNA loads in reality may represent a separate population of proliferating B-cells that may have nothing to do with development of PTLD. Instead, these proliferating B-cells may only reflect a general state of decreased T-cell surveillance in the transplant recipient.

Because of the many variables that may influence the immune response of the individual transplant recipient, such as level of immunosuppression, time after transplantation, concomitant infections, type of organ transplanted, but also genetic factors, an exact cutoff value of EBV-DNA load critical for the development of PTLD in the individual patient cannot be defined.

Therefore, rising EBV-DNA loads in the individual patient, instead of using a cutoff value, may be more appropriate to identify the individual patient at risk for the development of PTLD [23,100].

Because of the shortcomings of EBV-DNA load measurements as a single parameter for predicting PTLD development, and the supposed relation between high EBV-DNA loads and overimmunosuppression [101], it has been suggested that concomitant combined monitoring of EBV-DNA load and EBV-specific cytotoxic T lymphocytes (CTL) responses (the absence of which to be used as a marker for possible overimmunosuppression) might better identify the individual patient at risk for PTLD development [102]. The positive predictive value of high EBV-DNA loads as a predictor for PTLD development might be improved with this method [103]. Some preliminary reports, indeed, suggest that this may be the case. Smets *et al.* [104] showed that high EBV-DNA loads in patients who underwent primary EBV infection were indicative for PTLD development only if there was a low concomitant cellular immune response. More recently, a strong correlation between a lymphocyte activation assay to closely measure the immunosuppression status of paediatric liver transplant recipients and high EBV-DNA loads was identified, which might be useful for the interpretation of persistently high EBV loads detected in absence of symptoms of PTLD development [103].

Because a low EBV-specific CTL response might also be the result of a genetic predisposition (see risk factors), it would be of interest to further study whether genotyping of transplant recipients (to identify the patient with an inherent low cellular immune response) might also aid in the identification of patients at particular risk for PTLD development.

## IL-10 monitoring

Some reports have suggested that levels of IL-10 might be predictive for PTLD development [105–107]. Although the exact relationship between IL-10 and the development of PTLD has not been fully elucidated yet, IL-10 can act as an autocrine growth factor for EBV-transformed B-cells [108]. Although this may lead to higher local levels of IL-10, it seems doubtful that this is also reflected by a higher total IL-10 load in the peripheral blood of the transplant recipient. Given the small number of studies so

far and the lack of evidence regarding the exact relation between IL-10 and the development of PTLD, the relevance for identification of the patient at risk for PTLD development is not clear.

## FDG-PET imaging of PTLD

Conventional diagnostic methods to visualize PTLD include ultrasound, endoscopy and magnetic resonance imaging (particularly in case of CNS involvement) and CT scanning [109–112]. These methods have been the main tools for PTLD visualization over the past years [113].

However, FDG-PET scanning is increasingly used as an important tool in the visualization of malignant lymphoma, especially for the detection of extranodal localizations and post-treatment evaluation [114,115], and has shown to be superior over conventional diagnostic methods to differentiate between residual masses as a result of vital tumour or scar tissue.

Because PTLD frequently presents at extranodal localizations [17], we and others have evaluated the use of FDG-PET in the visualization of PTLD [116–118].

In a series including 12 patients we found PTLD to be highly FDG avid. FDG-PET scanning proved superior compared with conventional CT scanning for staging as well as treatment evaluation. Additional sites of extranodal localizations of PTLD not visualized on CT scanning (an example is shown in Fig. 2) were found in 50% of all patients [118]. In concordance with the results of FDG-PET in other malignant lymphoma types, FDG-PET scanning was highly predictive for outcome after treatment. This indicates that FDG-PET may also be very useful for staging and evaluation of PTLD. Given the high sensitivity of FDG-PET to detect PTLD lesions, the usefulness of FDG-PET for the early detection of sites of possible PTLD involvement in patients clinically suspected of PTLD needs further investigation.

## Future directions

Post-transplant lymphoproliferative disorder still is one of the most severe and often fatal complications observed after solid organ transplantation. A better understanding of the exact pathophysiologic mechanisms involved in

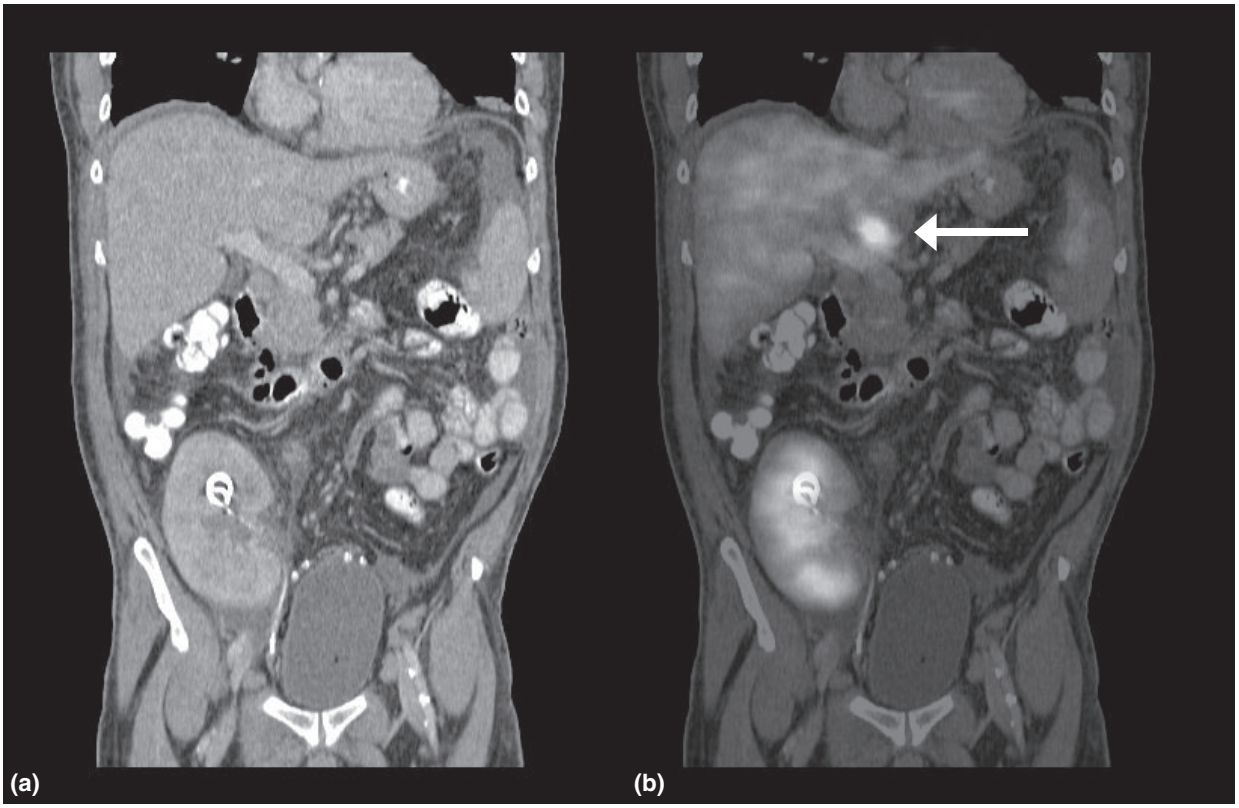


**Figure 2** Computerized tomography (CT) abdomen (a) and fluorodeoxyglucose (FDG)-positron emission tomography fused with the same CT scan (b). Note the histologically confirmed focal high uptake of FDG in the liver (arrow in panel b), whereas the CT scan (panel a) does not show any abnormalities at the site of high FDG uptake. The high uptake in the allograft, including the kidney calices and pyelum is physiological, as is the moderate uptake in liver and spleen (adapted from ref. [118], printed with the permission of Blackwell Publishing).

PTLD development is warranted. In this review, we have hypothesized that local inflammatory processes and allogeneic stimulation by the allograft may be involved in PTLD development. It might be of interest to further elucidate this proposed relationship. The relation between HLA-matching and PTLD development should also be further investigated in this respect.

Early detection and possible prevention of PTLD will be the major challenge in the next future. EBV-DNA load measurements, especially if serially applied in the individual patient, are an important step forward in the early identification of patients at risk. However, given the limitations of EBV-DNA load monitoring as predictor for PTLD, this can never be the sole parameter to rely on. Preliminary, results with concomitant measurements of CTL responses and genotyping of transplants recipients are promising. Possibly, these combined methods might be helpful in better identifying the patient at risk for PTLD development and subsequently guide pre-emptive treatment. Combined with advances in prophylactic treatment options, especially for EBV-seronegative transplant recipients, this may very well lead to lower incidences of PTLD in the next future.

Furthermore, it would be of interest to investigate whether FDG-PET may be of particular help in identifying possible sites of involvement in patients suspected of PTLD (e.g. by rising EBV-DNA load).

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