Post-transplant lymphoproliferative disorder in adult renal transplant recipients: case series and review of literature

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Abstract

Post-transplant lymphoproliferative disorder (PTLD) is serious life-threatening complication of transplantation. The clinical picture differs from lymphomas observed in the general population, with different manifestation, histopathology, higher aggressiveness with involvement of sites beyond the primary lymph node, and poorer outcome.

The objective of the study was to present nine cases of PTLD observed in our centre among the kidney transplant recipient population and discuss the results with up-to-date literature. We performed a retrospective single-centre assessment of PTLD incidence in the cohorts of kidney transplant recipients followed by our centre. We found nine cases of PTLD, five men and four women, aged from 26 to 67 years at the time of diagnosis (mean [SD] 48 [5] years), transplanted between 1997 and 2013.

The disease was diagnosed between 2002 and 2017, from 6 to 440 months after transplantation (mean [SD] 96 [137] months). A diffuse large B-cell lymphoma was found in seven cases early as well as late after transplantation, and two patients presented T-cell lymphoma. Five patients achieved complete remission with no relapses after 6 to 13 months of treatment. In three cases the remission was achieved by switching to mammalian target of rapamycin inhibitors (mTORi) only. Four recipients died from 2 weeks to 15 months after PTLD was diagnosed.

Although the diagnostic criteria of different forms of PTLD are commonly known, rapid and correct diagnosis is not easy. PTLD is a relatively a rare disease, so there are too few studies and little consensus on the optimal treatment.

Key words: lymphoma, post-transplant lymphoproliferative disease, kidney transplantation.

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Introduction

The cumulative incidence of cancers is high among solid organ recipients and exceeds 4% over a five-year period. The incidence of particular types of cancers varies between the type of transplanted organ with the highest incidence for lung recipients and the lowest incidence for kidney transplant recipients [1]. The most commonly observed cancers in kidney transplant recipients are skin cancers, followed by kidney cancer, colorectal cancers, bladder cancers, breast cancer, prostate cancer, and lung cancers [2].

Post-transplant lymphoproliferative disorder (PTLD) is the term introduced in 1984 by Thomas Starzl [3] describing serious life-threatening complications of solid and bone-marrow transplantation. The incidence of post-transplant lymphomas in solid organ recipients is 3- to 21-fold higher than that in the general population. The incidence of non-Hodgkin lymphomas varies from 0.09% to 3.8% and is highest in thoracic organ recipients [1, 5].

In kidney transplant recipients the risk of lymphoma was 11.8-fold higher than that in a matched non-transplanted population, with the highest incidence in the first post-transplant year and varying from 1 to 3% [6]. A previously published paper of our kidney transplant cohort in the years 1983–2006 reported that non-Hodgkin lymphoma and PTLD comprised 16% of neoplasms in kidney transplant recipients [7]. The clinical picture differs from lymphomas observed in the general population with different manifestation, histopathology, higher aggressiveness...
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In this paper we present nine cases of PTLD observed in our centre among a kidney transplant recipient population (about 1100 recipients) and discuss the results with up-to-date literature.

**Case report**

We performed a retrospective single-centre assessment of PTLD incidence in the cohorts of kidney transplant recipients followed by our centre (around 1100 recipients) in the last 20 years (1997 to 2017). The recipients lost to follow-up because of graft failure or transfer to another transplant centre were excluded from the study. We found nine cases of PTLD. They were five men and four women, aged from 26 to 67 years at the time of diagnosis (mean/SD: 49/16 years). They were transplanted between 1997 and 2013; for three of the recipients it was a second kidney transplantation. None of the recipients presented any rejection episode before PTLD diagnosis. Pretransplant Epstein-Barr virus (EBV) status was positive for five recipients and corresponding donors. One recipient presented EBV-negative status before transplantation (the data of corresponding donor were not known). He developed diffuse B-cell lymphoma 35 months after transplantation. Five patients suffered from chronic hepatitis B, and three recipients suffered from hepatitis C before diagnosis. Two recipient survived cytomegalovirus (CMV) after transplantation.

Demographic features of the patients, transplant course, and immunosuppression are presented in Table 1.

**Primary clinical symptoms**

The disease was diagnosed between 2002 and 2017, from 6 to 440 months after transplantation (mean/SD: 96/137 months) – in most cases between 35 and 50 months after transplantation.

Patient No. 1 was admitted to hospital due to fever, throat-ache, and tonsillar enlargement with cervical lymphadenopathy. Imaging examination revealed mediastinal lymphadenopathy and splenomegaly.

Patient No. 2 suffered from malaise, night sweats, fever, abdominal pain, and weight loss. Imaging diagnostics revealed enlargement of the spleen and liver as well as cervical, supraclavicular, mediastinal, and abdominal lymph nodes.

Patient No. 3 presented nodular mass from liver to stomach (dimensions: 9.6 × 5.5 cm) and para-aortic nodules.

Patient No. 4 suffered from malaise, night sweats, fever, abdominal pain, and weight loss. Imaging diagnostics revealed enlargement of the spleen and liver as well as cervical, supraclavicular, mediastinal, and abdominal lymph nodes.

Patient No. 5 in control imaging examination presented nodular mass from liver to stomach (dimensions: 9.6 × 5.5 cm) and para-aortic nodules.

Patient No. 6 was admitted to the hospital due to three-day appendicitis-like symptoms: pain in right lower abdominal quadrant, subfebrile temperature (37.5°C), and general malaise. Imaging studies showed an oval hypoechoic capsulated lesion (42 × 49 × 39 mm) in the inferior pole of the graft. Intraoperatively, an organised ab-

### Table 1. Demographics and post-transplant clinical course of the recipients

| Recipient | Year of tx | Age at tx (years) | Primary kidney disease | eGFR before PTLD (ml/min/1.73 m²) | Immunosuppression | Donor EBV | Recipient EBV | HBV/HCV/CMV |
|-----------|------------|-------------------|------------------------|-----------------------------------|-------------------|-----------|---------------|--------------|
| Recipient 1 | 2003 | 22 | Diabetes | 50 | TAC/MMF/PRED | + | + | HBV/CMV |
| Recipient 2 | 2000 | 30 | Glomerulonephritis | 29 | CSA/AZA/PRED | + | + | HBV |
| Recipient 3 (previous tx 1987) | 2003 | 50 | Unknown | 49 | CSA/AZA/PRED | + | + | HBV |
| Recipient 4 | 1998 | 41 | Chronic pyelonephritis | 60 | CSA/AZA/PRED | – | | HCV |
| Recipient 5 (previous tx 2003) | 2011 | 64 | Chronic pyelonephritis | 40 | TAC/MMF/PRED | – | | |
| Recipient 6 (previous tx 2003) | 2013 | 58 | Glomerulonephritis | 49 | TAC/MMF/PRED | + | – | HBV |
| Recipient 7 | 2001 | 40 | Glomerulonephritis | 70 | TAC/MMF/PRED | + | | HCV |
| Recipient 8 | 1997 | 28 | Glomerulonephritis | 65 | CSA/MMF/PRED | – | | |
| Recipient 9 | 1997 | 41 | Unknown | 30 | CSA/MMF/PRED | + | | HCV/CMV |

*tx – kidney transplantation, PTLD – post-transplant lymphoproliferative disorder, TAC– tacrolimus, CSA – cyclosporine A, MMF – mycophenolate mofetil, AZA – azathioprine, PRED – prednisone, eGFR – estimated glomerular filtration rate
scess-like mass was removed with pain disappearance as well as normalisation of temperature and laboratory markers of inflammation.

Patient No. 5 was admitted to the hospital because of severe diarrhoea (10 or more bowel movements per day) and weight loss (6 kg). Microbiological tests for bacterial as well as viral infections were negative. Gastroscopy revealed Helicobacter pylori presence with antral erosion and active gastritis with some plasma cells. Imagine examination (USG, chest X-ray) as well as colonoscopy showed no abnormalities. The symptoms diminished when mycophenolate sodium was replaced by azathioprine. Three months later the patient presented subcutaneous tumour in the right hypochondrium. Computed tomography (CT) scan revealed extensive infiltrative changes including the following: hepatic flexure of the colon, part prepyloric and antrum of the stomach, porta hepatitis, and visceral adipose tissue. Numerous intra-abdominal lymph nodes were also observed.

Patient No. 6 developed fever, malaise, abdominal pain, and weight loss. Computed tomography scans showed a nodular tumour between the liver and stomach (96 × 55 mm) and para-aortic lymph node enlargement. Patient No. 7 presented with skin infiltrates forming tumours on calves bilaterally, with no bone marrow, lymph node, or other organ involvement.

Patient No. 8 developed sudden jaundice; ultrasonography and magnetic resonance revealed a massive tumour behind the pancreas, 120 × 110 mm in size, with enlarged abdominal lymph nodes with no bone marrow involvement.

Patient No. 9 (described previously) [9] presented worsening of general condition, nausea, diarrhoea, sudden appearance of memory disorders, and speech abnormalities. Computed tomography without contrast showed nonspecific changes in the left temporal-parietal-occipital region, which were later described in the magnetic resonance imaging as possibly caused by progressive multifocal leukoencephalopathy. Autopsy revealed monomorphic primary central nervous system post-transplant lymphoproliferative disorder (M-PCNS-PTLD) presenting itself as spreading destructive lymphocytic lesions in the structures of central nervous system with angiocentric pattern of brain infiltrates.

**Diagnosis**

The diagnosis, clinical course, and treatment of PTLD are summarised in Table 2. In three cases the diagnosis was based on the histological examination of lymph nodes (Patient No. 1, 3, and 6), in the remaining cases (Patient No. 2, 4, 5, 7, and 8) the diagnosis was established based on histology of the removed tumour and in one case (Patient No. 9) during autopsy.

A diffuse large B-cell lymphoma was found in five cases early as well as late after transplantation, monomorphic B-cell lymphoma EBV-positive in one case and Burkitt lymphoma in one case, whereas Patient No. 2 and 7 presented T-cell lymphoma 50 and 47 months after transplantation, respectively.

**Treatment**

In eight cases primary immunosuppression was switched to mammalian target of rapamycin inhibitors (mTOR) (sirolimus in six cases, trough levels 5-8 ng/ml, everolimus in one case – Patient No. 4) and prednisone. The change of immunosuppression alone was successful in three recipients, leading to complete remission within 5-12 months (Patients No. 1, 3, 6 and 7). Patient No. 8 and 9 died shortly after diagnosis, before treatment was introduced.

Patient No. 5 lost his kidney allograft shortly after diagnosis and died due to disease progression three months after diagnosis being haemodialysed.

In Patient No. 2 (T-cell lymphoma) abdominal pain vanished and the general condition improved after switch of immunosuppression, but allograft function gradually deteriorated, and three months later the recipient returned to haemodialysis treatment. Sirolimus therapy was discontinued from the beginning of haemodialysis therapy. The lymphoma progressed in spite of the introduction of chemotherapy (CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone), and the patient died 15 months later from diagnosed PTLD.

Patient No. 4, after removal of a graft tumour (monomorphic B-cell lymphoma) and switch of immunosuppression, presented no allograft rejection signs and no infiltrates in terms of CD20 or EBV-positive cells in control graft biopsy. Four months after diagnosis local recurrence in the previously affected area was observed in USG and CT with two focal lesions localised in the right lung just above the diaphragm. Rituximab treatment (375 mg/m², weekly, for four weeks) was started with no side effects. After six months CT revealed disappearance of lesions localised in the right lung but progression of infiltration in the area of the lower pole of the transplanted kidney located in the right iliac fossa (39 × 53 × 47 mm) with enlarged inguinal lymph node round up to 14 mm below the graft. Chemotherapy with vincristine, doxorubicin, and dexamethasone (VAD) protocol was introduced with no complications (for five months). Follow-up imaging diagnostics at the end of the chemotherapy course showed complete regression of graft infiltration with no further recurrence after the next 40 months.

Patient No. 8 died two weeks after diagnosis before treatment was introduced, and Patient No. 9 died three weeks after diagnosis.

**Outcome**

Five patients achieved complete remission with no relapses after 6 to 13 months of treatment (four with B-cell and one with T-cell lymphoma). In three cases the remis-
Table 2. Diagnosis, clinical course, and treatment of post-transplant lymphoproliferative disorder (PTLD)

| Recipient | Year of PTLD | Age at PTLD (years) | Time from tx to PTLD (months) | Organ involvement | Histological diagnosis | Ann Arbor staging/ international Prognostic Index | Treatment | PTLD outcome | eGFR after PTLD (ml/min/1.73 m²) |
|-----------|--------------|---------------------|------------------------------|-----------------|-----------------------|--------------------------------|-----------|--------------|-------------------------------|
| 1         | 2003         | 26                  | 6                            | Fever, throat-ache, tonsillar enlargement, cervical and mediastinal lymphadenopathy, splenomegaly | Diffuse large B-cell lymphoma, [CD20 (+), CD3 (-); Ki-67 (+)] | IV/3 | Switch to sirolimus and prednisone | Resolved after 5 months | 50 |
| 2         | 2004         | 34                  | 50                           | Cervical, supraclavicular, mediastinal, abdominal nodules, splenomegaly, hepatomegaly | T-cell lymphoma, [CD 3 (+), CD 43 (+); Ki-67 (+) in 2% of cells; Bcl-2 (-/+) | III/3 | Switch to sirolimus and prednisone | Died after 14 months | Graft loss after 3 months |
| 3         | 2006         | 53                  | 34                           | Nodular mass from liver to stomach and para-aortic nodes | Diffuse large B-cell lymphoma, [CD 20 (+), LCA (+), CD3 (-); Ki-67 (+) – in most of the CD20 cells; Bcl-2 (-)] | II/2 | Switch to sirolimus and prednisone | Resolved | 48 |
| 4         | 2012         | 55                  | 168                          | Oval hypoechoic capsulated lesion in the inferior pole of the graft | Monomorphic: B-cell lymphoma [CD20 + in 100% cells, CD3 (+) in 1% cells, CD79a (+), 5-8% of tumour cells EBV positive, Ki-67 (+) in 2-3% cells, Bcl-2 (-)] | IE/1 | Switch to everolimus and prednisone – relapse added rituximab – PTLD progression – VAD | Resolved in 13 months | 50 |
| 5         | 2014         | 67                  | 35                           | Infiltrative changes included: colon, stomach, liver, visceral adipose tissue, numerous intra-abdominal lymph nodes | Diffuse B-cell lymphoma [CK7 (-), CK20 (-), CD20 (+), CD3 (-); Ki-67 (+) in 87% of cells, Bcl-2 (-)] | IV/5 | Switch to sirolimus and prednisone | Died after 3 months | – |
| 6         | 2015         | 61                  | 38                           | Nodular tumour between liver and stomach and para-aortic lymph nodes | Diffuse large B-cell lymphoma, [CD20 (+), CD3 (-); Ki-67 (+) in most of the cells, Bcl-2 (-), LCA (+)] | II/2 | Switch to sirolimus and prednisone | Resolved in 6 months | 50 |
| 7         | 2005         | 44                  | 47                           | Skin tumours on both calves | T-cell lymphoma [CD 3 (+), CD 43 (+); Ki-67 (+) in 2% of cells; Bcl-2 (+/–)] | IV/3 | Switch to sirolimus and prednisone, then surgery | Resolved in 12 months | 55 |
| 8         | 2002         | 33                  | 43                           | Abdominal tumour behind pancreas | Burkitt lymphoma, [CD20 (+); CD79a (+); CD3 (-); CD45RO (-); Tdt (+/–)] | IV/4 | Discontinuation of MMF, cyclosporine and prednisone continued | Died in 2 weeks | – |
| 9         | 2017         | 61                  | 440                          | Destructive lymphocytic lesions in the in the left temporal-parietal-occipital region | Large B-cells lymphoma | V/6 | Switch to methylprednisolone only | Died in 3 weeks | – |

* Tx – kidney transplantation, CHOP – cyclophosphamide/doxorubicin/vincristine/prednisone, VAD – vincristine/doxorubicin/dexamethasone, eGFR – estimated glomerular filtration rate
sion was achieved by switch to mTORi only (all the three cases of diffuse large B-cell lymphoma). Four recipients (aged 33, 61, 34, and 67 years) died – from 2 weeks to 15 months after PTLD was diagnosed.

The allograft function within normal limits before PTLD was diagnosed in five cases (estimated glomerular filtration rate [eGFR] from 40 to 70 ml/min) and deteriorated in one case (Patient No. 2 – eGFR 28 ml/min). All patients who died lost their graft functions shortly after switch of immunosuppression. In the three recipients who died within three months of diagnosis of PTLD the graft loss was caused by lymphoma progression and multiorgan failure rather than graft rejection. In Patient No. 2, with a survival time of 15 months, the deleterious effect of immunosuppression reduction and lymphoma invasion was added to the nephrotoxic effect of chemotherapy with CHOP. In the remaining five survivors the allograft function did not change significantly during the time (mean eGFR 52 vs. 50 ml/min). However, in Patient No. 6, irrespective of stable graft function with GFR around 50 ml/min, proteinuria rose up to 4-6 g/24 h after conversion. No anti-rejection treatment was applied due to malignant process. After two years the graft function deteriorated and the patient returned to haemodialysis treatment (eight years after KTxs). He was haemodialysed for 24 months and received the third kidney allograft in 2015 with immunosuppression consisted of basiliximab, tacrolimus, mycophenolate mofetil, and prednisone. The graft function was normal with GFR above 50 ml/min with no proteinuria and no symptoms PTLD recurrence.

**Discussion**

Post-transplant lymphoproliferative disorder is one of the unsolved problems among solid organ recipients. In the era of modern, strong immunosuppression, the rising incidence of this complication leads to the death of 30-60% of affected solid organ transplant recipients.

**Risk factors**

Among the risk factors of PTLD, EBV infection and immunosuppressive treatment are the most recognised. PTLD is associated with EBV infection in the majority of cases – 80% of B-cell origin PTLD and less in T-cell proliferations. After infection, B-cells incorporate EBV DNA into the cellular genome, which leads to decreased rate of apoptotic cell death through Bcl-2 induction and stimulates extensive proliferation of B-cells leading to lymphoblastic transformation. EBV-transformed B-lymphocytes in the transplant recipients under immunosuppressive treatment escape from the surveillance of T-lymphocytes and expand to various forms of PTLD [10]. EBV-negative PTLD was more likely to have monomorphic histology (90% vs. 65%) but was not more likely to be associated with high-risk clinical features. Paediatric recipients – very frequently EBV-negative – are especially prone to developing PTLD, and the incidence of PTLD among them varies from 0.4 to 10%, compared to adults at 1-2.3%. However, there are conflicting data regarding EBV-matching of donor and recipient in relation to PTLD development. Donor EBV-positive status as well as recipient EBV-negative status increases the risk of PTLD development five times in comparison to those matched for EBV sero-status [11]. However, more current wide studies did not recognise EBV status as a risk factor for PTLD in the European population [12, 13]. In our cohort two out of six recipients were EBV-negative with EBV-positive donors. They both developed PTLD in the form of diffuse B-cell lymphoma, 35 and 38 months after transplantation.

The other well-recognised risk factor of PTLD is immunosuppressive therapy. Whereas therapy with OKT3 or ATG, but not with anti-IL2 receptor antibodies, increases the risk of PTLD [6, 14], the reports of other types of drugs are conflicting. In the era of dual immunosuppressive therapy with azathioprine and prednison incidence of PTLD was very low, and it increased with an introduction of calcineurin inhibitors and mycophenolate. Also, the treatment of acute rejection episodes with OKT3 or ATG increased the risk in patients who did not receive antibody in induction after transplantation. Moreover, in patients who received polyclonal antibodies in induction, rejection treatment (ATG or OKT3) further attenuated the already increased lymphoma risk [15]. The use of belatacept was related to increased incidence of PTLD, especially with central nervous system localisation [16, 17]. The data from large transplant registries show that incidence of PTLD in patients treated with tacrolimus and an antimetabolite was two-fold higher compared to cyclosporine-based immunosuppression [18]. A significantly decreased risk of late-onset PTLD was seen in recipients treated with corticosteroid maintenance [19]. Surprisingly, in an investigation of 114,000 kidney transplant recipients, treatment with an mTORi together with tacrolimus increased the risk of PTLD compared to mycophenolate with tacrolimus [20].

Currently, the total immunosuppressive load rather than the use of any particular agent is thought to be critical for the development of PTLD [21-23]. In our cohort none of the recipients received mono- or polyclonal therapy in induction of immunosuppression. They were all treated with calcineurin inhibitor (cyclosporine – 5, tacrolimus – 4) with antiproliferative drugs (azathioprine – 3, mycophenolate – 3) and prednisone [9]. None of the recipients received steroids or polyclonal antibodies in the treatment of rejection episodes. The total burden of immunosuppression in the Polish population is lower than standard protocols used in western Europe and especially the US, which at least partially can explain the low number of PTLD cases in our cohort.

None of the minor risk factors including HTLV-1, BK, and CMV infection was shown to increase the incidence of PTLD. Neither HBV nor HCV contribute to non-Hodgkin
lymphoma development in immunocompromised individuals [24]; however, in a Swedish population of transplant recipients there was an association between EBV-negative lymphoma and HCV infection [25]. In our group seven patients were HBV/HCV positive and two recipients survived CMV infection after transplantation.

Timing

The time period after transplantation influences the PTLD course. Early PTLD related to immunosuppression intensity is usually associated with EBV infection frequently located in the graft, among young recipients. The late PTLD is less frequently associated with EBV infection in older patients and is frequently extranodal [26]. Quinlan et al. in their analysis considered 762 cases of PTLD among 156,740 kidney transplant recipients and showed that for early-onset PTLD, significantly increased risk was associated with young age at transplantation (HR 3.97 for <20 vs. 20-50 years), non-Hispanic white race/ethnicity, and seronegativity for EBV and CMV at transplantation. Those associations were not seen in late-onset PTLD. For late-onset PTLD, higher risk with older age reflected lymphoma patterns in the general population [19].

Localisation

PTLD can be localised in any organ. EBV-positive lymphomas more frequently involved the allograft (lung/liver/kidney), more rarely in bone marrow [25]. The potential mechanism leading to a preferential allograft localisation may include the effect of chronic antigen stimulation, presence of passenger lymphocytes in the graft, or development of lymphoma from donor lymphocytes. In kidney transplant recipients the transplanted organ is not the most frequent localisation, with gastrointestinal tract involvement in about 15% and relatively often involvement of the central nervous system [18, 27]. In our cohort isolated lymphadenopathy was seen in two recipients, four recipients presented intra-abdominal tumours, one recipient presented a tumour in the graft accompanied by enlargement of lymph nodes, one recipient presented brain infiltrates, and one recipient presented skin tumours.

Histopathology

There are several classifications of PTLD due to its heterogeneous morphological picture [8]. The newest WHO classification describes four main histological types with many subtypes [28, 29]. They are as follows: 1. Early lesions (florid follicular hyperplasia, plasmacytic hyperplasia, infectious mononucleosis-like lesion). 2. Polymorphic PTLD. 3. Monomorphic PTLD: – B-cell neoplasms: diffuse large B cell lymphoma, Burkitt lymphoma, plasma cell myeloma, plasmacytoma-like lesion, – T-cell neoplasms: peripheral T cell lymphoma, NOS, hepatosplenic T-cell lymphoma. 4. Classical Hodgkin lymphoma type PTLD.

Most B-cell PTLD were related to positive EBV status, in contrast to T-cell PTLD, which were less frequently attributed to EBV infection. The 2016 classification of the World Health Organisation of EBV-related lymphoproliferative disorders showed that EBV led to a wide range of B-cell lymphoproliferative disorders whereas T-cell lymphoproliferative disorders included peripheral T-cell lymphomas, angioimmunoblastic T-cell lymphomas, extranodal nasal natural killer/T-cell lymphomas, and other rare histotypes [30]. After organ transplantation more than 85% of PTLDs derive from B-cells, 14% from T-cells, and about 1% from natural killer cells [21]. Early-onset PTLD (i.e. within the first two years after transplant, N = 361) was more likely to be monomorphic than polymorphic, and late-onset PTLD (more than two years after transplant) was shown to be even more likely to have monomorphic pathology [31]. In our cohort two cases of T-cell lymphoma developed 50 and 47 months after transplantation occurred in EBV-positive recipients who received a kidney from an EBV-positive donor. The remaining recipients presented monomorphic B-cell lymphomas.

Treatment

There is no consensus about the optimal treatment of PTLD, with a lack of randomised phase III trials. Several therapies are used, and most of them start from immunosuppressive therapy reduction. The underlying idea is the restoration of the recipient’s immunity to limit the EBV infection. In a retrospective study the response rate to reduction of immunosuppression alone was reported in 45% with the relapse rate of 17% and the risk of acute rejection above 30% [32]. Conversely, in a small prospective study a response to immunosuppression reduction was seen in only 6% of cases with no complete remission [33].

Current guidelines recommend discontinuation of antimetabolites, reduction of calcineurin inhibitors, and maintenance of corticosteroids. However, the effect of particular immunosuppressive agents on PTLD outcome is unclear. European best practice guidelines for renal transplantation from 2002 recommended reduction of calcineurin-inhibitor by 50%, cessation of all other IS, and maintenance of steroids [34]. The recent version published in 2009 recommends reduction or cessation of immunosuppressive medication with no further details [35].

A switch to proliferation signal inhibitors is often used when PTLD is diagnosed. In vitro data on Burkitt lymphoma-derived cells showed that the combination of cyclosporin A with everolimus is preferred to the combination of tacrolimus and everolimus [36]. Conversion to everolimus was shown to be effective in preservation of graft function and control of disease progression [37]. In a study of PTLD among liver transplant recipients, switching from
calcineurin inhibitor to sirolimus at the time of diagnosis improved survival compared with only decreasing immunosuppression [38]. A series case report also showed that sirolimus induces remission of PTLD [39]. However, another study reported that mTORi use after transplantation does not decrease the risk of PTLD [20], and other studies showed conflicting results [40-42].

It was observed that reduction of immunosuppression together with removal of neoplastic B cells by rituximab and chemotherapy are the most effective modalities for long-term survival. Reduced immunosuppression during chemotherapy was shown not to increase the risk of graft function deterioration [43]. Management of PTLD should be based on histological assessment of its subtypes. In early type of PTLD presenting 100% association with EBV infection, reduction of immunosuppression alone causes complete regression, and rituximab is used for non-responding patients. Polymorphic PTLD respond well to reduction of immunosuppression with rituximab monotherapy. Conversely, monomorphic PTLD rarely responds to reduction of immunosuppression with rituximab and usually requires treatment with parallel or sequential use of chemotherapy. Most centres use anthracycline-based drug combinations, such as CHOP with granulocyte colony-stimulating factor support.

Anti-CD20 monoclonal antibody – rituximab – is widely used to treat PTLD and was shown to be effective and safe in retrospective and prospective studies on PTLD treatment, especially when combined with chemotherapy. The first study by Fisher showed its efficacy in treatment of polymorphic forms of PTLD and lack of effect in monomorphic forms with fatal outcome [44]. Some studies have shown that rituximab monotherapy has higher response rate for PTLD than in immunocompetent patients of the nontransplantation population. Some small studies showed its usefulness as first-line therapy [45-47]. It was shown that EBV status has no impact on response to therapy including reduction of immunosuppression alone and chemotherapy or survival from the time of diagnosis [48]. Earlier EBV-negative recipients were reported to respond poorly to rituximab, which was not confirmed in a more recent prospective trial [49, 50]. We, like other authors, showed no correlation between the recipient’s EBV status and response to therapy. The good and bad responses were observed in both EBV-positive and EBV-negative groups.

Surgical resection or radiation therapy may be used as adjunctive therapy in cases of advanced stage of the disease. Early surgery is recommended in the case of localised lesions (tonsillectomy, lung or liver resection with eventual re-transplantation). Radiotherapy is used in central nervous system involvement and in the rare cases of the extranodal NK/T-cell lymphomas (the only form in which radiotherapy appears to yield favourable outcomes).

The novel T-cell-based immune therapies, such as donor lymphocyte infusions and the adoptive transfer of EBV-specific cytotoxic T-lymphocytes (CTLs), are rarely used to treat PTLD. EBV-transformed B-lymphoblastoid cell lines are ideal antigen-presenting cells for the activation of T-cells used in immunotherapy expressing the same 10 viral antigens. The potential methods include the following: donor unmanipulated lymphocyte infusions or donor EBV-specific CTLs infusions, mostly studied in haematopoietic stem cell transplantation recipients. Very few attempts were performed in solid transplant recipients with promising effects [51]. Antiviral agents were used in a limited number patients, which precludes definitive conclusions. It seems reasonable to use ganciclovir in the case of prevention of PTLD in EBV-seronegative patients and/or overimmunosuppressed recipients, but there is still insufficient evidence to support this thesis.

Outcome

Although the histopathological types of PTLD reflect the types of lymphoma in immunocompetent patients, PTLD after solid organ transplantation may carry a poorer prognosis than lymphoma in immunocompetent individuals. The study of Trusson et al. showed that the response to first-line chemotherapy and overall survival are similar in PTLD and non-transplant patients. However cause of death in immunocompetent patients due to progression of the disease concerned 94% of them whereas transplant recipients died mostly of infectious other treatment-related complications [52]. In the analysis of 135 lymphomas after solid organ transplantation the five-year overall survival was 42% in all treated patients. The poor prognostic factors were older age, systemic symptoms of fever, night sweats, weight loss, poor Eastern Cooperative Oncology Group Performance Status, kidney/pancreas/heart recipients (probably due to higher immunosuppression burden compared to kidney transplant recipients), T-cell lymphoma, and HCV-infection [25].

Conclusions

Although the diagnostic criteria of different forms of PTLD are commonly known, rapid and correct diagnosis is not always easy. PTLD may appear at any time after transplantation, and it is often presented in a non-specific way – regular physical examination and imaging diagnostics should be performed as well as regular EBV infection monitoring, especially in patients with high immunosuppressive burden.

PTLD is a relatively a rare disorder, so there are too few studies and little consensus on the optimal treatment. Because the origin of PTLD is not exactly known, it is difficult to generate new treatments, and therefore large, randomised trials should be conducted.

The authors declare no conflict of interest.
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