Early post-transplant lymphoproliferative disorder – Case of fatal lymphoma after kidney transplantation

Mojca Čokaj1,2, Jasmina Marković-Lipkovski1,3, Tatjana Teržić2,3, Nataša Jovanović1, Marjana Milinković1, Radomir Naumović1,2
1Clinical Center of Serbia, Clinic of Nephrology, Belgrade, Serbia; 2University of Belgrade, School of Medicine, Belgrade, Serbia; 3University of Belgrade, School of Medicine, Institute of Pathology, Belgrade, Serbia

SUMMARY
Introduction Post-transplant lymphoproliferative disorder (PTLD) is a common malignancy following organ transplantation. Risk for PTLD is associated with the use of anti-thymocyte globulin in the prevention and treatment of acute rejection following kidney transplantation.
Case Outline We report a case of fatal PTLD presented with sudden onset of fever. A 33-year-old male patient with primary diagnosis of left kidney agenesis underwent kidney transplantation six years following hemodialysis treatment initiation. Deceased donor was a 66-year-old female whose cause of death was cerebrovascular accident. Immunosuppressive regimen consisted of basiliximab, corticosteroids, tacrolimus, and mycophenolate mofetil. Six months upon transplantation the patient was hospitalized due to fever of unknown origin. All microbiological samples were negative, but abdominal ultrasound revealed round solid mass in the right native kidney. Right nephrectomy was performed showing tumor 35 × 35 × 20 mm in size within the 70 × 40 × 35 mm kidney. Pathohistological analysis confirmed very rare monomorphic B-cell PTLD – B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.
Conclusion We consider this case of PTLD following kidney transplantation particular because of the tumor mass in native kidney after basiliximab induction and rare pathohistology. In a transplanted patient with fever, PTLD must always be considered, irrespective of immunosuppressive regimen.
Keywords: kidney transplantation; post-transplant lymphoproliferative disorder; immunosuppression; fatal outcome

INTRODUCTION
Post-transplant lymphoproliferative disease (PTLD) is a common cause of cancer-related mortality following solid organ transplantation that occurs in 2–3% of solid organ recipients [1, 2]. Five-year mortality is between 35% in the United States and 60% in Europe [3, 4]. Mortality is higher in recipients with disseminated lymphoma, brain localization, invasion of serous membranes and T-cell PTLD [5]. The outcome of early onset PTLD in adult organ recipients is also shown in Table 1 [6–13].
PTLD is typically aggressive, with a rapid onset. According to the most recent World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, PTLD is divided into three categories: early lesions, polymorphic PTLD, and monomorphic PTLD [14]. Monomorphic PTLD is mostly of B-cell origin, while T-cell PTLD and Hodgkin lymphoma-like PTLD are uncommon. Overlapping morphological features rarely appear. Almost 90% of B-cell PTLD as well as 15% of T-cell PTLD are associated with Epstein–Barr virus (EBV) infection [15]. Type of organ transplanted, recipient age, and intensity of immunosuppression are some of PTLD risk factors [16]. Incidence is high immediately after transplantation, decreasing subsequently, then rising again four to five years after the transplantation.
Generally, treatment entails reducing immunosuppression or administering anti-cancer agents and rituximab [17].

CASE REPORT
A 33-year-old Caucasian male patient with left kidney agenesis and end stage right kidney disease underwent a deceased donor kidney transplant from a 66-year-old Caucasian female donor. The patient had been treated with hemodialysis for six years prior to the transplant. Hypertension, chronic anemia, appendectomy, and subtotal parathyroidectomy were evident in the patient’s medical history.
Viral serology of the donor and recipient prior to the transplant detected both (EBV) and cytomegalovirus (CMV) IgG antibodies. Recipient human leukocyte antigen (HLA) typing confirmed A26, -; B38, 61; DR 4,11, while the donor had A 11, 31; B 38, 62; DR 4, 15. Immunosuppressive regimen included basiliximab 20 mg on days 0 and 4, followed by corticosteroids, tacrolimus (TAC), and mycophenolate mofetil (MMF). Prophylactic valganciclovir was applied to prevent CMV infection. The recipient was treated with hemodialysis for...
five weeks after the transplantation due to delayed graft function. Six weeks following transplantation the patient developed severe leukopenia that required MMF temporary discontinuation and recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) administration. Sternal puncture revealed toxic, hypocellular bone marrow. Abdominal computed tomography (CT) confirmed end-stage right kidney without solid mass. Adverse events also included urinary tract infection, diarrhea and worsening anemia. The patient was discharged after almost three months with serum creatinine level of 236 μmol/l, creatinine clearance of 39 ml/min, and proteinuria of 1 g/24 hours.

Six months post-transplantation the patient was hospitalized due to a fever. All microbiological samples were negative, but abdominal ultrasound revealed round solid mass in the right native kidney. Right nephrectomy was performed showing tumor 35 × 35 × 20 mm in size within 70 × 40 × 35 mm kidney (Figure 1).

A few days following the nephrectomy, the patient complained of pain in the lower abdomen. Abdominal CT detected multiple focal lesions in the liver and spleen, enlarged paratracheal, paraaortic, and paracaval lymph nodes, bilateral diffuse infiltrative lung lesions and pleural effusions on both sides. Microscopic examination of the tumor tissue revealed large lymphoid cells with oval or irregular nuclei, scant cytoplasm, of centroblast and immunoblast type, with rare large multinuclear cells, some of which correspond to classical Hodgkin and Reed–Sternberg cells (Figure 2A, B). There were CD3+/CD5+ T lymphocytes and rare histiocytes around the neoplastic cells. Immunohistochemistry confirmed that tumor cells were negative for epithelial membrane antigen (EMA), terminal deoxynucleotidyl transferase (TdT), CD3, CD5, CD10, CD21, cyclin D1, anaplastic lymphoma kinase-1 (ALK-1) and human herpes virus-8 (HHV-8). Notably, positivity was identified for vimentin, leukocyte common antigen (LCA), PAX-5, CD79-alfa, CD43, CD23, and p53. In addition, tumor cells were positive for CD20, Multiple Myeloma Oncogene -1 (MUM-1), CD30, CD15 (focal in HRS cells) and bcl-2 (Figure 2C-G). Proliferative activity was moderate and almost 60% of the tumor cells expressed Ki-67. HRS cells were EBV-latent membrane protein (LMP) positive (Figure 2H).

Unfortunately, the patient died before the initiation of treatment.

Table 1. Early PTLD case reports with patient outcome in adult organ recipients.

<table>
<thead>
<tr>
<th>Author (et al.)</th>
<th>Transplanted organ</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Kitajima K, et al. [8]</td>
<td>Kidney</td>
<td>Remission</td>
</tr>
<tr>
<td>Vishnu P, et al. [12]</td>
<td>Liver</td>
<td>Remission</td>
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</tbody>
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Figure 1. Macroscopic examination of the kidney: white–gray homogeneous tumor with homogeneous appearance without necrosis and hemorrhage in small native cystic kidney after long term dialysis

Figure 2. Microscopic examination: B-cell lymphoma, unclassifiable, with features of both diffuse large B-cell lymphoma and classical Hodgkin lymphoma; (A) diffuse proliferation of large lymphoid cells with scattered pleomorphic cells resembling lacunar and Hodgkin cells (arrows) (hematoxylin and eosin staining, ×200); (B) sheets of large cells with scanty cytoplasm and oval to round vesicular nuclei with prominent nucleoli (hematoxylin and eosin staining, ×1,000). Tumor cells were strongly positive for (C) CD20 (x400), (D) MUM1 (x400), (E) CD30 (x400), (F) CD15 (x400), (G) bcl-2 (x400), and (H) Epstein–Barr virus (x400).
DISCUSSION

The frequency of PTLD differs in response to many variables, including allograft type, EBV seropositive status, intensity of immunosuppression and recipient age. Our patient had higher age-related risk for early PTLD [15]. The recipient had HLA A26, B38 that are strongly related to higher incidence of EBV-positive PTLD [18]. The donor was without PTLD protective HLA A1, B8, or DR3. The overall number of HLA mismatches was not associated with higher PTLD risk [15].

While EBV and CMV IgG negative patients have higher PTLD risk, our patient was both EBV and CMV IgG positive [19, 20].

Studies suggest that PTLD risk seems to be correlated with cumulative immune suppression [21]. Stronger immunosuppressive properties of TAC comparing to cyclosporine A might be associated with higher PTLD risk [22]. Monoclonal antibodies, such as basiliximab, do not increase the PTLD risk, while repeated treatment of acute rejection might increase it [24]. In the presented case, the patient was not treated by additional immunosuppression for acute rejection and only TAC treatment might be related to higher PTLD risk.

Although renal graft lymphoma infiltration was reported, this is an unusual case of PTLD lymphoma within native kidney [25]. Previously, native kidney PTLD lymphoma infiltration has been commonly described in recipients of non-renal solid organs [26]. Rare cases of PTLD with tumor mass in native kidney after kidney transplantation might be suspected as renal cell carcinoma [27].

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma is a new entity in the updated World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, which introduces provisional borderline categories for lymphoma that demonstrate overlapping between well-established entities [14].

We consider this case of PTLD in renal transplant recipient noteworthy because of (1) tumor mass in native kidney after kidney transplant, (2) PTLD appearance after basiliximab induction, and (3) pathohistological features overlapping between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

REFERENCES


Рана посттрансплантациона лимфопролиферативна болест – случај лимфома са смртним исходом после трансплантације бубрега

Мирјана Лаушевић1,2, ЈасминаМарковић-Липковски3, Татјана Терзић2,3, Наташа Јовановић1, Марија Милинковић1, Радомир Наумовић1,2

1Клинички центар Србије, Нефролошка клиника, Београд, Србија;
2Универзитет у Београду, Медицински факултет, Београд, Србија;
3Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија

Увод
Посттрансплантационална лимфопролиферативна болест (ПТЛБ) често је малигно обољење после трансплантације органа. Ризик болести је повећан у случају примене антитимоцитног глобулина за превенцију и лечење акутног отбацивања после трансплантације бубрега.

Приказ болесника
Приказан је случај ПТЛБ, са смртним исходом, који се манифестовала изненадном појавом повишене температуре. У трансплантацији бубрега, у редовима после шест година лећења дијагнози болеснику мушког пола, старости 33 године, са агенезијом левог бубрега. Доносец била је жена старости 66 година преминула од могућног удара. Имуносупресивна терапија се састојала од басиликсимаба, кортикостероида, микофенолат мофетила и такролимуса. Шест месеци после трансплантације болесник је хоспитализован због повишене температуре непознатог узрока. Сви микробиолошки узроци су негативни, али је ултразвучни преглед абдомена указао на кружну солидну промену у десном бубрегу величине 70 × 40 × 35 mm. Патохистолошки налаз је потврдио редак облик мономорфне ПТЛБ – Б ћелијски лимфом, некласификован, са особинама дифузног крупноћелијског Б лимфома и класичног Ходгкиновог лимфома.

Закључак
Осим ретког патохистолошког облика ПТЛБ после индукције басиликсимабом, случај је значајан због реткой локализације у нативном бубрегу код болесника који је претходно лечен хемодијализом. Код примаоца аллографта бубrega у случају повишене температуре непознатог узрока увек мора диференцијално дјагностички разматрати ПТЛБ независно од примењеног имуносупресивног протокола.

Кључне речи: трансплантација бубрега, посттрансплантационална лимфопролиферативна болест, имуносупресија; смртни исход

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