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Paper Accepted* **ISSN Online 2406-0895**

Case Report / Приказ случаја

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Post-Transplant Lymphoproliferative Disorder After Kidney Transplantation

Посттрансплантациона лимфопролиферативна болест после трансплантације бубрега

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Received: January 31, 2017
Revised: March 6, 2017
Accepted: March 17, 2017
Online First: March 31, 2017
DOI: 10.2298/SARH170131099P

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SUMMARY

Introduction Post-transplant lymphoproliferative disorder (PTLD) is one of the most severe and often fatal complications observed after solid organ and bone marrow transplantations.

Case report We presented a case of a patient, born 1989, who underwent live-related donor renal transplantation at the age of 16. Induction therapy implicated administration of anti-thymocyte globulin (ATG) and corticosteroids, and maintenance therapy encompassed combination of three immunosuppressive agents: tacrolimus, mycophenolate mofetil and corticosteroid. The patient experienced first complications six months after transplantation, manifested as aggravation of tonsillitis symptoms and subsequent dysphagia. Histopathological and immunohistochemical finding of tonsillectomy specimens suggested polymorphic PTLD (with high expression of Epstein-Barr virus latent membrane protein antigen-EBV LMP antigen). Definitive diagnosis of diffuse large B-cell lymphoma (CD20+) was established upon analysis of oesophageal bioptate. Antiviral therapy was applied, along with rituximab and combination of: cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine and prednisolone (CHOP therapy), whilst the dosage of basic immunosuppressive drugs was reduced. Complex diagnostic procedures confirmed the absence of disease recurrence and stable graft function five years after completing PTLD therapy.

Conclusion The presented case who developed PTLD after renal transplantation, demonstrated that an appropriate early diagnosis, reduction of immunosuppressive regimens and vigilant application of immunomodulatory and chemotherapy could result in complete disease remission, yet preserving and maintaining the stable function of the transplant.

Keywords: kidney transplantation; post-transplant lymphoproliferative disorder; immunosupression

САЖЕТАК

Увод Посттрансплантациона лимфопролиферативна болест (ПТЛБ) је озбиљна и често фатална компликација која се развија у примаоца после трансплантације солидних органа или коштане сржи.

Приказ случаја Приказан је случај болесника рођеног 1989. коме је урађена трансплантација бубрега од живог, сродног даваоца у 16. години живота. Индукциона терапија је обухватила примену анти-тимоцитног глобулина (АТГ) и кортикостероида, а терапија одржавања комбинација три имуносупресивна лека: такролимус, микофенолат-мофетил и кортикостероид. Прве тегобе се јављају шест месеци после трансплантације у виду погоршања хроничног тонзилитиса, а затим и појаве дисфагичних тегоба. После тонзилектомије патохистолошким и имунохистохемијским испитивањем добијен је налаз који указује на полиморфни облик ПТЛБ са високим степеном експресије Epstein-Barr вирусног антигена. Дефинитивна дијагноза дифузног крупноћелијског лимфома порекла Б лимфоцита (CD20+) је постављена анализом биопсије једњака. Примењена је антивирусна терапија уз редукцију постојећих имуносупресива, ритухимаб, хемиотерапија: циклофосфамид, доксорубицин (худрохудауномуцин), винкристин и преднизон (ЦХОП терапија). Сложеним дијагностичким процедурама потврђено је одсуство рецидива болести и стабилна функција графта пет година након завршене терапије ПТЛБ.

Закључак Код болесника са развијеном ПТЛБ после трансплантације бубрега, правовременом дијагнозом, редукцијом имуносупресивног режима и пажљивом применом имуномодулаторне и хемиотерапије може се постићи комплетна ремисија болести уз одржавање стабилне функције трансплантата.

Кључне речи: трансплантација бубрега; посттрансплантациона лимфопролиферативна болест; имуносупресија

INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) has been broadly defined as a lymphoid proliferation or lymphoma that develops as a consequence of pharmacological immunosuppression following the solid organ or bone marrow transplantation [1]. The histological subtypes of PTLD range from the early Epstein-Barr virus (EBV)-associated polymorphic lymphoid proliferation resembling infectious mononucleosis, to more aggressive EBV-positive or –negative monomorphic lymphomas of B-cell or less often T-cell origin. The majority of cases are EBV-associated, of B-cell original, and express CD20 antigen. The highest risk of developing PTLD is during the first year after

transplant. In solid organ transplant recipients, the median time of onset of PTLD is about 6 months. The occurrence of the disease in this period is associated with administration of high-dose immunosuppressive agents, such as OKT3 and ATG. 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 [1-5]. The risk of lymphoma depends on the type of allograft, and the highest incidence is reported in recipients of lung and intestinal transplants (5-20%). When speaking of solid organ transplants, the lowest incidence of PTLD (1-3%) was observed in renal allograft recipients. The strong variation of incidence rates is primarily associated with the differences in the intensity of immunosuppressive therapy during the early post-transplant period. Most cases of PTLD following solid organ transplant are due to reactivation of EBV, which is latent in B-cells of 95% of the adult population, but in bone marrow transplant cases, EBV is usually acquired from the donor cells. In an immunocompetent host, EBV evokes a cellular immune response in which the proliferation of infected B-cells is controlled by CD4- and CD8-positive cytotoxic T-cells. In immunosuppressed patients, depletion of the T-cells causes this mechanism to fail. Some 20% of PTLD were EBV-negative; whilst in renal transplant recipients the incidence rate reached even 50%. Generally, PTLD is considered an iatrogenic complication of immunosuppressive therapy (indispensable after transplantation of solid organs or bone marrow), which leads to decrease in function of specific T-lymphocytes, thus resulting in uncontrolled proliferation of EBV-infected B-lymphocytes / cells. However, some EBV-negative PTLD forms were recorded, which typically tend to occur later after transplantation [6].

PTLD is characterized by extranodal involvement, typically including organs of the gastrointestinal tract, other organs including skin and CNS, as well as the allograft itself.

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 list include PTLD in the differential diagnosis. Conventional diagnostic methods to visualize PTLD include ultrasound, endoscopy, magnetic resonance imaging and CT scanning. FDG-PET scanning has been increasingly used as an important tool in the visualization of malignant lymphoma, especially for the extranodal localizations and post-treatment evaluation, and has shown to be superior over conventional diagnostic methods to differentiate residual masses as a result of vital tumour or scar tissue. Definitive diagnosis is established by biopsy of the affected organ, i.e. histopathological analysis of the bioptates. The World Health Organization classification of PTLD into four main categories is most commonly used [7-9].

The cornerstone of successful treatment of PTLD is the reduction or withdrawal of immunosuppression, independent of histology, which inherently carries the risk of allograft dysfunction or loss. This reversibility, partial or complete, with reduction of immunosuppression, differentiates PTLD from the lymphoproliferative disorders observed in patients who are

immunocompetent. If pathological changes persist after the therapy, monoclonal antibodies, rituximab (particularly in CD20-positive PTLD in various settings), as well as conventional cytotoxic chemotherapy, such is CHOP (cyclophosphamide, adriamycin, vincristin, prednisone) are introduced. Monoclonal antibodies play an important role in the management of PTLD because of their low immunosuppressive properties, targeting of lymphocyte and potential activation of the immune system. Rituximab is a chimeric anti-CD20 IgG monoclonal antibody. It has three potential mechanisms of action including apoptosis, complement activation, and antibody-dependent cell-mediated cytotoxicity [1]. It is effective for CD20-positive PTLD in various settings. It has been frequently applied and is now widely regarded as first line treatment. Chemotherapy is reserved for patients in whom other treatment options have failed or when PTLD is CD20 negative [8,10].

Furthermore, antiviral drugs, such as acyclovir or ganciclovir, are administered. Generally, the mortality rate for PTLD is high and has been estimated at about 60% after solid organ transplants and 80% after the bone marrow transplantation [1,11].

CASE REPORT

In this study, we presented the case of a patient born 1989. Alport syndrome underlying the end-stage renal insufficiency, in the presence of positive relevant family history, was diagnosed in the patients at age of three. Twelve years after diagnosis, the patients developed end-stage renal insufficiency and was subjected to ambulatory peritoneal dialysis (APD). The therapy has been continued during one-year period, until renal transplantation. In October 2005, live-related donor renal transplantation from the father was performed. HLA typing of the donor and the recipient revealed haplo-identity at A, B, DR loci (MM 3/6), identical blood group (A Rh positive) and negative cross match. Analysis of virus antibody status before transplantation revealed positive IgG against EBV both in the donor and in the recipient.

Induction therapy encompassed administration of antithymocyte globulin as follows: 7mg/kgTT at transplantation day, 4mg/kgTT on days 1 and 2 post-transplant, along with pulse corticosteroid therapy (750mg on day 0. 500mg on day 1 and 250mg on day 2 post-transplant).

The maintenance therapy involved combination of three immunosuppressive agents: tacrolimus, mycophenolate mofetil and corticosteroid.

Initial tacrolimus dose was 0.15 mg/kgTT and was adjusted according to drug level in line with the recommendations (tacrolimus trough C0 concentrations); the dosage of mycophenolate mofetil was 1500 mg/day. Postoperative course was unremarkable, without complications, and with good immediate graft function. Control examination revealed stable values of nitrogen content, whilst tacrolimus levels were within the recommended range. The patient experienced croup problems for the first time in March 2006, i.e. five months after transplantations. The examination revealed pharyngeal hyperaemia; both tonsils were moderately prominent and the presence of lacunar purulent deposits was suspected. Antimicrobial therapy was introduced; however, the problem persisted

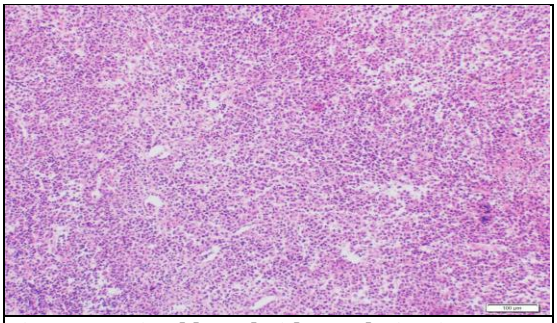

Figure 1. Mixed lymphoid population in tonsillar tissue (H&E, x100).

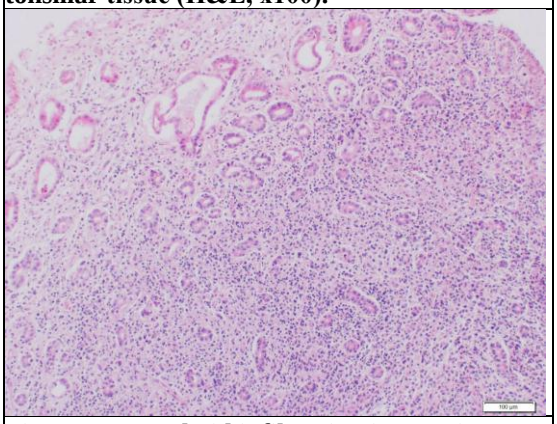

Figure 2. Lymphoid infiltration in gastric-oesophageal mucosa (H&E, x100).

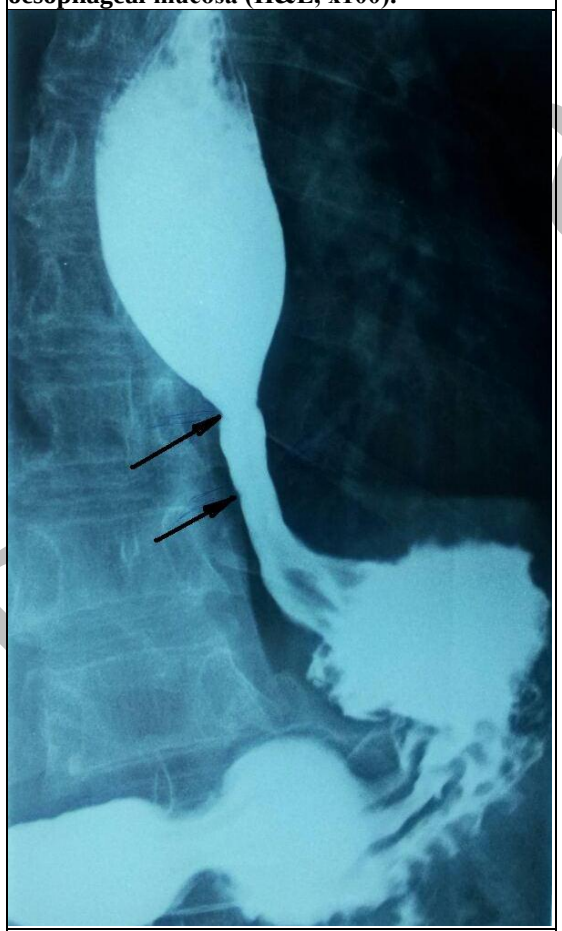

Figure 3. X-ray pictures of the oesophagus with barium contrast. Oesophageal stenosis as the only consequence of the PTLD.

associated with subfebrile condition. First hospitalization occurred in April 2006, and Tonsillitis chronica exacerbata necroticans was diagnosed. Upon recommendation of ENT-specialist, tonsillectomy was performed in April 2006. The histopathological analysis demonstrated that most part of the tonsillar parenchyma was affected by lymphoid cell proliferation compatible with a lymphoproliferative disorder (Figure 1). Immunohistochemical examination revealed morphologic features largely corresponding to a polymorphic PTLD (lymphoid tissue was characterized by high expression of EBV LMP antigen). Virology findings indicated the reactivation of EBV infection, thus antivirus therapy (acyclovir) was introduced with a reduction of ongoing immunosuppressive therapy. After one month, dysphagic problems and aggravation of anaemia syndrome was apparent, thus additional laboratory and radiological analyses were performed. Endoscopy of the upper gastrointestinal tract revealed stenosis of the distal part of the oesophagus. Histopathological diagnosis and immunohistochemical analysis of the oesophageal biopsy tissue revealed monomorphic PLTD, i.e. the definitive diagnosis of diffuse large B-cell lymphoma (CD20+) was established (Figure 2). Computed tomography (CT scan) of the chest and abdomen demonstrated soft-tissue mass in the right lower lung field, as well as lymphadenomegaly in the region of the porta hepatis and retroperitoneal space. Bone marrow puncture and biopsy also confirmed the bone marrow infiltration by lymphoproliferative tissue. Rituximab treatment was initiated (once weekly at a dose 375mg/m^2 during one month). Persistent dysphagia problems and oesophageal stenosis, as

well as prolonged lung infiltration and retroperitoneal lymphadenomegaly, indicated introduction of CHOP therapy.

The therapy regimen consisted of III CHOP, I R-CHOP and III R (the planned CHOP in combination with rituximab was discontinued prematurely because of leucopoenia). For the period of administration of monoclonal antibodies and chemotherapy, the dosage of basic immunosuppressive drugs was reduced while maintaining stable graft function, that is, tacrolimus 2mg/day with level range 1.5 to 3.5 ng/ml; total daily dose of MMF decreased to 250mg/day. Eighteen months after diagnosing PTLB, MMF was excluded and mTOR inhibitor (sirolimus) was introduced at a dosage providing average drug concentration of 5ng/ml.

Disease reassessment 6 months after the onset of immunomodulatory and chemotherapy revealed regression of the pathological changes in the lungs and regression of lymphadenomegaly in the abdomen; however, the oesophageal stenosis persisted. After a five-year and ten-year period, the application of aforementioned diagnostic procedures along with additional PET scan of the neck, chest and abdomen confirmed the absence of recurrent disease. Graft function stability was preserved, whereas oesophageal stenosis was identified as the only consequence of the PTLD therapy (Figure 3).

DISCUSSION

PTLD are different from lymphoproliferative disorders that occur in the general population. Patients with PTLD appear to have different histological findings, a more aggressive clinical course, less likelihood of responding to conventional treatments for lymphoma, and poorer outcomes when compared with immunocompetent hosts who develop malignant lymphomas [12].

Most reports in the available literature indicated the highest risk of the disease during the early post-transplantation period, particularly after lung/heart transplantation, whereas only 20% recipients of renal transplants experience the disease in the first year after transplantation [13]. Our patient developed PTLD in the first year after renal transplantation, which is most likely due to the administered induction therapy, which is similar to some cases of pediatric patients reported by other authors [14].

Identification of extranodal manifestation of the disease with primary involvement of tonsils was crucial to early diagnosis and initiation of prompt and adequate treatment. Extranodal manifestation of the disease required a complex diagnostic procedure based on a multidisciplinary team approach, involving different medical specialists, other than nephrologists - ENT-specialist, haematologist, gastroenterologist.

According to the referent recommendations and guidelines, the first step in the therapy is the reduction of immunosuppressant dose to the level that would not compromise the stable allograft function as was the case in our patient described in this article [11–17].

Disease remission in our case was achieved by combining monoclonal anti-CD20 antibody and chemotherapy.

Post-transplant lymph proliferative disorder still is one of the most severe and often fatal complications observed after solid organ transplantation. The presented case of patient developing PTLD demonstrated that an appropriate early diagnosis, reduction of immunosuppressive regimens and vigilant application of immunomodulatory and chemotherapy could result in complete disease remission, yet preserving and maintaining the stable function of the transplant.

ACKNOWLEDGEMENTS

The authors are grateful to dr V. Čemerikić-Martinović, dr Z. Bogdanović, dr S. Knežević-Ušaj and dr N. Šolajić who provided adequate interpretation and pictures of histopathological and immunohistochemical findings.

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