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Prikaz bolesnika/ Case reports

DEVELOPMENT OF HODGKIN LYMPHOMA IN THE ILEOCECAL REGION IN KIDNEY TRANSPLANT PATIENT ON LONG TERM IMMUNOSUPPRESSIVE THERAPY - A Case report

RAZVOJ HODŽKINOVOG LIMFOMA U ILEOCEKALNOJ REGIJI PACIJENTA SA TRANSPLANTIRANIM BUBREGOM NA DUGOROČNOJ IMUNOSUPRESIVNOJ TERAPIJI - *Prikaz slučaja*

Correspondence to:

Aleksandra Buha

Univerzitet u Beogradu - Farmaceutski fakultet / Katedra za toksikologiju "Akademik Danilo Soldatović" 11000 Beograd Vojvode Stepe 450

Tel: 011/395-12-48 (aleksandra@pharmacy.bg.ac.rs)

Vladimir Đorđević¹, Aleksandra Buha², Željko Radojković¹, Nemanja Zarić¹, Slavenko Ostojić¹, Nebojša Lekić¹, Aleksandar Ninić¹, Milica Ćulafić³, Biljana Mihaljević⁴, Darko Antić⁴, Vojin Vuković⁴, Mirko Kerkez¹

- Clinical Center of Serbia Clinic for Digestive Surgery, First Surgical Clinic, Belgrade, Serbia
- ² University of Belgrade Faculty of Pharmacy, Department of Toxicology "Akademik Danilo Soldatović"
- ³ University of Belgrade Faculty of Pharmacy, Department of Pharmacokinetics and Clinical Pharmacy
- ⁴ Clinical Center of Serbia Clinic for Hematology, Belgrade

Ključne reči

neželjena reakcija; imunosupresivna terapija; malignitet; takrolimus; toksičnost

Key words

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Sažetak

Nakon transplantacije organa, pacijenti primaoci organa se stavljaju na režim imunosupresivne terapije, a u primalaca bubrega ta terapija je doživotna. Bez obzira na poboljšanje preživljavanja nakon transplantacije organa, brojne su komplikacije koje se mogu javiti nakon transplantacije, a razvoj maligniteta usled imunosupresije nastavlja da bude značajan problem. Jedan od najčešćih tipova maligniteta koji se sreće kod ovakvih pacijenata je limfoproliferativni poremećaj koji se verovatno razvija kao posledica pomenute imunosupresije. Opisan je slučaj limfoma u ileocekalnoj regiji u 45-godišnjeg muškarca sa transplantiranim bubregom, koji je bio na imunosupresivnoj terapiji zasnovanoj na takrolimusu, tokom 10 godina. Literaturni podaci ukazuju na drugačiju lokalizaciju limfoma kao neželjene reakcije nakon dugoročnog korišćenja takrolimusa, pa je prema našim saznanjima, ovo jedinstven slučaj razvoja limfoma u ileocekalnoj regiji. Ozbiljne neželjene reakcije i toksični potencijal takrolimusa naglašavaju značaj pronalaženja optimalnog balansa između efektivne koncentracije leka i rizika vezanih za njegovu upotrebu.

INTRODUCTION

Immunosuppressive therapy after solid organ transplantation has been steadily improved over the last few decades and due to the introduction of new immunosuppressive agents causes of mortality among renal transplant recipients have been changed. Nowadays, with the improvement of the long-term graft survival mortality occurrence due to malignancy has been increased with the incidence of 20% ten

years after the kidney transplantation ⁽¹⁾. Not only do the immunosuppressive drugs comprise defense against viral infections that act as malignancy promoters, but they also induce DNA damage and interfere with DNA repair mechanisms ^(2,3). The most common types of malignancies are skin cancer, post-transplant lymphoproliferative disease (PTLD) that may progress to lymphoma ^(4, 5). An increased incidence of malignant tumors is one of the major factors

influencing the long-term survival of kidney transplant patients and therefore needs to be addressed carefully.

Here, we presented the case of plasma cell type lymphoma in the ileocecal region of a 45-year-old male kidney transplant patient who was on the imunosupressive-based regimen for ten years. Although this case report was previously described ⁽⁶⁾, this paper focused primarily on immunosuppressive therapy.

CASE REPORT

The patient was 24-years-old when he underwent a unilateral nephrectomy due to left kidney calculus. Chronic insufficiency of the right kidney occurred in the following year, and the patient was treated with hemodialysis. Two years after nephrectomy, the patient received a transplant from living donor. After an episode of acute rejection of the transplanted graft, the patient was subjected to the appropriate therapy and allograft function was stabilized. Initially, patient has been on triple therapy with cyclosporine, azathioprine, and prednisone, according to previous standard transplantation practice. In 2004, the patient was converted to a newer regimen - firstly from azathioprine to mycophenolate mofetil and secondly from cyclosporine to therapy that included tacrolimus (1mg twice a day), mycophenolate mofetil (250 mg twice a day), and prednisone (10 mg once a day).

In September 2013, 20 years after the first nephrectomy, the patient was hospitalized again, this time due to sepsis and the signs of respiratory insufficiency. Moreover, profound inflammatory syndrome, hydronephrosis, pyelonephritis and right kidney atrophy, were observed. These complications precipitated the right nephrectomy in February 2014. The overall renal function was subsequently ascertained by the previously transplanted kidney. Multislice Computed Tomography (MSCT) of the abdomen showed visualized transplanted kidney of the following dimensions 108x52x12mm and no signs of urinary obstruction. Above the upper half of the transplanted kidney, inter-intestinally

homogeneous collection (size 60x40mm) was observed. Furthermore, areas of inflammation containing two formed abscesses with hypervascularized walls of 3.5 mm thickness were detected below the right lobe of the liver zone in the block with associated intestinal convolutions. "Staging" MSCT findings showed enlarged lymph node in right iliac fossa and right femoral fossa (Figure 1).

Surgical removal of visualized abscess collection was intended. However, on admission, laboratory values showed leukocytosis (17x10 9 /L), anaemia (erythrocytes 3.53x10 9 /L, hemoglobin 10 7 g/L), elevated inflammatory markers (SE 125mm/h, CRP 188 mg/L and fibrinogen 5.6g/L), increased urea (15.8 mmol/L) and creatinine (231 µmol/L). After detailed preoperative assessment and preparation, laparotomy with midline incision was performed.

Additional exploration verified the existence of the block tumor of 10 cm in diameter, at the level of terminal ileum and cecum, accompanied with regional lymphadenopathy in the block with an appendix. The tumor was situated above well placed transplanted kidney without any infiltration. A urologist confirmed the normal findings of the kidney transplant and carefully removed tumor lesions with associated lymph nodes using standard right hemicolectomy with lymphadenectomy. Slices of the right colon, tumor changes in the block and lymph nodes were sent for further histopathological analysis.

Relatively well-circumscribed nodular tumor localized in the fatty tissue of retroperitoneum spreading to the wall of ascending colon, terminal ileum and appendix were described. The tumor had tough, solid texture, it was capsulated and clearly separated from adipose tissue (Figure 2). Right next to the tumor nodose were two enlarged lymph nodes measuring 25x20x15mm and 10x10x5mm in size, as well as the unclear infiltrate of 20x20x15mm in size, similar to a nodular tumor and located about 1 mm from the line of fat tissue resection. From the remaining adipose tissue, 6 more lymph nodes were isolated.

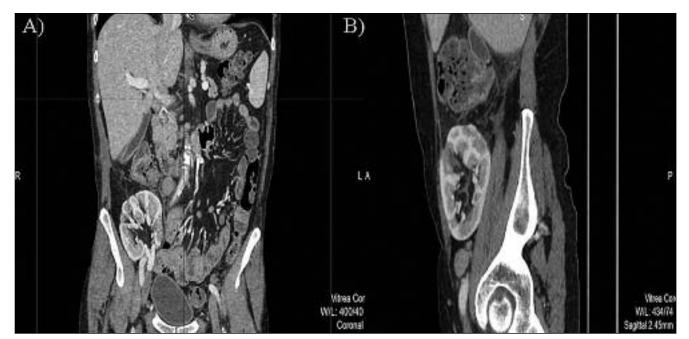


Figure 1. MSCT findings showing enlarged lymph node in right iliac fossa (A) and in right femoral fossa (B).



Figure 2. Relatively well-circumscribed nodular tumor with tough and solid texture was excised. (Taken from Mihaljević et al, 2016)

Histological sections of the tumor mass showed the proliferative change of organization from multinodular to diffuse, consisting of a relatively monomorphic population of large cells that might correspond to atypical lymphoid cells. The peripheral proliferation of small lymphoid cells was observed. In described nodular areas, large blastoid cells with various zones of necrosis, moderate mitotic index and atypical mitosis were detected. Tumor mass consisted of Reed-Sternberg cells which were CD15, CD30 and EBV-positive and PAX5, CD20, CD3, CD5, BCL2, Alk1 negative based on histopathological and immunohystochemistry findings. Obtained result indicated nodular sclerosis type of Hodgkin lymphoma.

The postoperative course was usual, and the patient was discharged in good general condition, metabolically and hemodynamically stable. Treatment involved modification of the immunosuppressive drug regimen (tacrolimus and MMF were discontinued), resection of localized disease, and chemotherapy.

All relevant information from the patient's history is graphically presented in the timeline (supplementary material).

DISCUSSION

Patient survival time after renal and other solid organ transplantations has been substantially increased, partly due to modern immunosuppressive treatment. Nevertheless, the frequency of tumors is 2 to 4-fold higher when compared to the non-transplanted population, the most prevalent being Kaposi's sarcomas, non-Hodgkin lymphomas, and nonmelanoma skin cancers with the rate over 20 times greater than the one in general population (7, 8). In a study that included 2224 solid-organ transplant recipients who underwent transplant between 1985 and 2013, 27 of 2224 patients developed PTLD. The mean interval between transplant and diagnosis of PTLD was 65 months. Most patients with PTLD have extranodal involvement, with the gastrointestinal tract being the major site of clinical presentation-35% of all cases (9). In a retrospective single-center study conducted to assess the occurrence of de novo neoplasms in renal patients, malignancy was observed in 4.8% of patients of which 22% developed urinary tract tumors while 16% of recipients developed non-Hodgkin lymphoma with PTLD ⁽¹⁰⁾.

In this case study, some interesting points have been presented. It is known that Epstein-Barr virus (EBV) plays a major role in the development of post-transplant lymphoproliferative disorders, although an increasing awareness of EBV-negative PTLD has been recently shown (11). Positive EBV immunostain of the tumor mass observed in this particular case confirmed that PTLD and lymphomas development in kidney transplant patients are highly correlated with EBV infections. A long lasting scientific debate on the possible influence of immunosuppressive regimen on malignancy incidence among kidney transplanted patients have pointed to the association between malignancy incidence and duration of therapy rather than a particular therapy regimen (12). Some studies report significantly lower malignancy in recipients on tacrolimus treatment (13). In this particular case, tacrolimus-based regimen produced malignancy development after ten years suggesting the duration of exposure as the more relevant factor of malignancy incidence. The ileocecal localization of plasma cell type lymphoma observed in this case study should be especially emphasized since it is to our knowledge, unique in literature.

The importance of careful monitoring of posttransplant patients in regards to side-effects and toxicity of immuno-suppressants is essential and emphasized through this case report. Timely recognition and treatment may show the benefit beyond survival. Serious adverse drug reactions and potential toxicity of tacrolimus underline the importance of finding the optimal balance between effective drug concentration and the risk associated with its use.

Competing interests

The authors declare that they have no competing interests.

Consent to Publish

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

supplementary material.

24-years-old patient Unilateral left kidney nephrectomy Chronic right kidney insufficiency On hemodialysis Received a kidney transplant Myocardial infarction Patient on posttransplant taerolimus-based triple regimen-(Tac/MMF/steroids) Sepsin Signs of respiratory September insufficiency Inflammatory syndrome Hydronephrosis 2013 Pyclonophritis Right kidney atrophy Multiplice Computed Tomography (MSCT) initial treatment: Inter-intestinally homogeneous Right nephrectomy collection (size 60x40mm) observed above the upper half of the transplanted kidney Areas of inflammation (two formed abscesses) detected below Surgical removal of visualized shacesa the right labe of the liver zone collection with intestinal convolutions Laparotomy with midline "Staging" MSCT incision Enlarged lymph node in right ilise fossa and right femoral fossa rebruiny 2014 Standard right hemicolectomy with Surgical exploration lymphadenectomy Subhepatic abscess collection of limited necrosis in the right side · To remove temor lesions with associated lymph nodes Wall Block tumor (10cm in diameter) Histopathological analysis at the level of terminal ileum and Immunohystochemistry cenum, accompanied with regional lymphadenopathy in the Bone marrow biopsy block with an appendix, situated above transplanted kidney Modification of the immunosuppressive drug regimen Diagnosis · Facrolinus discontinued Hodgkin lymphoma, nodular Resection of localized disease aclerosis type Chemotherapy No lymphomatous involvement

Patient discharged in good general condition Metabolically and hemodynamically stable

Abstract

Following solid organ transplantation, the patient's management includes the provision of immunosuppressive therapy to the recipient. All kidney transplant recipients require lifelong immunosuppression. Regardless the improving survival following solid organ transplantation, post-transplant complications such as the development of malignancy due to immunosuppression remain to be an issue. One of the most common malignancies encountered in the post–solid organ transplant is lymphoproliferative disorder likely developed as a consequence of immunosuppression. We report a case of plasma cell type lymphoma in the ileocecal region of a 45-year-old male kidney transplant patient who was on a tacrolimus-based regimen for ten years. Although literature data indicate differently localized lymphoma as an adverse reaction to the long term use of tacrolimus, to our knowledge, this is the first described case of lymphoma in the ileocecal region. Serious adverse drug reactions and potential toxicity of tacrolimus emphasize the importance of finding the optimal balance between effective drug concentration and the risk associated with its use.

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