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Long-term therapy of Kaposi's sarcoma with the use of prospidium chloride and mTOR receptor inhibitors in a patient after kidney transplantation

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A case of a long-term management of a patient with Kaposi's sarcoma developed as presumably related to a "standard" immunosuppressive therapy after kidney transplantation has been described. Immunosuppressive therapy conversion to motor receptor inhibitors and administering chemotherapy with presidium chloride allowed for a long-term remission of the disease and a satisfactory clinical outcome.

Keywords: Kaposi's sarcoma; proliferate signal inhibitors; immunosuppressive therapy

CDM, Central Doppler mapping
CMV, Cytomegalovirus
EBV, Epstein-Barr virus
GFR, Glomerular filtration rate
HHV-8, Human herpes virus type 8
KS, Kaposi's sarcoma

Introduction

Kidney transplantation is a promising method of treating patients with end-stage chronic renal disease, significantly improving the patient quality of life, but it is associated with the risk of immunosuppressive therapy complications [1]. One of the most serious complications is Kaposi's sarcoma (KS), a systemic multifocal tumour disease of vascular origin predominantly affecting the skin, lymph nodes, and visceral organs, which was first described by the Hungarian dermatologist Moritz Kaposi in 1872 [2–4]. Iatrogenic KS related to immunosuppressive therapy in chronic systemic diseases after organ and tissue transplantation [5, 6]. The authors followed up a patient with a severe form of KS for 9 years, and could keep the KS progression controlled by using the therapy with mTOR inhibitors. This case report is presented to demonstrate the potentially efficient treatment of immunosuppression-associated KS even in its advanced forms.

Clinical case report

Patient K., 70 years old. He fell ill at the age of 30, when abnormal urinalysis results (protein, erythrocytes) were obtained after tonsillitis.

Chronic glomerulonephritis was diagnosed (renal biopsy was not performed). From the age of 48 (1998), gradually increasing blood creatinine levels were documented. The kidney function had been lost by 2003, the end-stage chronic renal disease developed; the treatment with programmed hemodialysis via native arteriovenous fistula was initiated. The patients tolerated the dialysis therapy satisfactorily; a moderate blood pressure increase up to 180/100 mm Hg was documented. The patient was placed on the waiting list for kidney transplantation. He underwent cadaveric allotransplant surgery on 15.08.2008 from a 37-year-old posthumous donor who died as a result of severe traumatic brain injury with circulatory arrest; the cold ischemia time was 6 hours, the number of HLA phenotyping mismatches was 3/6. The graft function was immediate. The early postoperative period was uneventful, the recipient was discharged from hospital after 42 days, having creatinine levels of 100 μmol, glomerular filtration rate 62 mL/min×m^2. Urinalysis results were without abnormalities. The patient received a three-component immunosuppressive therapy: prednisolone, cyclosporine A up to 300 mg/day, mycophenolic acid at a dose of 1440 mg/day. There had been no reasons for hospitalization for 7 months. The patient was hospitalized in February 2009 for cytomegalovirus (CMV) infection replication and clinical signs of enterocolitis. The viral load was 6000 CMV copies per mL, herpes simplex virus and Epstein-Barr virus (EBV) viral particles were also found in blood. The condition was qualified as excessive immunosuppression, its reduction was undertaken: the mycophenolic acid dose was reduced to 720 mg/day, antiviral therapy with intravenous ganciclovir 500 mg/day was administered). At discharge from hospital, creatinine was 110 μmol/L, no abnormal signs in urinanalysis were seen. EBV DNA was detected in blood, HHV-8 viremia was absent. The patient continued to take valganciclovir at a dose of 900

mg/day on an out-patient basis. In May 2009, for the first time, he noted a purple-cyanotic lesion on the 1st toe of the right foot that further progressed extending to the upper third of the thigh and causing multiple rashes (Fig. 1). In September 2009, a skin biopsy of the 1st toe area was performed, and the KS diagnosis was histologically confirmed (Fig. 2), so the immunosuppression conversion was undertaken (cyclosporine A was cancelled, sirolimus 2.5 mg/day, was administered, mycophenolic acid dose was 720 mg/day). On November 26, 2010, a renal graft biopsy was taken; light microscopy revealed no graft pathology. The decision was made to cancel mycophenolic acid. From November, 2010, the patient received immunosuppressive therapy with prednisolone 10 mg/day. Due to the unavailability of sirolimus therapy, everolimus 1.5 mg day was prescribed and prednisolone therapy was discontinued. There was a gradual increase of rashes spreading on the entire right lower limb; edema of the right lower limb was increasing. In this regard, treatment with prospidium hydrochloride (prospidin) were given for 6 months. After chemotherapy completion, the remission of the disease was achieved with a satisfactory graft function. During the treatment, the patient's condition improved significantly, the edema of the right lower extremity diminished, and the rash intensity in some areas slightly decreased. The blood level of everolimus at discharge from hospital was 7.7 ng/mL. The patient received metabolic, antimicrobial, infusion therapy, no signs of an active inflammatory process in the graft were revealed at examination. Currently, the patient is being followed-up by the group of authors. No evident progression of KS has been noted since 2011 so far. In February, 2012, epicystostomy was performed for reflux nephropathy of the graft with the subsequent development of recurrent pyelonephritis. Due to a deteriorated graft function, further chemotherapy was not performed. Klebsiella pneumoniae 10^6 CFU/mL was isolated in urine culture. At that

time, according to ultrasonography results, the graft size was 103 × 44 mm, parenchyma was 17 mm, cortical-cerebral differentiation was kept normal. The cortex echogenicity was unchanged. The cortex echo structure was homogeneous. The cortical layer thickness was 6.7 mm. The pyramid is 9.5 mm high, 6.7 mm wide. Cortical blood flow at CDM (central Doppler mapping): to the subcapsular sections. The number of flow signals at CDM was retained. The renal sinus was 17 mm. The patient's urinary tract was not dilated. Glomerular filtration rate $(GFR)_{MDRD}$ *was 40.0 mL/min. The blood level of everolimus was 7–8 ng/mL. Immunosuppressive therapy with everolimus 1.5 mg/day was continued, methylprednisolone was cancelled. From 2011, against the background of recurrent urinary tract infection and constant antibiotic therapy, there was a gradual increase in creatinine levels. For the following 5 years the creatinine level remained stable and made about 200 μmol/L. Since 2018, the patient has been receiving ketosteril, the graft function has stabilized at a GFR of 18 mL/min. No KS progression has been seen.*

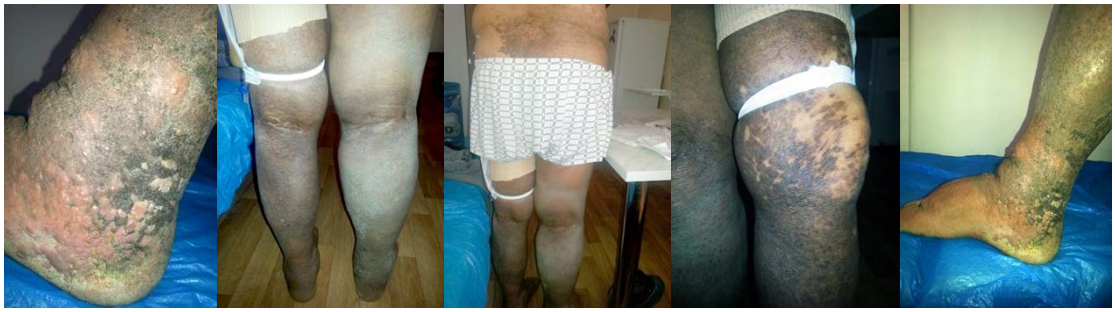

Fig. 1. Cutaneous manifestations of Kaposi's sarcoma in patient K. Published on patient's consent

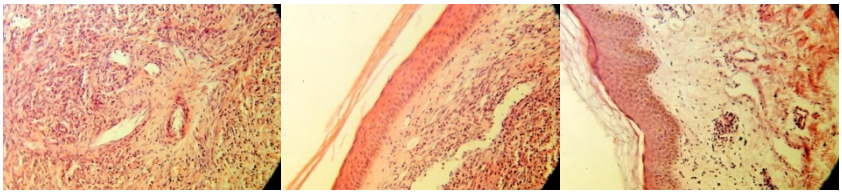

Fig. 2. Histological pattern of skin lesions in patient K.

Currently, there is an increase up to 370 μmol/L in creatinine levels, up to 25 mmol/L in urea. Diuresis is kept at a volume of 2 liters, the patient receives everolimus monotherapy at a dose 1.75 mg/day. Despite chronic renal transplant dysfunction manifestations, it is currently possible to refrain from returning to dialysis.

Discussion

This patient underwent a successful kidney transplantation, which significantly improved his quality of life. A year later, a severe complication in the form of KS developed. The cause of the tumour process onset could be excessive immunosuppression carried out according to routine practice which triggered the activation of a viral infection caused by a group of herpes viruses [5, 6, 11]. An unsatisfactory response to a dose reduction of antiproliferative drugs is typical of viral infected patients after kidney transplantation [4, 6]. In this case, a two-fold decrease in the dose of mycophenolic acid at a year after transplantation due to the detection of replicating opportunistic EBV and CMV viruses did not lead to an improvement in the clinical situation. Moreover, 3 months later, in May 2009, the patient developed the initial clinical manifestations of KS. An effective function of B cells causes intense proliferation, and therefore the administration of antiproliferative drugs and the drugs from the antimetabolite group that reduce B-cell immunity is justified. Meantime, as most authors point out, B-cell immunity is necessary, first of all, to resist bacterial infections [1, 6, 9, 10]. Calcineurin inhibitors, cyclosporine and tacrolimus, mainly suppress T-cell immunity, which is necessary to resist infections of a viral, fungal, and tuberculous origin. The progression of virus-associated KS was stopped after the patient had been switched from cyclosporine to

sirolimus. In 2003, the efficacy of replacing cyclosporine with sirolimus, instead of the currently popular scheme of the combined use of low doses of calcineurin inhibitors and proliferation signal inhibitors, was demonstrated in the study performed at the RSCS named after Academician B. V. Petrovsky [11]. Proliferation signal inhibitors are represented by two drugs: sirolimus and everolimus. Efficacy against KS and PTLD-associated EBV was initially established with regard to sirolimus [12]. With the advent of the second drug in the group of proliferation signal inhibitors in clinical practice, the efficacy of sirolimus against virus-associated cancers was extrapolated to everolimus. However, the similar efficacy of sirolimus and everolimus in relation to their effect on the progression of KS and EBV-associated PTLD has not been proven and, according to our observations, is questionable. Specifically, in our case, the forced replacement of sirolimus with everolimus a year after the start of therapy led to the disease progression and required chemotherapy with prospidium chloride.

In the presented case, a rather early diagnosis and timely immunosuppressive therapy conversion to proliferation signal inhibitors, as well as the course of chemotherapy using prospidium chloride, made it possible to slow down the spread of the tumour process and preserve the function of the transplanted kidney. Currently, the patient is experiencing a progression of the renal graft dysfunction due to recurrent urinary tract infection in the presence of reflux-nephropathy. The post-transplant period has made 11.5 years.

Conclusions

1. Timely adjustment of immunosuppressive therapy with a decrease in the dosage of calcineurin inhibitors and the rejection of

template regimens will help avoiding excessive suppression and the development of immunosuppressive therapy complications.

2. Early conversion to the proliferation signal inhibitors contributes to Kaposi's sarcoma regression in patients after kidney transplantation and preserves the kidney graft function.

3. In the immunosuppressive therapy regimen, sirolimus is the preferred drug from the group of proliferation signal inhibitors for patients with Kaposi's sarcoma developed after kidney transplantation. An important organizing task is to ensure the availability of this drug for patients, which has not been included in the "15 High-cost Nosologies Programme" yet.

4. Chemotherapy with prospidium chloride in patients with Kaposi's sarcoma after kidney transplantation provides a high clinical efficacy and a long-term disease remission.

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