JMS 2021;4(2):15-18
UDC:616.61-089.843-06:616.61-022.6

BK NEPHROPATHY AS A CAUSE FOR PROGRESSIVE LOSS OF FUNCTION IN A TRANSPLANTED KIDNEY

Galina Severova- Andreevska[1,3], Ana Stojanovska[1,3], Igor Nikolov[1,3],
Irena Rambabova- Bushletik[1,3], Gordana Petrushevska[2,3], Goce Spasovski[1,3]
[1]University Clinic of Nephrology-Skopje,
[2]Institute of Patology,
[3]Faculty of Medicine, Ss Cyril and Methodius University in Skopje, R.North Macedonia

Abstract

BK virus nephropathy is a serious complication of kidney transplantation. Although 10%–30% of kidney recipients have BK viremia, nephropathy occurs in approximately 2%. We present a case of a 27-year-old woman with kidney transplant loss due to BK nephropathy.

Transplantation was performed from a living donor mother, with a haploid HLA match. Treatment with basiliximab was induced and followed by a standard triple immunosuppressive therapy (corticosteroids, cyclosporin, mycophenolic acid). On the seventh day she was switched to tacrolimus (Tac), with serum Tac level up to 4,8 ng/ml. Three months after transplantation, the first increase in creatinine (sCr) up to 263 mmol/L appeared. The graft biopsy revealed: acute graft rejection, Banff classification (g2, and2, t2, a0, ah0, cg0, cc0, ct0, cd0) as well as an additional finding for BK polio infection (nuclear atypia in tubular epithelium, interstitial edema and mixed rich infiltration and acute tubulitis). The dose of Tac was reduced but also treatment with methylprednisolone pulse therapy was induced. Values for sCr were 173-280 mmol/L. After six months, a second biopsy was performed, with a finding of interstitial fibrosis and tubular atrophy. The Tac was switched to Cyclosporine.

Five months later, the patient was hospitalized due to prolonged fever, sCr 500- 600 mmol/L. The third graft biopsy established chronic allograft nephropathy. The patient was treated with chronic hemodialysis. All microbiological tests were negative. Despite the antibiotic therapy, the patient remained febrile until graftectomy.

This case may be a rare example of systemic BK virus infection. Monitoring of BK infection, as well as modulating the therapy is of great importance for graft survival.

Kew words:kidney transplantation, BK infection, immunosuppressive therapy, BK nephropathy

Introduction

BK virus belongs to the family Polyoma viruses. They are ubiquitous and tend to infect certain species of living creatures such as monkeys, rabbits, mice, birds and humans. In the general population, the prevalence of healthy individuals who are virus carriers reaches up to 70%. Only immunosuppressed individuals are affected. The virus has an affinity for the urogenital tract, but cases of generalized infection have also been reported. BK nephropathy occurs in 10% of transplant patients [1], and in 15-50% of them the damage progresses to permanent loss of graft function [2].

Treatment of BK infection is a major challenge, as excessive immunosuppression is cited as the cause. There is no specific treatment for it. The therapeutic measures indicated refer to the reduction of immunosuppressive therapy (mainly tacrolimus and mycophenolic acid).

Case report

We present a case of a 27-year-old woman, with undifferentiated primary renal disease, diagnosed in 2012. She was followed up on an outpatient basis at our Clinic, with a progressive deterioration of renal function towards end-stage chronic renal disease. Treatment with an active hemodialysis program was not started. In 2013, kidney transplantation was performed from a living donor – patients' mother, with a haploid HLA match. The right kidney was transplanted into a left iliac fossa. A

single vein and a single artery were used. A typical terminal - terminal anastomosis of the renal artery was created. The duration of the cold ischemia was 3 hours, and warm ischemia endured for 3 minutes. The patient was treated with induction therapy with Simulect 20 mg D (day) 1 and D4, as well as standard immunosuppressive therapy (corticosteroid 500 mg D-1, 560 mg D0, 250 mg D1, 125 mg D2, and then 1 mg per kg / TT with gradual reduction, mycophenolic acid 500 mg per D1, then 2x 750 mg per day and Cyclosporine A 2x125 mg per day from D1). Immediately after the intervention, diuresis of up to 8 liters was obtained in 24 hours. On the first day, serum creatinine was 42 mmol / L. During hospitalization, normal renal function was registered at all times, without need for blood and plasma substitution. Microbiological examination revealed urinary tract infection with *Escherichia coli*, as well as *Enterococcus* isolated from drainage material, treated according to an antibiogram with amp Vancomycin 500 mg / day and Amp. Ciprofloxacin 200 mg / day. The patient was discharged from the transplant center on D12, with serum creatinine values of 53 mmol / L. The therapy prescribed for home-care: tabl. Decortin 20 mg, caps. Tacrolimus a 1 mg 3x3, caps. Mycophenolate sodium a 250 mg 2x3, protection with tabl. Vanganciclovir a 450 mg 1x1, tabl. Bactim a 480 mg 3x per week, tabl. Ranital a 150 mg 2x2, tabl. Ciprofloxacin a 500 mg 2x1, tabl. Aldizem a 90 mg. During outpatient follow-up, the serum creatinine ranged from 64 up to 104 mmol / L. Decortin therapy was gradually reduced to 5 mg / day. Blood tacrolimus concentrations ranged from 3.4 to 1.8 ng/ml. Three months after transplantation, an increase in serum creatinine to 285 mmol / L was reported. The color Doppler ultrasonography was performed. The finding from the graft biopsy revealed acute graft rejection, Banff classification (g2, i2, t2, cg0, ci 0, ct 0) as well as an additional finding for BK polyoma infection (nuclear atypia in tubular epithelium, interstitial edema and mixed rich infiltration and acute tubulitis). Modulation of immunosuppressive therapy was performed - reduced dose of Tacrolimus 1g 2x2, but methylprednisolone injection of 500 mg / day was given in consecutive days, which was gradually reduced. Serum creatinine values ranged from 227 mmol / L to 173 mmol / L. In the following period, a gradual increase in serum creatinine to 288 mmol / L was observed. Six months after the transplant, a graft re-biopsy was performed. The pathohistological finding was in favor of interstitial fibrosis and tubular atrophy, in addition to acutely exacerbated chronic tubulointerstitial nephritis. In the following months, the serum creatinine was in continuous increase from 170 mmol / L to 393 mmol / l, and a reduced therapy with Mycophenolate sodium 250 mg 2x2, Tacrolimus a 1 g 2x1 was obtained. The concentration of tacrolimus was 3.5 ng/mmol. There were no decoy cells present in the urine. Acute hepatitis B was verified and treatment with tabl. Lamivudine a 100 mg 1x1 was initiated. Eleven months after the transplant, the patient was hospitalized again at our Clinic, suffering from diarrhea, serum creatinine 500 mmol / l and anemia. She was substituted with blood transfusion, and tacrolimus was replaced with Cyclosporine A 50 mg 2x1. One year after transplantation, a third graft biopsy was performed with a finding of chronic allograft nephropathy, Banff classification (g0, t1, v0, i1, ah2, cg1, ct 2, c2, cv1), with a predominant finding of tubular atrophy with interstitial fibrosis and inflammation. Serum creatinine was in the range between 500 to 600 mmol / L. Intravenous femoral venous catheter was inserted, and chronic hemodialysis treatment was started. For the next three months, the patient had persistent fever. All markers of inflammation as well as microbiological tests were negative. The graft was explanted, after which the patient was afebrile.

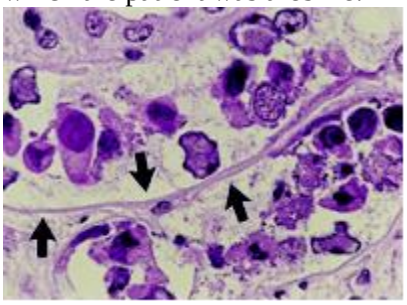

Fig.1. Tubular necrosis at BK nephropathy

Discussion

Predisposing factors for the development of BK nephropathy have been reported in the literature correlated with the use of immunosuppressive therapy with Tacrolimus and / or Mycophenolic acid [3]. In our case, the patient was initially treated with Tacrolimus and Mycophenolic Acid, with tacrolinaemia values within the reference range. The diagnostic methods that are currently recommended, such as PCR techniques for determining the presence of BK DNA in blood (specificity 100% and sensitivity 96%) and urine (specificity 100% and sensitivity 92%), were not yet available in our country at the time of the study [4].

The method that was available and that we used, was determining the presence of decoy cells in urine (sensitivity 24% and specificity 84%) [4].

In our case this finding was negative. From the clinical presentation there was no ureteral obstruction or hemorrhagic cystitis [5].

Only laboratory elevated serum creatinine occurred at the beginning. The first changes in the tubular epithelial cells on the other hand were detected on the first renal biopsy, three months after transplantation, although temporary changes can also occur later in the first year. The literature describes that the basic changes in BK nephropathy occur in the cells of the tubular epithelium. There are four types of changes that result from replication of the virus in the cells. It further leads to necrosis of the tubular epithelium. Similar changes can be seen in pro-infection with Cytomegalovirus. The changes in the interstitium are described as infiltration of a mixed type of inflammatory cells, which is why the presence of signs of acute rejection is often described, as it was presented in our case [6].

Our patient was treated with methylprednisolone because of the findings favoring acute rejection. Typically for the clinical course of BK nephropathy, a gradual and progressive deterioration of graft function occurred.

According to the recommendations, immunosuppressive therapy was reduced and tacrolimus was later replaced with cyclosporine, with no effect on progression of graft function deterioration [7].

Due to the development of acute hepatitis B, she was treated with antiviral therapy, also without effect on the progression of reduced graft function. One year after transplantation the pathohistological finding was in favor of chronic allograft nephropathy and the need for hemodialysis treatment was inevitable. Until that moment, there was presence of local BK nephropathy, only with graft-involvement. But for the next three months, the patient continued to have fever, with no signs of infection. The fact that the fever ceased after graft-explantation suggested a possible and rare form of systemic BK infection.

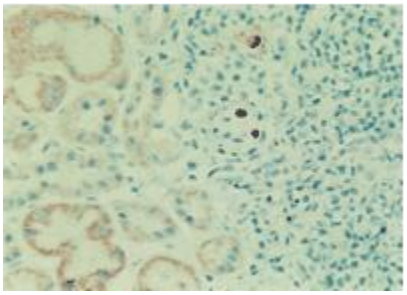

Fig. 2. Interstitial infiltration that suggests acute graft rejection

Conclusion

Sensitive and specific PCR techniques are not available in our country to diagnose BK infection, which is why this is probably the first case of BK nephropathy. In our case, tacrolimus therapy in combination with mycophenolic acid was a predisposing factor for the development of BK nephropathy.

Pathohistological changes and the clinical course of progressive graft function loss in the first year of transplantation were in favor of the diagnosis. The diagnosis of BK nephropathy and the strategy of modulating immunosuppressive therapy as the only method of managing BK nephropathy pose a major challenge in preventing the progressive loss of graft function.

References:

1. Hirsch HH et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation. 2005; 79(10):1277.
2. Wadei HM, Rule AD, Lewin M et al. Kidney transplant function and histological clearance of virus following diagnosis of polyomavirus-associated nephropathy (PVAN). Am J Transplant. 2006; 6(5 Pt 1):1025-32.
3. Olivier Prince1,2, et all. Risk factors for polyoma virus nephropathy Nephrol. Dial. Transplant. (2009)24 (3): 1024-33
4. Viscount H. B., Eid A. J., Espy M. J., et al. Polyomavirus polymerase chain reaction as a surrogate marker of polyomavirus- associated nephropathy. Transplantation. 2007; 84((3)):340–45.
5. Van Aslden MC et al. BK virus infection in transplant recipients: clinical manifestations, treatment options and the immune response. Neth J Med. 2012 May; 70(4):172-83
6. Nickeleit V, Hirsch HH, Zeiler M, Gudat F, Prince O, Thiel G, Mihatsch MJ. BK-virus nephropathy in renal transplants-tubular necrosis, MHC-class II expression and rejection in a puzzling game. Nephrol Dial Transplant. 2000 Mar;15(3):324-32. doi: 10.1093/ndt/15.3.324. PMID: 10692517.
7. Bertram L. Kasiske1 et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary; Kidney International advance online publication, 21 October 2009;doi:10.1038/ki.2009.377.