BK Polyoma Virus Infection in Renal Transplant Recipient

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ABSTRACT

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The survival of renal transplant recipients has improved over years thanks to better critical care facilities, better evaluation methods for poorly functioning grafts, and better immunosuppressant agents being available. A 27 years old patient had hypertension for 8 years, but was on irregular treatment. He was diagnosed to have renal failure one year back. Initially patient was on renal replacement therapy and then he underwent allograft renal transplantation. Intraoperative and post-operative periods were uneventful with steady decline of S. Creatinine which attained a nadir of 1.3mg% at the time of discharge. Patient was put on Tacrolimus, MMF and steroid. Patient was on regular follow-up with RFT monitoring. Serum creatinine value started rising after maintaining nadir for 3-4 months. On evaluation BK Virus infection was suspected. Urine was tested for BK Viruria using PCR assay which was then confirmed with renal biopsy. The case is reported mainly to draw attention to the fact that BKVN is a cause of graft dysfunction.

Keywords: Renal Graft dysfunction, BKVN, Polyoma Virus, IVIG, Retransplantation

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INTRODUCTION

With the introduction of new immunosuppressive agents, the outcome in renal transplant patients has significantly improved. Due to emergence of opportunistic infection specifically BK virus, a number of transplant patients continue to have progressive graft dysfunction. The prevalence of BK virus nephropathy varies 1- 10 %, usually occurs in the initial few months after renal transplantation. Up to 50% renal transplant recipients have been estimated to have renal allograft loss due to BKVN.[1] The incidence of graft failure secondary to BKVN has come down due to early detection of BKV infection using PCR assays associated with immunosuppressant agent dose reduction for BKVN. Although, BKV infection involves components of recipient, graft and viral factors,[2] the exact pathogenesis as well as risk factors of BKVN has yet to be established. Disruption in recipient immunologic function and viral replication is thought to cause BKVN.

CASE REPORT

A 27 years old patient had hypertension for 8 years, but was on irregular treatment. He was diagnosed to have renal failure one year back, when he was evaluated for fatigue, nausea, vomiting and pedal edema of 3 weeks duration. His serum creatinine was 12.8mg%. Initially patient was on renal replacement therapy and then he underwent allograft renal transplantation. Intraoperative and post-operative periods were uneventful with steady decline of S. Creatinine which attained a nadir of 1.3mg% at the time of discharge. Patient was put on Tacrolimus, MMF and steroid. Patient was on regular follow-up with RFT monitoring. Serum creatinine value started rising after maintaining nadir for 3-4 months. Patient was evaluated with urine routine and culture & sensitivity test when he developed dysuria and was found to have no bacteriuria. Possibility of BK Virus infection should be ruled out in patients with steadily rising serum creatinine, as it is a common cause of progressive graft dysfunction. Urine was tested for BK Viruria using PCR assay which was then confirmed with renal biopsy. BK Virus infection is mainly treated with reduction in dose of immunosuppressant, hence tacrolimus dose was modified and MMF was withdrawn.

DISCUSSION

The Polyoma viruses are small (30-45nm), icosahedral, non-enveloped, double-stranded, circular DNA viruses that replicate in the host nucleus.[3] It contains 4 serologic groups and genotypes categorized as I, II, III and IV, may have different virulence properties.[3] In immunosuppressant state, BKV starts replicating. Primary infection occurs in childhood by oral and respiratory exposures in around 60-80% of individuals.[3] Latent infection occurs in renal epithelium (transitional epithelium, renal tubular epithelium, parietal epithelium

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of Bowman capsule), bladder and lymphoid tissue.[4] The prevalence of BK viruria, BK viremia, and BKVN in renal transplant recipients is estimated to be 30%, 14%, and 8%, respectively.[1] BK induced nephropathy occurs in 1% to 10% of renal transplants, (mean incidence of 4.91%), usually in the first few months post-transplant, and may result in graft failure in 15% to 50% of affected patients.[4]

BKVN usually presents as asymptomatic infection without any clinical or laboratory signs. Initially patient presents with high level BK viremia and viruria without any renal allograft dysfunction.[5] BK reactivation in renal transplant patients is supposed to be reactivation of virus in donor kidney cells.[6] BK induced interstitial nephritis presents as rising serum creatinine with BK viremia or viruria. Decoy cells are BK-infected cells, containing an enlarged nucleus with basophilic intranuclear inclusions may be demonstrated in urine cytology. The urine BK virus DNA PCR>10^7 copies/ ml may indicate BKVN.[7] In case of allograft dysfunction biopsy should be performed when BKV load > 10^4 with in the blood and is the gold standard for diagnosis of BKVN.[8] Renal biopsy is also important in ruling out acute rejection which can lead to allograft dysfunction. Due to focal nature of BKVN disease and to avoid sampling error, a minimum of two biopsy cores including medulla should be taken. In 1/3 of cases we may get false negative result. The mainstay of treatment involves dose reduction or modification in immunosuppressive agent. Adjunctive treatment with antiviral therapy which includes cidofovir, leflunomide, fluoroquinolones, and intravenous immunoglobulin (IVIG) may have limited or no value.[9,10] Initially the dose of antiproliferative agents as MMF or Azathioprine is reduced by 50%, followed by reduction in calcineurin inhibitor by 25-50%. Antiproliferative agent is discontinued when therapeutic response is inadequate. The clearance of BKV viremia, increase in BKV-specific IgG antibody level, and stabilization of renal function are taken as successful treatment of BKVN. The aim of treatment is to maintain immunosuppressive agents at a certain level like tacrolimus <6ng/ml, cyclosporine <150ng/ml, sirolimus <6ng/ml and mycophenolate mofetil daily dosing <1000 mg[9] along with monitoring of serum creatinine level twice weekly, serum BK PCR two weekly and allograft biopsy in two months. Recovery usually takes 4-8 weeks.

Leflunomide is a prodrug, with immunosuppressive and antiviral activity.[11] Williams and colleagues described its role in progressive reduction in BK viral load in the blood and urine.[12]

Cidofovir is a nucleotide analogue of cytosine and may have activity against BKV.[13] But its role needs evaluation by randomized trials for BKVN when immunosuppressive agent dose reduction dose not resolve infection. Anterior Uveitis is of significant concern.[14] IVIG therapy is hypothesized to help with BKVN by supplying anti-BKV antibodies.[15,16] It is expensive and may cause aseptic meningitis, thrombotic events, bronchospasm and nephrotoxicity.[17]

Fluoroquinolones also inhibit BK virus growth through inhibition of DNA topoisomerase.[18] A small study showed that BK viruria was lower in group receiving ciprofloxacin (FQ) irrespective of corticosteroid use.[18] Further larger studies are needed to recommend its role for prevention and treatment.

PREVENTION

Renal transplant recipients should be screened for BKV for first 5 years post-transplant.[19] Guidelines suggest that screening for BKV using urine and plasma PCR should be done at least 3 monthly during first 2 years post-transplant followed by annually till 5 years. Additionally it should be done in a transplant recipient with rising creatinine not explained by other causes.

RETRANSPLANTATION

Case series demonstrate that kidney retransplantation has been performed successfully in 80-90% of patients with graft failure due to BKVN. Documented clearance of viremia before transplant is significantly associated with absence of BKV replication after retransplant.[20] Surgical removal of primary transplant is recommended in setting of retransplantation with ongoing serum BK viremia. But it does not protect against recurrent BKVN.

CONCLUSION

BKVN has been recognized as an important infection post renal transplantation recently. The diagnosis and monitoring of BKV infection and BKVN has become easy due to technical advancements. The mainstay of treatment of BKVN is reduction in dose of immunosuppressant agent. Progressive graft loss has decreased to approximately 15-50% compared to 40-60% in earlier BKVN series reports due to better diagnostic tools and preemptive treatment. The role of adjuvant therapies still has to be proven against BKV replication and warrants further larger controlled clinical trials.

END NOTE

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Conflict of Interest: None declared

Editorial Comments

Deteriorating Graft function and graft loss are dreaded complications.in the area of Renal transplantation. BKVN is obviously more common than suspected. This articles deals with the detection, treatment and natural history of BKVN. At present detection is made easier. The article is of contemporary interest.

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