LEFLUNOMIDE AND CIDOFOVIR FOR THE TREATMENT OF BK VIRUS NEPHROPATHY

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ABSTRACT

BK virus–associated nephropathy has become increasingly recognized cause of graft dysfunction among kidney transplant recipients and a definitive diagnosis requires a renal biopsy. While reducing the dose of immunosupressants is considered to be the standard therapy, adjunct agents (e.g., cidofovir) may be warranted. In the present case, BK nephropathy was suspected due to a progressive rise in serum creatinine. The blood and urine were tested for the presence of BK virus via polymerase chain reaction (PCR). Moreover, viruria without viremia was confirmed, following which a gradual reduction in the dose of immunosuppressive therapy was applied. Due to the failure of viral clearance and a steady increase in the serum creatinine levels, leflunomide was added to the treatment; however, effective viral clearance could not be obtained. Cidofovir treatment was then added to the leflunomide therapy, and this combined regimen provided effective viral clearance in the urine. Renal graft function was preserved for as long as eight weeks of treatment.

Keywords: *BK polyomavirus, nephropathy, cidofovir, leflunomide.* **Nobel Med 2017; 13(3): 66-68**

BK VİRUS NEFROPATİSİ TEDAVİSİNDE LEFLUNOMİD VE CİDOFOVİR

ÖZET

BK virüsü ile ilişkili nefropati, böbrek transplant alıcıları arasında greft disfonksiyonunun nedeni olarak giderek daha fazla tanınmaktadır ve kesin bir teşhis için böbrek biyopsisi gereklidir. İmmünsüpresanların dozunu düşürmek standart terapi olarak düşünülürken, ilave ilaçlar (örn., cidofovir) gerekebilmektedir. Bu vakada, serum kreatinininde ilerleyici bir yükselme olduğu için BK nefropatisinden şüphenildi. Kan ile idrar PCR yoluyla BK virüsünün varlığı açısından test edildi. Sonuç olarak, viremi bulunmayan virüri teyit edildi ve ardından immünsüpresif terapi dozu tedrici bir şekilde azaltıldı. Viral temizlenmede başarısızlık ve serum kreatinin düzeylerinde istikrarlı bir artış olması nedeniyle tedaviye leflunomid eklendi; Fakat etkin viral temizleme elde edilemedi. Daha sonra leflunomid tedavisine cidofovir tedavisi eklendi ve bu kombine rejim idrarda etkili viral temizlik sağladı. Renal greft fonksiyonu, sekiz hafta süreyle korundu.

Anahtar kelimeler: BK polyomavirüs, nefropati, cidofovir, leflunomid. **Nobel Med 2017; 13(3): 66-68**

INTRODUCTION

Polyomavirus (PV), a subgroup of the papovavirus family, is a double-stranded non-enveloped DNA virus.[1] Primary infection usually occurs early in life without clinical symptoms.[1] Moreover, PV frequently remains in a dormant state within the kidneys and ureters of healthy, immunocompetent individuals.[2,3] However, immunocompromised patients have an increased risk of developing clinical manifestations of a PV infection. Human disease can be caused by two PV strains: JC and BK. The JC strain causes progressive multifocal leukoencephalopathy, while the BK virus is associated with changes in the kidney and has also been associated with hemorrhagic cystitis and urethral stenosis.[1,4-5,6,7,8] Although immunosuppression increases the probability of latent BKvirus reactivation, clinical manifestation of the disease is rare. Although the diagnosis of BKN (BK virus nephropathy) can only be made histologically via a graft biopsy, the viral DNA can be detected in both the blood and inclusion-bearing cells in the urine. A quantitative real-time polymerase chain reaction (PCR) assay for BK virus DNA is a simple method that can be used to identify the virus in the urine and plasma with a detection limit of a little as 10 viral copies and an intra-assay coefficient of variation of 19%. BKN is limited to kidney transplants and the attached ureters, and there is no evidence that any other organs, including the native kidneys, are affected in humans. The morphological hallmarks consist of intranuclear viral inclusions observed exclusively in epithelial cells, and focal necrosis of tubular cells. Although cytopathic signs are evident along the entire nephron, they are most abundant in the distal tubular segments and collecting ducts. In the renal pelvis and ureters, viral inclusion bodies can be observed in superficial (differentiated) transitional cells, rarely in the proliferating basal cell layer.[9] Podocytes, as well as endothelial, mesenchymal, and inflammatory cells do not appear to be infected by the BKvirus in human allografts. Changes in the interstitial compartment vary. It is important to note that these morphological changes are typical but not pathognomonic for an infection with BKvirus. Herpes simplex virus, adenovirus, and (less likely) CMV must also be considered in the differential diagnosis. These viral infections can easily be excluded by immunohistochemistry or electron microscopy.[9]

Interstitial inflammation in BKN is poorly understood. The major challenge is distinguishing between virally-induced interstitial nephritis and cellular rejection. This distinction is not consistently made, yet appears to be crucial since this approach is not always sufficient, and various drugs, such as cidofovir, leflunomide, and quinolones may be required.

CASE

A 47-year-old male patient who underwent a renal transplantation three months prior was hospitalized due to a gradual increase in his serum creatinine levels. Upon physical examination, he was normotensive and there were no observed pathological findings. The last measured serum creatinine level was 1.9 mg/dL (baseline creatinine: 1.4 mg/dL). His immunosuppressive medical treatment consisted of 5 mg/daytacrolimus, 2g/day mycophenolate mofetil (MMF), and 5 mg/day prednisone. He did not use any other medication. The patient's serum level of tacrolimus was 8ng/mL. The renal resistive index values by Doppler ultrasonography were normal. The blood and urine BK virus PCR values were 3 x 10^6 copies/mL and 1 x 10^9 copies/mL, respectively. Regenerative changes in the renal tubule epithelial biopsy, growth in the core, hyperchromasia, and intranuclear inclusions revealed lymphocyte infiltration into the interstitium. SV 40 staining showed adiffuse positive reaction in the tubule epithelium (Figures 1 and 2), and C4d was negative. The dose of Tacrolimus was reduced and the blood trough level was set tobelow 6ng/mL. The MMF dose was also tapered gradually. However, after the first month of treatment, the patient's serum creatinine levels remained high.

Tacrolimus was then replaced with everolimus. The trough levels of everolimus were set at 6-8 ng/mL and MMF was given at a dose of 750 mg/day. Oral leflunomide therapy was initiated at a 100 mg/day loading dose for three days and then continued at a maintenance dose of 20 mg/day. One month later, the control serum creatinine was 2.3 mg/dl,and cidofovir was added to the leflunomide therapy as a parenteral dosage of 0.25 mg/kg per week.The isotonic saline infusion was administered simultaneously with the cidofovir therapy to ensure sufficient hydration. The control blood BK virus PCR value after eight weeks of cidofovir therapy was negative and the urine BK virus load was 3 x 10^3 copies/mL by PCR detection. The serum creatinine level was gradually reduced and set at 1.8 mg/dL. The patient was then moved to the regular out-patient control program.

DISCUSSION

Unless it is well screened and treated, BKN may result in graft loss. Although the typical treatment approach is to reduce the level of immunosuppressive therapy, providing the patient with the opportunity to clear the viral infection, recovery could not be obtained by changing the immunosuppressive treatment in the presented case. Moreover, viral clearance was only achieved after treatment with leflunomide and cidofovir, thus graft function was preserved in this patient.[10,11]

BKN appears to be promoted by the concurrent presence of several risk factors, among which immunosuppression is a prerequisite. Based on the early detection of decoy cells preceding BKN, it is conceivable that asymptomatic viral activation is an initial, fully reversible step in the development of nephropathy another promoting factor (possibly the most important one) may be the administration of a "high dose" of new immunosuppressive drugs (e.g., tacrolimus and

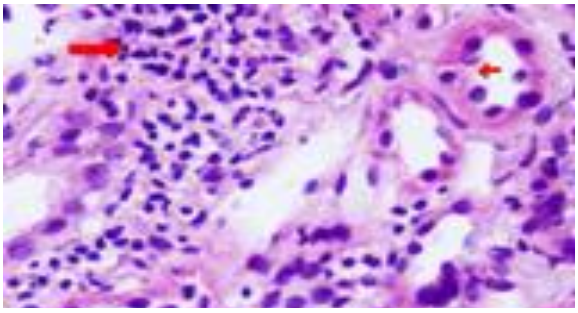

Figure 1. Note the dense lymphocytic infiltration (large red arrow) and the tubule epithelial damage (small red arrow). H&E stain; 100 x original magnification.

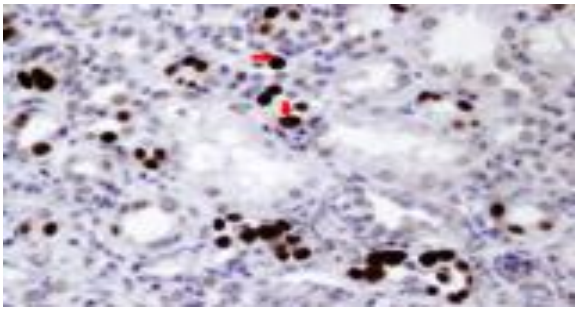

Figure 2. Note the SV40-positive staining of the tubular epithelial cells. SV40 stain; 40x original magnification, in color.

mycophenolate-mofetil).[12] It is likely that specific changes in the allograft must be present to promote BKN since the native kidneys appear uninvolved. One such condition may be tubular injury or regeneration which renders the renal cells susceptible to the BK virus.[13] Presumably, the BK virus infects new cells via cell to cell spread as suggested by the viral particles observed on apical tubular cell surfaces by electron microscopy.[9] In addition, the BK virus can follow an ascending route of infection from the superficial transitional cell layer to the collecting ducts and tubules. Lysis of inclusion-bearing tubular cells releases the viral particles into the tubular lumen, leaving behind denuded basement membranes. The virus may enter the bloodstream when a tubular fluid containing viral particles leaks into the interstitium that is rich in capillaries, resulting in BK viraemia. The spread of viral infection to the renal cortex could further be facilitated by viremia. Once the BK virus gains access to the bloodstream, it is possible that the virus can colonize the renal cortex and infection can spread along the entire nephron via tubular cells, resulting in evitable graft loss.

CONCLUSION

In BKN, the primary clinical goal is to early identify infected renal-allograft recipients and attempt viral clearance, thereby limiting graft damage. The therapeutic algorithm for patients under tacrolimus and/or mycophenolate mofetil immunosuppression is to first search for high numbers of "decoy cells" in the urine (i.e.,>5 decoy cells per 10 high-power fields). If decoy cells are repeatedly present, it is recommended that PCR be performed on the plasma to search for BK virus DNA. If the plasma PCR results are positive, the next step is to obtain a graft biopsy to establish a definitive diagnosis (including immunohistochemistry).[14] If BKN is diagnosed, immunosuppression must be lowered; if this is sufficient, virally induced tubular necrosis will begin to resolve and renal function will significantly improve. To monitor the treatment efficacy of low-dose immunosuppression (i.e., viral clearance), PCR on plasma samples and the quantification of decoy cells in the urine must be performed. PCR analysis on plasma samples also appears to be particularly useful as a non-invasive tool to screen for viral clearance and limit the duration of low-dose immunosuppression. However, a high level of suspicion regarding rejection episodes must be considered during low dose immunosuppression, and the physician must be alerted even when serum creatinine levels increase minimally, but gradually.

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