

Coexistence of tubulointerstitial and glomerular lesions in a renal transplantation recipient with BK virus infection: response to cidofovir

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ABSTRACT

BK Polyomavirus nephropathy is a frequent and serious complication in renal transplant patients and one of the infectious causes of graft loss. Diagnosis is made by biopsy and demonstration of viral inclusions in renal tissue. Histologic damage is usually tubulointerstitial with minimal glomerular involvement. We present the case of a 49 year-old patient who developed polyomavirus BK nephropathy eight months after receiving a renal transplant, expressed as an increase in proteinuria, hypertension, and a rise in serum creatinine levels. Biopsy revealed the typical tubulointerstitial lesion with intranuclear viral inclusions, as well as glomerular involvement with moderate endocapillary proliferation, with numerous neutrophils and reduction of the capillary lumens, mesangial and subendothelial immunoglobulin (IgG, IgM, IgA), C₃ and fibrinogen-related antigen, imitating the typical pattern of acute postinfectious glomerulonephritis. Lesions compatible with acute cellular rejection were also observed. Treatment consisted of bolus steroids followed by reduction in immunosuppression and low-dose cidofovir, with good clinical and laboratory results.

Renal function normalised, with a complete disappearance of proteinuria, and the follow-up biopsy showed a significant improvement in histological damage. Polyomavirus BK nephropathy may manifest histologically with glomerular and interstitial damage and treatment by immunosuppression reduction and cidofovir at low doses is capable of reversing these lesions.

Key-Words:

BK polyomavirus, cidofovir, tubulointerstitial lesions.

CASE REPORT

Polyomavirus type BK infection in patients with a functioning renal transplant has an incidence ranging from 1 to 8% depending on the author¹. Its histologic expression is the basis for diagnosis and typically consists of the presence of intranuclear viral inclusions in tubular epithelial cells with tubular necrosis, accompanied by interstitial inflammation with plasma cells and tubulitis, and minimal glomerular involvement.

We present the case of a 49 year-old patient with chronic renal failure who received a renal transplant from a cadaveric donor. The immunosuppressive regimen consisted of basiliximab, cyclosporine, mycophenolate mofetil and steroids. Eight months after transplantation and with serum creatinine stabilised at around 1 mg/dl, he began to experience symptoms of malaise, generalised oedema, poor blood pressure (BP) control of 150/90 mmHg, and an increase in proteinuria (15g/day) and serum creatinine up to 2.8 mg/dl, in only one month. His serum complements were normal. Suspecting a possible acute cellular rejection, a renal biopsy was performed, revealing the focal tubular lesions showing viral intranuclear inclusion bodies with signs of moderate tubulitis (t2 according to Banff classification) (Figure 1), accompanied by an intense interstitial infiltrate composed predominantly of lymphocytes and plasma cells (i3 according to Banff classification), with 8-10 mononuclear cells for tubular section. Mesangial hypercellularity was also observed in two of 14 glomeruli of the biopsy specimen, with a marked reduction of vascular spaces, moderate endocapillary proliferation and neutrophil karyorrhexis (Figure 2). Immunofluorescence showed peripheral mesangial and sub-endothelial IgG, IgM and weak IgA deposits. Immunohistochemistry was negative for C4d. Electron microscopy analysis was not performed.

PCR performed in blood and urine was positive for BK virus with 5.23×10^6 copies/ml in urine and

1.63×10^6 copies/ml in blood. Both CMV antigenaemia and urine culture were negative. Urinary sediment showed severe haematuria and renal Doppler ultrasound showed resistance indexes in the upper limits of normal with occupation of the urinary tract by echogenic material, possibly haematic. Prior to performing the renal biopsy and based on the suspicion of acute cellular rejection, it was decided empirically to switch the patient from cyclosporine to tacrolimus. Subsequently, and given the histological findings compatible with polyomavirus infection, glomerulonephritis with a mesangiocapillary pattern and acute cellular rejection, rescue treatment was carried out with 3 bolus of steroids (500 mg of metilprednisolone each one) followed by a reduction in immunosuppression, maintaining serum levels of tacrolimus below 6 ng/ml and mycophenolate doses below 1 g/day. Due to the severity of the histologic lesions and late diagnosis of polyomavirus infection, treatment with low-dose intravenous cidofovir (5 doses of 0.25 mg/kg every two weeks) was carried out simultaneously. These measures led to a progressive improvement in renal function and a reduction in proteinuria, accompanied by inhibition of viral replication as demonstrated by the negative PCR results in blood and urine. Five months after treatment, a follow-up renal biopsy was performed that was reported as an acute developing and histologically nonspecific patchy tubulointerstitial lesion and glomerular signs of mild-to-moderate mesangial proliferation without hyaline accumulations, with a

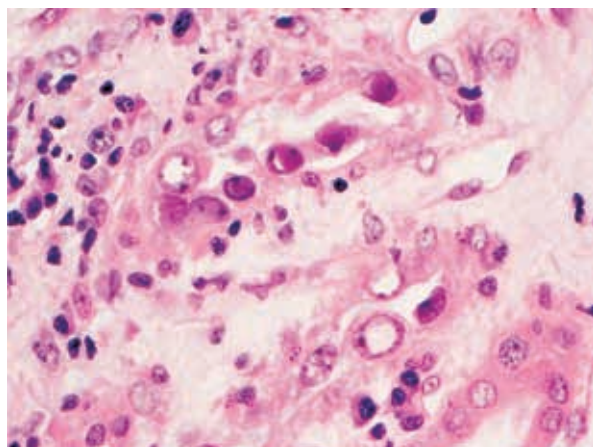


Figure 1
Typical viral intranuclear inclusion bodies observed in renal biopsy suggesting BK nephritis (HE 40X)

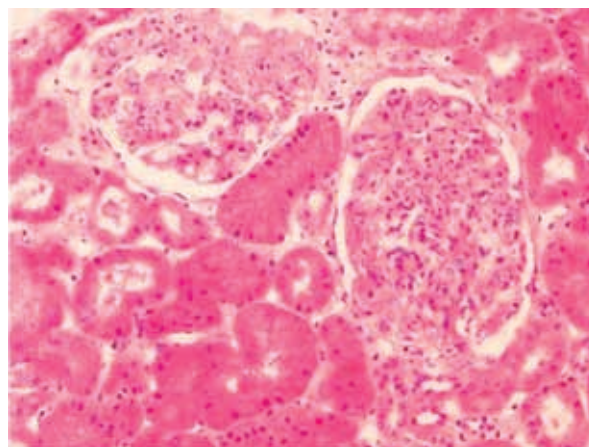


Figure 2
Moderate endocapillary proliferation, mesangial hypercellularity and reduction of vascular spaces observed in renal biopsy (HE 20X)

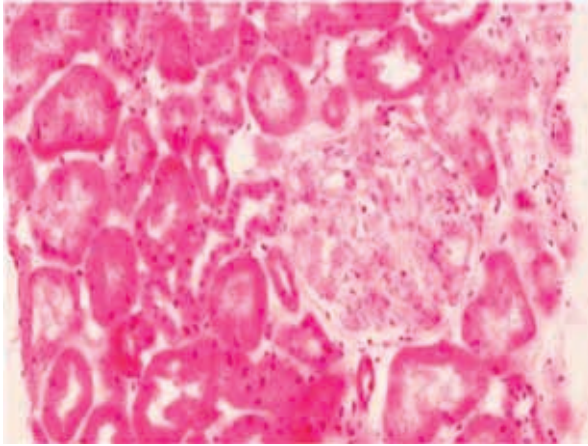


Figure 3

Improvement of histological damage after treatment

maximum of two neutrophils per glomerulus and mild mesangial IgM and complement (C₃) deposits, suggestive of resolving postinfectious glomerulonephritis (Figure 3). The patient had a serum creatinine of 1.49 mg/dl and a proteinuria of less than 1 g/d at that time, and at present (one year later) has a serum creatinine of 1.2 mg/dl without proteinuria.

DISCUSSION

Polyomavirus BK (BKV) infection in renal transplant recipients, one of the three polyomaviruses affecting man together with JC virus (JCV) and simian virus (SV40), is characterised by its cytopathic effect on the tubular epithelium, affecting first the distal tubules and medullary collecting ducts and then the proximal tubules, with involvement of the parietal epithelium of Bowman's capsule and formation of crescents observed in severe infections². The incidence of infection is very low in immunocompetent patients and may cause asymptomatic and self-limiting viral activation in the urothelium³. Replicative activation of BKV concomitantly with another virus is anecdotal, with two cases having been reported in the literature, one with an adenovirus and one with a cytomegalovirus³. Asymptomatic viraemia with BKV is common in the renal transplant population, with 60-80% of patients serologically positive⁴. Infection by this virus usually presents

within 2 and 60 months of transplantation, although one case of infection 6 days after transplantation has been reported and another one 6 years after transplantation³. This infection leads to graft loss in up to 45% of infected patients⁵. The increased prevalence of BK virus-induced nephropathy is thought to be related to the greater potency of current immunosuppressive regimens, but no clear association has been established with the use of any particular immunosuppressant, although the data are contradictory in this regard⁶. Khamash *et al.* analysed a series of 1027 recent kidney transplant recipients and found 74 biopsy-proven infections. They reported a higher incidence of infection with older recipient age and with allografts from female donors⁷. Though renal biopsy is currently the principal diagnostic procedure in BKV nephritis, a recent study of Singh *et al.* suggests that detection of Haufen (cast-like polyomavirus aggregates) in urine may serve as a non-invasive means to diagnose BK nephropathy⁸. In our case, diagnosis of BKV nephritis was based on isolation of BK in blood and urine and the demonstration of intranuclear viral inclusions accompanied by signs of cytopathic effect.

Typical histologic involvement is predominantly tubulointerstitial with viral intranuclear inclusions in epithelial cells and focal necrosis of tubular cells, with abundant cytopathic signs in distal tubular segments and collecting ducts, occasionally affecting the parietal epithelial cells of Bowman's capsule and rarely visceral epithelial cells, possibly because of their reduced proliferative capacity. With regard to glomerular involvement, Celik *et al.*³ reported in a series of 124 biopsies of grafts affected by BK virus nephropathy slight cytopathic glomerular changes visible by light microscope in 17% of biopsies and an additional 12% when immunohistochemistry was used. Crescents were found in 12% of biopsies, which are not usually associated with rapidly progressive glomerulonephritis in clinical practice. Other findings such as the increase in mesangial matrix, ischaemic glomerulopathy and chronic transplant glomerulopathy are considered normal in the biopsy because of their frequent presence in transplant patients and do not appear to be related to BK infection. The development of immune complex-associated glomerulonephritis and its presence in the tubular basement membrane is still a subject of debate; while in the Celik study it was assumed to

be associated with systemic lupus erythematosus, other authors consider its occurrence frequent¹ and this is a commonly accepted view in association with other viral infections such as those caused by cytomegalovirus and parvovirus². The presence of these immune deposits would imply greater severity of the infection and the tubulointerstitial lesion. Ultrastructural analysis by electron microscopy can demonstrate the presence of glomerular subepithelial humps⁹. Although this technique was not available in our case, it is thought that immune deposits are formed in the glomerular basement membrane in the initial location of the viral antigens⁹ and may imitate the deposits observed in postinfectious and membranoproliferative glomerulonephritis.

Presence of *de novo* postinfectious glomerulonephritis (PIGN) in patients with a renal allograft is scarcely reported in the literature, and the type of causal infection is heterogeneous¹⁰. Plumb *et al.* described three patients affected with PIGN 6-30 months after receiving a renal allograft. In one of them *S. Aureus* was identified, in other no microorganism could be isolated, and in the third serum CMV DNA was positive. This patient was treated with ganciclovir with complete recovery of renal function 19 months later¹¹. His serum complements were normal in that lapse of time and CMV DNA was negative after the treatment. In this direction, Andresdottir *et al.* suggests the relation among primary viral infections such as Epstein Barr and CMV and recurrence of type I membranoproliferative nephritis in renal allograft recipients^{12,13}. In spite of these promising approaches, the role of viral agents as triggers of *de novo* or recurrent glomerulonephritis after renal transplantation still remains unclear, but correlation in time observed between the decrease of viral load and recovery of renal function lead us to think this could be possible, even in our case.

The primary treatment for polyomavirus-associated nephropathy is immunosuppression reduction. Strategies such as discontinuation of tacrolimus or mycophenolate or switching from tacrolimus to cyclosporine have been used, but this is not always associated with a reduction in viral activity¹⁴ and is a risk for patients with concomitant biopsy-proven acute rejection. Steroid pulse treatment followed by subsequent reduction in immunosuppression is a commonly accepted strategy in these cases¹⁴ and it was the method used in our patient. Other therapeutic

approaches include the use of intravenous immune globulin therapy, leflunomide, cidofovir, and fluoroquinolones, with differing results¹⁴⁻¹⁷. In our case, the switch to tacrolimus immunosuppression was made empirically before receiving the results of the histology study due to the high suspicion of acute rejection. This did not lead, as might be expected, to a worse outcome of the nephropathy, although knowledge of the result of the biopsy did influence the decision for concomitant use of cidofovir, a drug approved for cytomegalovirus retinitis in HIV⁺ patients, which was given early in low doses; intermediate-dose cidofovir is usually coadministered with probenecid to prevent its accumulation in tubular cells and its known nephrotoxicity although in our case we did not consider it necessary, as seen in previous papers^{18,19}. However, role of cidofovir doses has been discussed. A recent paper shows that cidofovir can reduce *in vitro* the intracellular BKV load in renal epithelial cells about 90% at a concentration of 40 µg/ml²⁰. To reach this concentration, the dose of cidofovir should be much higher than used in our case. However, Kuypers *et al.* described serum cidofovir concentrations of 0.77-3.07 µg/ml in eight patients with BK nephropathy treated with reduced immunosuppression and low dose cidofovir with good results²¹. Our total dose was very similar to that proposed by other authors^{19,21,22}.

In conclusion, the presence of glomerular involvement in BK virus nephropathy is a rarely reported entity, but whose incidence may be significant depending on the series. Treatment with cidofovir and reduction in immunosuppression can cause regression of these lesions and suppression of viral replication.

Conflict of interest statement. None declared.

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