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Case Report

The case of BK virus infection in which it was difficult to differentiate from acute rejection

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Abstract: BK virus (BKV) nephropathy is one of the major causes of allograft dysfunction or graft loss in kidney transplant recipients. Early diagnosis and timely reduction in immunosuppressant is important for proper treatment. We report a 35-yr-old male case of cadaveric renal transplantation with BK viral related tubulointerstitial nephritis complicated by acute rejection. The diagnostic biopsy showed severe inflammatory infiltrates, tubulitis, and peritubular capillaritis. Discontinuation of mycophenolate mofetil, prednisone pulse therapy, and r-globulin was successful in relieving allograft dysfunction.

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Key words: acute rejection – BK virus – renal transplantation – SV40 – tubulointerstitial nephritis

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BK virus (BKV) nephropathy is one of the major causes of allograft dysfunction or graft loss in patients in an over-immunosuppressive state. It has been reported that the median time to detect BKV nephropathy after kidney transplantation is 9.5 months but the duration regarding graft failure is only four months after incidence of BKV nephropathy (1). Bonvoisin et al. (2) showed that 45% of patients with BKV nephropathy progressed to irreversible graft failure with tubular atrophy and interstitial fibrosis. Although immunosuppressive agents are essential for therapy after organ transplantation, these agents regretfully increase the incidence and deteriorate the severity of infection. Calcineurin inhibitors and mycophenolate mofetil (MMF) play an important role in reactivation of latent BKV infection (3).

Diagnosis for BKV nephropathy is based on histological appearances characterized by lymphocytic interstitial infiltrates and the nuclear reaction to the anti-SV-40T antibody as evidence of viral replication, and positive polymerase chain reaction for BKV DNA. In fact it is difficult to make a clear differential diagnosis between BKV nephropathy and acute cellular rejection. Moreover, it is well known the coexistence of these diseases in the same

patient, and the relationship between their cause and effect remains controversial. We lack specific and effective antiviral treatment; thus, a decrease or discontinuation of immunosuppressive agents is essential as initial treatment for BKV nephropathy.

There are difficult and unresolved problems in the precise diagnosis and treatment for BKV infection. We present here a case of BKV nephropathy complicated with acute rejection. We could reverse the impairment of graft function with combination therapy including reduction in immunosuppressive agents, immunoglobulin infusion, and methylprednisolone pulse therapy.

Case report

A 35-yr-old man with end-stage renal disease because of IgA nephropathy received a cadaveric renal transplantation. The donor was a 32-yr-old man whose cause of death was acute myocardial infarction. There were three mismatches in their human leukocyte antigen (HLA)-A, HLA-B, and DR typing. Immunosuppressive therapy started with four immunosuppressants, including MMF, cyclosporine, methylprednisolone, and basilixímab. Renal graft functioned well, and the protocol biopsy performed on post-operative day (POD) 30 showed no evidence of acute rejection. His clinical course after transplantation is shown in Fig. 1. Serum creatinine on discharge was 1.34 mg/dL. The trough levels of cyclosporine had been maintained within the ideal ranges throughout the two months before his readmission. On POD 88, his serum creatinine level increased to 1.9 mg/dL without any clinical symptoms. Decoy cells were first noticed by urine cytology (Fig. 1). Ultrasonography did not show a decrease in allograft blood flow. Analysis for serum cytomegalovirus (CMV) viral load was negative. Polymerase chain reaction (PCR) of his blood sample was performed and found to be positive for BKV DNA. We reduced MMF 1000–500 mg/d because of the high possibility of BKV nephropathy. A renal biopsy was performed on POD 112 (Fig. 2), which showed diffuse infiltration of inflammatory cells in the interstitium (i3) and prominent tubulitis with disruption of the tubular basement membrane (t3). Severity of tubulitis in the cortex was almost equal to that of medulla. Disruption of the tubular basement membrane was observed more frequently in the cortex than in medulla (10 in the cortex vs. 6 in the medulla). Inflammatory cells mainly consisted of mononuclear cells, monocytes, and plasma cells. No infiltrates were found in the arterial intima or glomeruli but numerous inflammatory cells were seen in enlarged peritubular capillary lumens (ptc2*). These findings indicated aspects of acute T cell-mediated rejection IB. Immunohistochemistry showed partly positive C4d in the peritubular capillary and tubular basement membrane (Fig. 3). We could not diagnose AMR correctly because we did not undertake donor-specific antibody measurement on POD 112. Light microscopy revealed enlarged finely granular nuclear alteration of tubular epithelial cells, but typical intranuclear basophilic ground glass inclusion bodies for BKV infection could not be confirmed. Immunohistochemistry using antibodies against the SV-40T antigen revealed positive staining in the nuclei of parenchymal tubular epithelial cells (Fig. 4). The number of SV-40T antigen-positive tubular epithelial nuclei in ten high-power fields of the medulla is three times greater than that in the cortex. Reanalysis of his

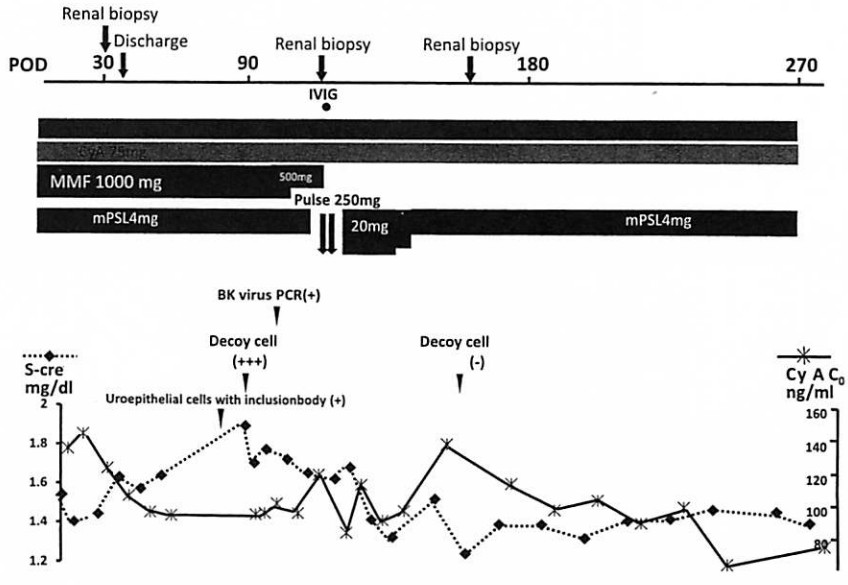

Fig. 1. Clinical course after discharge. CyA, cyclospoline; MMF, mycophenolate mofetil; mPLS, methylprednisolone; s-Cr, serum creatinine concentration; CyA C0, cyclospoline fasting level after 12 h from last dose.

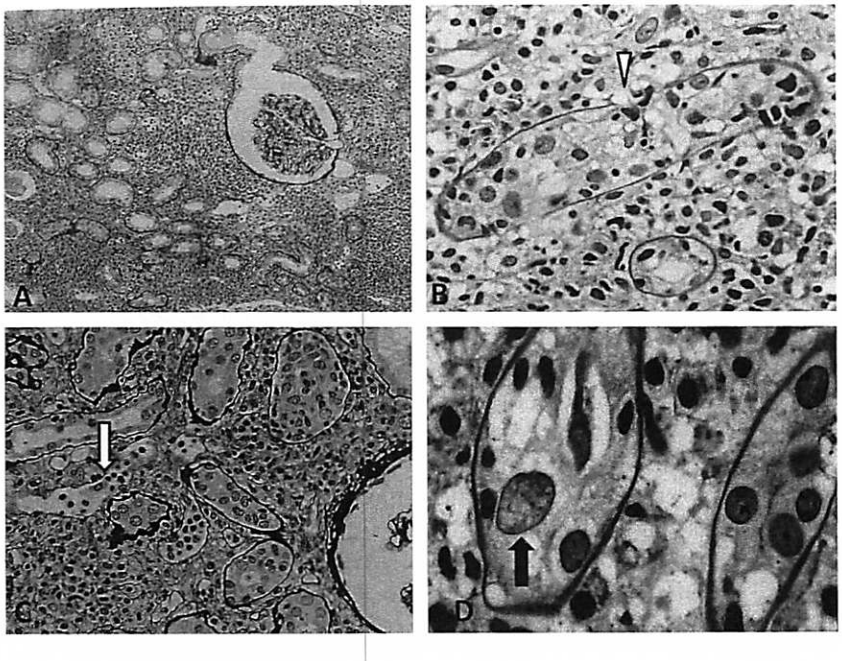

Fig. 2. Light micrographs of the post-operative day 112 biopsy. (A) Diffuse interstitial infiltrates in renal parenchyma. (i3) There was no glomerulitis. (g0) Periodic acid schiff (PAS) stain section, ×100 original magnification. (B) tubular basement membrane destruction was accompanied by severe tubulitis (t3; white arrow head) PAS stain section, ×600 original magnification. (C) Peritubular capillaries with capillaritis, with luminal inflammatory cells (ptc2*; white arrow) were recognized. Periodic acid-methenamine-silver (PAM) stain section, ×500 original magnification. (D) Enlarged finely granular nuclear alteration of tubular epithelial cells were observed in the kidney cortex (black arrow). Hematoxylin and eosin (H&E) stain section, ×800 original magnification.

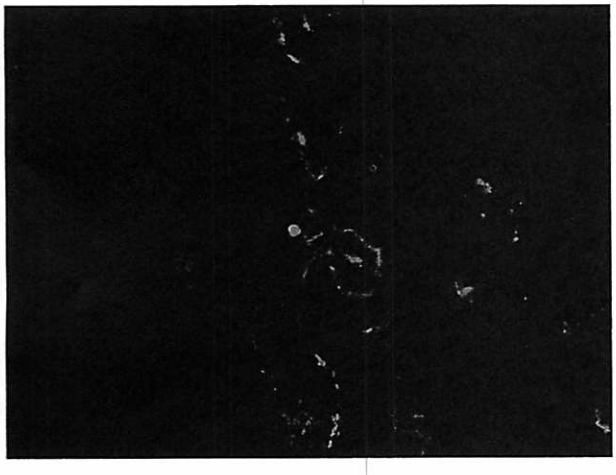

Fig. 3. Immunohistochemistry of the specimen from the biopsy on day 112 after renal transplantation. Cd4 was partly positive in PTC and TBM (×200 original magnification).

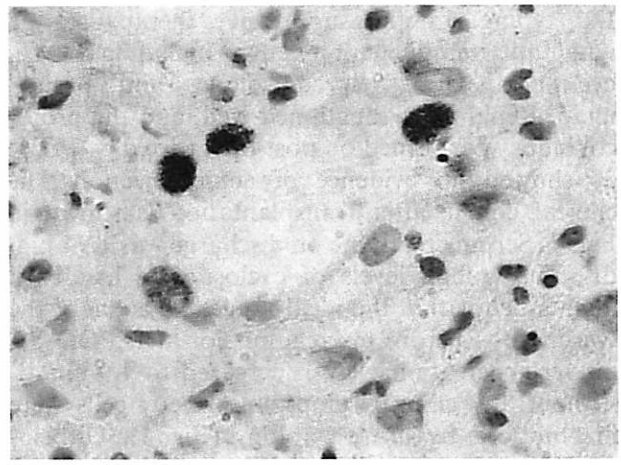

Fig. 4. Immunohistochemistry of the speciemen from the biopsy on day 112 after renal transplantation. The SV40-T antigen was positive on tubular epithelial cells. Formalin-fixed paraffin-embedded tissue section, antibody directed against the SV-40 T antigen, ×600 original magnification.

protocol biopsy sample on POD 30 demonstrated weak positive staining for the SV-40T antigen (Fig. 5). Mycophenolate mofetil therapy was discontinued, and therapies of immunoglobulin (0.2 g/kg) infusion and methylprednisolone bolus infusion (250 mg, two d) were started. Serum creatinine levels gradually decreased and decoy cells in urine diminished (Fig. 1). On POD160, a renal biopsy was performed to evaluate the effect of treatment (Fig. 6). A decrease in the infiltration of inflammatory cells and disappearance of tubulitis were confirmed on light microscopy. Minimal interstitial fibrosis and focal tubular atrophy remained. There was total negative staining for SV-40T by immunohistochemistry, whereas focal C4d staining in the tubular basement membrane remained positive. The patient was discharged with a serum creatinine level of 1.25 mg/dL.

Discussion

Childhood infection of BKV leads to a lifelong latent infection of the renal and urinary tract epithelial cells and asymptomatic infection of BKV can be detected in 70% of the healthy adult population (4). The occurrence of BKV nephropathy is well known to be associated with an excessive immunosuppressive state. The typical

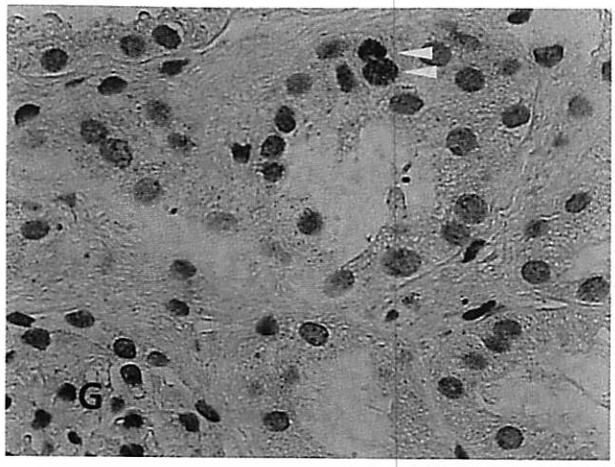

Fig. 5. Immunohistochemistry of the speciemen from the biopsy on day 30 after renal transplantation. The SV40-T antigen was weakly positive on parenchymal tubular epithelial cell (yellow arrow head). Formalin-fixed paraffin-embedded tissue section, antibody directed against the SV-40 T antigen, ×600 original magnification. G, Glomerulus.

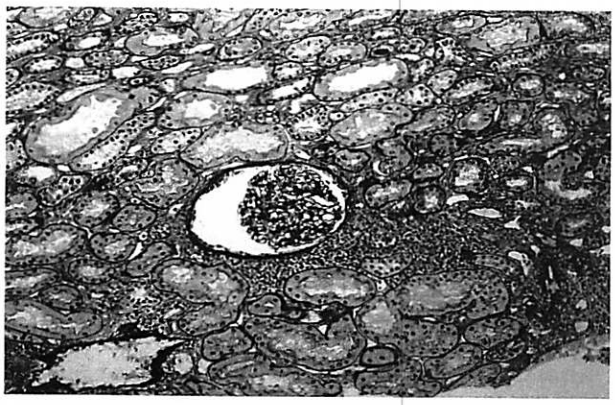

Fig. 6. Light micrograph of the post-operative day 160 biopsy. Interstitial infiltrates had remarkably decreased. Focal interstitial fibrosis and infiltrates remained. Periodic acid schiff stain section, ×100 original magnification.

course of BKV nephropathy begins with an asymptomatic period of viruria within some weeks and BK viremia follows thereafter. The appearance of BK viruria with concurrent BK viremia is pathognomonic of renal parenchymal involvement. Concurrence of BK viruria and viremia usually contribute to the later elevation of serum creatinine within a few months (5). We did not check viruria in our case; however, decoy cells in urine and presence of BKV DNA in the blood suggested advanced BKV nephropathy.

The allograft biopsy on POD 112 was compatible to florid interstitial inflammation classified as pattern B, the late stage of BKV nephropathy. The histological pattern of BKV nephropathy is classified into patterns A, B, and C based on the progression of the disease. The early phase of BKV nephropathy (pattern A) shows minimal inflammation in the interstitium. Viral reactivation is limited, and false negative for SV-40T staining is commonly found in the renal biopsy. At this stage, decline of renal function is not usually observed. Florid BKV nephropathy (pattern B) is characterized by marked tubular injury with interstitial inflammation. The late phase of BKV nephropathy (pattern C) is characterized by advanced fibrosis and tubular atrophy (5, 6). Interstitial injury is reversible and allograft function can be maintained if reduction in immunosuppressants is undertaken at on early stage (5, 6). Delay of diagnosis will certainly lead to irreversible tissue scarring (7). Additionally, the coexistence of BKV nephropathy and acute rejection, for both of which the cause and effect relationship has remained unknown, has been reported in a patient with a single transplanted kidney (8). It is not easy to morphologically distinguish T cell-mediated rejection without endarteritis or glomerulitis from viral infection-induced tubulitis. Hirsch et al. (7) described that tubular HLA-DR expression, lymphocytic infiltrate, and marked tubulitis in areas lacking polyomavirus replication may support the diagnosis of concurrent T cell-mediated rejection. In this case, there was no endarteritis and glomerulitis but severe tubulitis and peritubular capillaritis appeared not only in the medulla but also in the cortex. The disruption tubular basement membrane often existed in the tubules showing negative reaction for SV-40T antigen, and the level of the severity of the inflammation in the cortex was equal to that of medulla, regardless of higher positive reaction for SV-40T antigen in medulla. Regretfully we could not performed immunohistochemical staining for HLA-DR, whereas we thought it was difficult to neglect wholly the possibility of coexistence of BKN and T cell-mediated acute rejection in our case. We performed double staining of C4d and CD34 as a marker of endothelial cell. The localization of C4d partly corresponded with that of CD34. To clarify the location of C4d, we additionally performed double staining of C4d and anti-human epithelial membrane antigen (EMA) as a marker of tubular epithelium. Co-localization of C4d and EMA was also recognized (data was not shown). Batal et al. (9) reported diffuse C4d staining on the tubular basement membrane, and Bowman's capsules were confirmed in BKV nephropathy. In addition, Honsova et al. (10) reported focal C4d deposition on PTC could be seen in BKV nephropathy. They suggested the possibility of complement activation or complement production in areas where active

BK virus infection progressed. The biopsy specimens obtained before and after perfusion did not respond to the anti-SV-40T antibody.

The protocol biopsy, which was examined on POD30, revealed weak positive staining for the anti-SV-40T antibody in the normal shape nucleus of cortex tubular epithelial cells (Fig. 5). These results may imply that BK viral reactivation may have begun on POD 30 without histological signs of interstitial inflammation. A retrospective survey such as this one is useful for the recognition of beginning of BKV nephropathy, but should be started soon after initial treatment after diagnosis. According to the diagnosis of the graft biopsy on POD 112, MMF therapy was terminated and both of immunoglobulin (0.2 g/kg) and methylprednisolone infusion (250 mg, two d) were started simultaneously. Cidofovir, leflunomide, and fluoroquinolones are known as effective antiviral agents in some cases (11–13), but the usage of these agents is not covered by the medical insurance system of Japan. Fortunately, the reduction in immunosuppressants and simultaneous immunoglobulin infusion and steroid pulse therapy succeeded to relieve allograft dysfunction. The patient discharged with a serum creatinine level of 1.25 mg/dL. We present here a case in which it was difficult to differentiate BKV nephropathy from acute rejection.

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