Co-infection by cytomegalovirus and BK polyoma virus in renal allograft, mimicking acute rejection

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Introduction

Cytomegalovirus (CMV) and BK polyoma virus (BKV) are ubiquitous infections in which the primary infection in childhood becomes latent. Reactivation of both these viruses can occur in immunosuppressed states, such as renal transplantation, and can rarely result in virus-associated tubulointerstitial nephritis in renal allografts. The clinical picture can mimic, co-exist with or herald the rejection process [1,2]. Definite treatment for CMV is available. However, BKV is treated by meticulous titration of immunosuppression, as experience with antiviral drugs is limited as yet [3]. It is known that CMV infection can co-exist with human herpes virus (HHV)-7 [4] and CMV infection can result in reactivation of Epstein–Barr virus (EBV) [5]. After transplantation, the activation of BKV usually is not associated with co-activation of CMV, and BK nephropathy is not associated with other graft infections [6]. Rarely, BKV nephritis has been reported in patients with co-existing CMV infection of other sites/serology [7–10]. We document the first case where CMV and BKV co-exist in sequential renal allograft biopsies in a patient with post-transplant graft dysfunction, mimicking cellular rejection.

Case

A 47-year-old male patient developed end-stage renal disease in January 2000, due to neurogenic bladder and secondary reflux nephropathy. He received a live unrelated transplant from his wife in July 2000. Both donor and recipient were seropositive for CMV. Pre-transplant T-lymphocyte crossmatch was negative and post-transplant immunosuppression consisted of cyclosporin (8 mg/kg, tapered to 1.5 mg/kg in 3 months), azathioprine (75 mg/day) and prednisolone (0.5 mg/kg/day tapered over 3 months, then 12.5 mg/day). An allograft biopsy, done on post-transplant day 5, had two cores including cortex and medulla; glomeruli (n = 16) were normal. There was moderate tubulitis and interstitial inflammation (35%), comprising lymphomononuclear cells. There were no morphological features, such as glomerulitis, acute tubular necrosis, fibrinoid necrosis of arteries or mononuclear cells in the peritubular capillaries. There was no evidence of vascular rejection. Complement 4d (C4d) could not be assessed due to local limitations. Overall features were consistent with the diagnosis of acute cellular rejection (Banff type 1a). He was treated with five pulses of methylprednisolone (500 mg). As graft functions did not normalize, a repeat biopsy was done on day 15, which was adequate including 10 glomeruli and two arteries; it showed features of acute cellular rejection (moderate tubulitis, 40% lymphomononuclear infiltrate, Banff type 1a). There was no evidence of vascular rejection or morphological features suggestive of humoral rejection. C4d could not be assessed due to local limitations. No viral inclusions were reported in either of the biopsies. He was treated with OKT3 (intravenous; five doses, 5 mg once daily), with which his serum creatinine stabilized at 2.5 mg/dl for another 2 months.

Two months later, he was re-admitted with a decrease in urine output and a rise in serum creatinine to 6.6 mg/dl. Haemoglobin was 8.0 g/dl, platelets 72 000/mm³, total leucocyte count 6800/mm³, serum bilirubin 6.3 mg%, conjugated bilirubin 4.9 mg%, serum alanine/aspartate transaminases 51/24 IU and prothrombin tissue index 88%. Urine culture grew Klebsiella pneumoniae, sensitive to amikacin. CMV pp65 antigenaemia assay was strongly positive. BKV serology was not done. Ultrasonograph of graft was...
normal with no evidence of obstruction. In view of thrombocytopenia, graft biopsy was not attempted and he received three pulses of intravenous methylprednisolone (1 g) with no improvement. CMV disease was treated with gancyclovir (2.5 mg, intravenous) and once platelet count improved to 138,000/mm³, a graft biopsy was done. The graft biopsy showed 20 glomeruli in two cortical cores including two arteries. There was moderately dense tubulointerstitial inflammation (40%) with large granular casts in the dilated tubules in one of the cores. The tubular epithelial cell, interstitial macrophages and endothelial cells of peritubular capillaries showed cytomegaly and characteristic CMV nuclear and cytoplasmic inclusions (Figure 1). Along with it, there was evidence of mild–moderate tubulitis characteristic of acute cellular rejection. There was no glomerulitis, tubular necrosis or arteritis. C4d could not be done due to local limitations. On immunostaining, all the three biopsies (days 5, 15 and 60) showed presence of CMV antigen (monoclonal mouse anti-CMV, clone CCH2, dilution 1:20; DAKO, Glostrup, Denmark). The first two biopsies had focal CMV immunoreactivity in nuclei of tubular cells with mild interstitial inflammation. The third biopsy showed severe tubulointerstitial nephritis and the presence of CMV antigen in the nuclei as well as cytoplasm of tubular epithelial cells, endothelial cells and inflammatory cells in the areas of tubulointerstitial inflammation. Occasional parietal epithelial cells and glomerular endothelial cells were also positive. In addition, BKV immunostaining (monoclonal mouse anti-SV40 large T antigen, clone Pab 100; BD Biosciences PharMinger, California, USA) of the three biopsies showed immunoreactivity in the first and third biopsies in the nuclei of tubular cells (Figure 2) and cellular casts in the medulla. There was an equal amount of CMV and BKV positivity, although BKV-positive tubular nuclei were in areas distinct from areas with CMV positivity and tubulointerstitial inflammation. BKV-positive cells were accompanied with mild inflammatory response. There was no tubulitis in these areas. Immunostaining for the viral antigens on the first two biopsies was done retrospectively at the time of analysis of the third biopsy. Review of the slides showed occasional BKV inclusion. As both the viral antigens were identified on retrospective analysis of the first two biopsies after the third biopsy showed CMV inclusions, plasma/urine polymerase chain reaction or pp65 antigen were not available at that point of time.

In view of the absence of glomerulitis and arteritis and presence of tubulointerstitial inflammation in close association with CMV inclusions (confirmed by immunostaining) and CMV antigenemia, diagnosis of CMV-induced tubulointerstitial nephritis was considered. Tubulitis present in the third biopsy was considered to be part of the tubulointerstitial nephritis, as it was in the areas with CMV inclusions and inflammation. After 3 weeks of intravenous gancyclovir therapy, the patient’s CMV antigenemia assay became negative and his serum creatinine dropped to 2.5 mg/dl; thrombocytopenia and liver function tests normalized. His immunosuppression was tapered as per routine schedule, as we did not consider the possibility of BKN because BKV antigen-positive nuclei were not accompanied by significant inflammation. The patient came for follow-up for 4 months. At that time his creatinine was 3.1 mg/dl. A repeat biopsy was not done as the patient did not give his consent.

Discussion

Viral infections in renal transplant are particularly important, as their effect on the renal allograft are protean and can vary from a direct cytopathic effect to indirect effects ranging from acute and chronic graft rejection, oncogenesis and augmentation of exogenous immunosuppression. On routine histomorphology, viruses like CMV and BKV have diagnostic features, including presence of characteristic viral inclusions in a well-established case. However, the use of immunohistochemistry with specific antibodies can detect viral
antigens with greater sensitivity and, perhaps, earlier than routine haematoxylin and eosin staining.

CMV infection of renal allografts can produce direct cytopathic effects, resulting in CMV-induced tubulointerstitial nephritis or glomerulonephritis. The graft failure in such cases can be attributed to CMV infection rather than to a rejection process. There are studies that suggest an indirect role of CMV in both acute or chronic rejection as well as allograft nephropathy [2,11–14]. The definitive criteria for distinguishing interstitial nephritis due to CMV from acute cellular rejection have not been established. The minimal criteria of virus-induced interstitial inflammation should include the demonstration of a productive infection in renal parenchymal cells or infiltrating mononuclear cells, cytopathic changes, CMV proteins or mRNA (not just the CMV genome) [15]. The present case had cytopathic changes with tubulointerstitial inflammation and granular casts in dilated tubules along with CMV inclusions. No BK polyoma inclusions were seen in these areas. CMV antigen was present in cytomagic tubular epithelial cells, peritubular endothelial cells and macrophages, indicating that the tubulointerstitial nephritis (including tubulitis) was related to the CMV infection rather than an acute rejection process. The clinical course with response to specific antiviral treatment further supports this possibility.

Rarely, viruses may co-exist in renal transplant recipients. Concomitant CMV and HHV-7 infection has been associated with a greater risk of developing CMV disease [4] and CMV infection can result in reactivation of EBV [5]. Polyoma virus usually is not associated with co-activation of CMV, and BKV nephropathy is not associated with other graft infections [6]. There are occasional case reports of renal allograft recipients who had BKV nephritis and co-existing CMV that affected other organs, such as the gastrointestinal tract, sparing the renal graft [7–9]. A similar situation of BKV nephropathy diagnostic urine cytology and CMV antigenaemia has been reported following bone marrow transplantation [10]. We document the first case where CMV and BKV co-existed in sequential renal allograft biopsies in a patient with post-transplant graft dysfunction that mimicked cellular rejection.

In the present case, BKV antigen was present on immunohistochemistry in tubular nuclei. There were no histological features of BKV nephritis, but presence of BKV antigen might have accelerated the process of rejection and interstitial nephritis due to CMV. Simultaneously, CMV infection might have accelerated the process of rejection and reactivation of BKV. A synergistic effect of the two viruses and the rejection process resulted in the fulminant clinical course seen in this patient.

This case illustrates two important features. Firstly, these viral infections can mimic acute cellular rejection in the absence of fully evolved histomorphological features, such as viral inclusions, and immunohistochemistry can help in the early detection of viral antigens, which can be of therapeutic importance in cases of refractory rejection. Secondly, CMV and BKV antigen can co-exist in the same allograft biopsy, compounding the processes of rejection and virus-induced nephritis.

Conflict of interest statement. None declared.

References


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