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Absence of JC Viremia in a Case with JC Virus Nephropathy: A Case Report and Literature Review

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ABSTRACT

BK virus associated nephropathy (BKVAN) is an important cause of graft dysfunction with a high rate of graft loss. Current literature describes the pathophysiology of Polyoma Virus Associated Nephropathy (PVAN) induced by BKV but it lacks detailed definition of allograft nephropathy induced by JC virus (JCV). BKVAN is typically associated with BK Viremia, and the latter is the most commonly used screening measure for BKVAN in most transplant centers [1]. We are reporting a case of JCV associated nephropathy in renal allograft recipient who did not have JC viremia during the entire course of his disease and did not respond to reduction of immunosuppression and antiviral therapy.

Key Words: JC polyomavirus, Kidney transplantation, Nephropathy

INTRODUCTION

The human Polyomaviruses JCV human is a small non enveloped DNA virus that infects the majority of humans. Approximately 60–80% of adults in the United States have detectable antibodies against JC virus [2]. It is genetically similar to BKV and SV40. The BKV genome shares 75% homology with JCV, but differences exist in organ involvement.

Primary infection with JCV occurs during adolescence and early adulthood via oral and/or respiratory exposure and it presents as benign and asymptomatic infection. Thereafter, JCV establishes lifelong latency in the kidneys, central nervous system, and hematopoietic progenitor cells [3,4]. Progressive multifocal leukoencephalopathy (PML) is the major disease caused by JCV [5]. However, PVAN and ureteral stenosis in renal transplant recipients and hemorrhagic cystitis in bone marrow transplant recipients are the major diseases caused by BK virus [6,7]. This is possible due to the specific tropism that BKV shows for transitional and tubular epithelium, while no evidence of renal receptors for JCV have been demonstrated.

To date, only few cases of polyomavirus associated nephropathy have been attributed to JCV [8,9,10] and only limited information is available with respect to JCV replication in kidney transplant patients and its impact on the graft function and survival.

CASE REPORT

A 32-year-old male underwent living unrelated kidney transplant secondary to IgA nephropathy in February 2011. He received thymoglobulin induction and then maintained on Tacrolimus and Mycophenolate mofetil. Baseline creatinine after Kidney transplantation was 1.7 mg/dl. In February 2012 he developed CMV viremia by plasma PCR required reduction in immunosuppressants and starting Valganciclovir. Renal biopsy was done 4 weeks later due to rapid deterioration of the graft function, which revealed BANFF Grade 1A rejection. SV40 was positive, immunohistochemical staining for CMV was negative, C4d and DSA were negative. Serum and urine BKV DNA by PCR were negative. JCV DNA by PCR was < 500 copies/ml in serum but it was positive with 459,746,300 copies/ml in urine. Patient was treated with 3 doses of intravenous Methylprednisolone and then started on prednisone tapering dose. Mycophenolate mofetil was also reduced and was continued on valganciclovir for CMV
viremia. He underwent second renal biopsy 4 weeks later due to persistent elevated serum creatinine which revealed no evidence of rejection and C4d was negative but diffuse positive staining for SV40, and immunohistochemistry stain for CMV remains negative with negative CMV DNA, and BKV DNA by PCR in the serum. Mycophenolate mofetil was discontinued and a patient was started on leflunomide. Despite immunosuppressive therapy reduction, his renal function continued to deteriorate slowly and he underwent for third kidney biopsy in 8 weeks, which revealed positive staining for SV40 in multiple tubular nuclei suggestive of persistent polyoma virus in the renal tubules. Vasculitis with microangiopathy of the glomerular arterioles consistent with Grade 2B rejection, and severe interstitial fibrosis with tubular atrophy (50-70 % fibrosis). Patient was re-started on renal replacement therapy due to graft loss in 16 weeks.

Further analysis of the allograft biopsy to explain the finding of positive SV40 stain associated with allograft rejection and failure by in situ hybridization confirmed the presence of JCV and the absence of BKV, in all three biopsy specimens.

DISCUSSION
The first case of JCVAN was described by Kazory et al in 2003 in a 37-year-old man, 6 years after he receive a second renal transplant [8]. However, Dorries et al. reported JCV nephropathy in the native kidney of patient with PML [11]. In addition, Boldorini and colleagues had identified JCV replication with development of cytopathic changes in the kidneys of 6.3% of Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) patients undergoing autopsy. [12]

Definitive diagnosis of PVAN can only be made histologically by intranuclear basophilic inclusions without surrounding halo in tubular epithelial cells and confirmed with immunohistochemical staining of anti-SV40 antibody and electron microscopic findings of intranuclear viral inclusions.[14] There are no morphological differences between the renal tubular cytopathic changes in JCVAN and BKVAN[13].

Drachenberg et al reported 6 cases of JCVAN in their biopsies out of 28 patients with JCV viruria. Four of these patients had concurrent JCV viremia, suggesting that measurable JCV viremia, even at low levels, correlates with parenchymal involvement as it does in the case of BKV. They also suggested that a significant proportion of renal transplant recipients have JC viruria but a small fraction will have JCVAN, and that inflammation is usually mild and graft loss was uncommon [13]. In a study by Cheng et al, JC viruria was detected in 16% of recipients. No recipient developed JC viremia, and no JCVAN was detected. He suggested that infection by one polyomavirus is negatively associated with reactivation of the other as he observed an inverse relationship between donor BK antibody titer and recipient JC viruria, and BK viruria seemed to have an inhibitory effect on JC viruria. [15]

In contrast, we present a case of JCVAN where there was significant inflammatory infiltrate, and rapid deterioration of allograft function, suggesting that JCV may cause severe nephropathy and rejection in kidney transplant patients early in the course even in the absence of detectable JC viremia. This case report highlights the fact that JC viruria may not be as benign as noted in other studies. JC virus may cause severe nephropathy in kidney transplant patients and urine JC virus PCR should be used as screening measurement for JCVAN. We suggest close renal monitoring and early biopsy should be performed to improve outcome of this disease.

Kantarci et all analyzed previous JCVAN reported cases and demonstrates that male gender, previous acute rejection episode, low incidence of JCV viruria, PVAN pattern B histology, and satisfactory results after reducing immunosuppression are the diagnostic touchstones for PVAN due to JCV. Also the study suggests that in addition to reduction of the immunosuppression, Intravenous immune globulin (IVIG) therapy and conversion from tacrolimus to sirolimus can be a preferable option for JCVAN treatment [9]. Unfortunately, our
patient had a rapid deterioration of renal function and the allograft was lost in a matter of 16 weeks.

CONCLUSION
Though JC viruria is not uncommon after transplantation, JCVAN may have a rapid course and may occur in the absence of viremia. JC viruria may not be as benign and surveillance measures are important to maintain graft function. Prospective large studies are needed for better understanding the preventive approaches.

References:

Figure 1. Tubular epithelial nuclei were stained for SV40 antigen by immunohistochemistry.
Figure 2. Interstitial inflammatory infiltrate, enlargement, atypia (decoy cells) and tubular cell loss (hematoxylin and eosin stain, magnification $\times$ 400).