

# Successful Management of BK Virus Nephropathy Following Kidney Transplant in Nigeria: A Report of Two Cases

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## Abstract

BK Polyomavirus Associated Nephropathy (BKVAN) is an important emerging complication of renal transplantation. BK Virus (BKV) is an opportunistic pathogen that actively replicates in those with impaired immunity and its emergence is attributed to the use of more potent immunosuppressive drugs following renal transplant. The virus induces cytopathic changes in renal cells with commonly asymptomatic presentation, but if left untreated, leads to nephropathy and graft loss. Management of this emerging complication in transplant centres in Nigeria has not been reported. We therefore describe the successful treatment of BKVAN in two patients who had progressive impairment of renal function post-transplantation. A reduction in the dose of tacrolimus and withdrawal of Mycophenolate Mofetil (MMF) in the case 1 and replacement of MMF with Sirolimus in addition to a reduced dose of tacrolimus in case 2 improved graft function remarkably without any drug side-effects or further complications.

**Keywords:** BK virus; Nephropathy; Kidney transplant; Nigeria

## Introduction

BK Polyoma Virus-Associated Nephropathy (BKVAN) is an important emerging complication of kidney transplantation. [1,2] BKVAN is estimated to occur in 2%-16% of transplant recipients and can cause graft loss in up to 50% of cases. [3-5] It usually occurs in the first year post renal transplant and is preceded by a BK viraemia and viruria. [1-3] First isolated in 1971 from a kidney transplant recipient whose initials BK it subsequently bears, it is an opportunistic pathogen that is becoming increasingly relevant in transplant medicine. [6] This is due to the increased potency of newer immunosuppressant drugs, particularly tacrolimus and Mycophenolate Mofetil (MMF). [1,2,7] Although these immune suppressants have improved graft survival by reducing incidence of rejection, they have antithetically increased the emergence of opportunistic infections such as BK Virus (BKV).

Early recognition and management of BKVAN remains a clinical challenge especially in transplant centres that have limited experience with such cases. A high index of suspicion is important especially in patients with risk factors classified as donor factors, transplant factors and recipient factors. [1] Donor factors include seropositive BKV status and absence of Human Leukocyte Antigen (HLA) C7. [1] Transplant factors like HLA mismatch, ischaemic/re-perfusion injury and episodes of rejection, as well as recipient factors like increasing age, background Diabetes Mellitus (DM), seronegative BKV status and increased immunosuppression also increase the risk of BKN. Clinical features of BKVAN include declining renal function, evidenced by increasing creatinine and diagnosis is made based on positive Simian Vacuolating (SV) 40 T-antigen staining on renal biopsy. Biopsy also shows cytopathic changes in tubular cells and tubulointerstitial nephritis which is similar to changes seen in acute rejection. [8,9]

At the time of this report, there is no specific cure or prophylaxis for the BK virus. [1-10] Therefore, current treatment of BKN is based on reducing immunosuppression, substituting the more potent immunosuppressants and slowing down viral replication. This has to be balanced against the risk of allograft rejection which could also lead to graft dysfunction and subsequently affect long and short term graft survival. Increased awareness, risk reduction, early recognition and diagnosis of BK virus, will go a long way in maximising outcomes of kidney transplantation and ensuring long term graft protection. [11]

Strategies to improve outcomes in an otherwise resource limited environment include comprehensive screening for opportunistic infections before transplantation and periodically after the procedure. [11] However, from reviews, there has been no case report of BKVAN in Nigeria. Therefore, the aim of this article is to describe a case of post renal transplant BKVAN that was successfully managed in our centre, in Nigeria.

## Methods

Presently, about 9 centres offer kidney transplant as a treatment modality for ESRD in Nigeria. [12-14] Zenith medical and kidney centre, Abuja started the renal transplant program 4 years ago with over 380 surgeries carried out already. During our post-transplant follow up, BK virus was isolated from 2 patients who had renal transplant months earlier and were on immunosuppressant medications. Clinical data for the

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two cases was collected from electronic medical records and organised into a case report. Informed consent was obtained from each participant before including him in this study and ethical approval for the study was obtained from the Hospitals Management Board Health Research and Ethics Committee.

### Case 1

A 66-year-old male who was first seen in our facility on 12th of September 2018 with stage 5 Chronic Kidney Disease (CKD) due to chronic hypertension and obstructive nephropathy. He was referred to our centre for assessment and possible renal transplant. He is not diabetic; however, surgical history included cystoscopy and robot-assisted laparoscopic radical prostatectomy for prostatic cancer. He also had blood transfusions in the past, with no complications and blood pressure was controlled between 120/70-135/80 mmHg. His serum creatinine was 670 µmol/l and eGFR by CKD-EPI was less than 10 ml/min/1.73 m<sup>2</sup>. Ultrasound done showed poor cortico-medullary distinction. Concentric left ventricular hypertrophy with grade 1 diastolic dysfunction was seen on echocardiography. He was commenced on thrice weekly maintenance haemodialysis *via* tunnelled right internal jugular vein 5 days later.

He underwent renal transplantation 7 months later from a living unrelated donor with HLA mismatch 1-0-1. Basiliximab was used for immunosuppression induction and triple maintenance immunosuppression was continued with mycophenolate mofetil 1 g twice daily, prednisolone 10 mg once daily and Tacrolimus 5 mg twice daily. Serum Tacrolimus level was maintained between 11-15 ng/ml. Post-transplant urea and creatinine remained sub-optimal; on first day post-transplant urea was 9.9 mmol/L and creatinine was 544 µmol/L. Doppler ultrasound did not indicate any vascular abnormality. Graft function gradually improved with ninth day post-transplant urea and creatinine of 6.8 mmol/L and 139 µmol/L respectively. The serum creatinine was steady a month after transplantation at 122 µmol/l. Thereafter, there was a progressive/ relentless increase in the serum creatinine over the following 5 months [Table 1]. There were no features on clinical examination and blood pressure remained controlled between 120/70-135/80 mmHg. The graft in the right iliac fossa

was not tender and there was no bruit on examination. There was no significant change in urine output.

Dipstick urinalysis showed 1+ blood and 2+ proteinuria. Serum Tacrolimus 3.8 ng/ml while on 6 mg bd of tacrolimus. Urine cytology using early morning samples revealed numerous decoy cells. Blood and urine samples were sent to PCR lab to test for BK virus, Cytomegalovirus and Epstein Barr Virus. Results showed BK viruria with BK virus DNA by PCR of 7,200,000 copies/ml and 16,000 copies per ml in the blood sample. Diagnosis was confirmed on biopsy and SV-40-T antigen staining with numerous positive tubular nuclei and occasional positive glomerular parietal epithelial cells seen. Biopsy also showed dense interstitial inflammation, tubular epithelial cell inclusions, lymphocytic tubulitis and acute tubular injury. Tacrolimus was reduced from 6 mg twice daily to 4 mg bd and MMF was withdrawn. The serum creatinine started reducing and has remained within acceptable limits thereafter with no further complications as at last follow-up 9 months after transplant.

### Case 2

A 49-year-old man with Diabetes Mellitus (DM) for 18 years, hypertension for 17 years and stage 5 chronic kidney diseases diagnosed 3 years ago. He started twice weekly haemodialysis and presented for renal transplantation. He had stem cell transplantation 3 years ago with no complications. Investigations done showed obesity with BMI of 38, impaired renal function with urea of 20.8 mmol/L and creatinine of 1086 µmol/L. Ultrasound scan showed increased parenchymal echogenicity with reduced cortico-medullary distinction.

Living related kidney transplantation was carried out in November 2018 and postoperative recovery was uneventful. Renal function was optimal until three months after transplantation when a slow but progressive increase in serum creatinine was observed [Table 2].

Urine and blood samples were sent for BK virus detection by PCR, revealing the presence of BK viruria and viraemia. Widespread acute tubular injury with florid tubulointerstitial inflammation and cellular infiltration was seen on renal allograft biopsy and SV-40 staining was positive, confirming BKVAN. Tab MMF was replaced with Sirolimus 2 mg daily and Tacrolimus was reduced to 1 mg daily. Subsequently, the renal function improved, and the viral load reduced after the change in medications. There were no complications reported as at last follow-up 14 months post-transplant.

## Discussion

Transplantation is the favoured treatment modality for patients with end stage kidney disease as it is associated with longer

**Table 1: Increasing post-transplant serum creatinine over time. All values shown represent nadir results for the month.**

July 2019	169 µmol/l
August 2019	198 µmol/l
September 2019	215 µmol/l
October 2019	227 µmol/l

**Table 2: Increasing post-transplant serum creatinine over time against tacrolimus level and dosage. All values shown represent nadir results for the month.**

Timeline post-transplant	May 2019	June 2019	July 2019	August 2019
Serum creatinine µmol/l	91	102	122	169
Tacrolimus level	4.6 g/ml	5.2 ng/ml	14.4 ng/ml	13.6 ng/ml
Tacrolimus dosage	4 mg bd	5 mg bd	5 mg bd	4 mg bd

survival and better quality of life. [15] Deliberate induction and maintenance of immunosuppression is one of the key pillars of renal transplantation. [14] However, with more potent immunosuppression, the risk of complications from opportunistic infections increases. BK polyoma virus is a small DNA virus that is found in most of the world's population in which it is quiescent. [1-3] The virus is estimated to be present in about 90% of the population by age 23. [16] It has tropism for the renal tubular and uroepithelial cells and after initial exposure in childhood, the virus becomes latent in uroepithelial tissues. [1-3] In immunocompromised patients and in the context of potent immunosuppression, there may be reactivation and uncontrolled viral replication resulting in nephropathy. [1-3] Clinicians may therefore struggle to balance the risk of acute rejection against that of BKVAN. The emergence of BKVAN therefore represents a recent challenge for clinicians.

An ideal immunosuppressive regimen seeks to limit toxicity and prolong the functional life of the graft and this includes not allowing infections to emerge frequently; this balance is a moving target for most transplant physicians and surgeons. The risk of acute rejection is highest in the first few months after transplantation and diminishes afterwards. [14] Immunosuppression is therefore usually more intense in the immediate post-transplant period and is deliberately gradually reduced as the graft gets older. Presently conventional maintenance immunosuppressive protocols consist of a triple therapy regimen: a calcineurin inhibitor, corticosteroids and another agent. [1-4,10,11,14,17-19] In our protocol, this agent is usually the antiproliferative mycophenolate mofetil, MMF.

BKN and T-cell mediated acute rejection share similar features. [8] For our 2 patients, the initial suspicion was allograft rejection due to inadequate immunosuppressant. The initial presentation of a slow unexplained decline in allograft function with increasing serum creatinine noted in our cases is identical to what is described in wider literature. [1-10,17-19] The centre protocol ruled out the initial suspicion of other infections and inadequate blood drug concentration in both patients. Screening for cytomegalovirus, BK virus and Epstein Barr virus was subsequently carried out as part of the protocol for review of declining graft function and diagnosis was made based on biopsy findings.

Early detection of BKV by programmed screening allows for adjustment of immunosuppression, reconstitution of recipient immunity and potential viral clearance. [20] This may therefore grant greater preservation of allograft tissue and function. However, this is expensive to do on a regular basis as outlined in some studies. [21,22] The prevalence of BK viremia is estimated at about 25% in renal transplant patients but does not always translate into BKVAN and may even spontaneously resolve. [22] Furthermore, a unique case of BKVAN without detectable viraemia or viruria has been reported, [23] raising concerns around specificity and sensitivity. The experience from our centre suggests that BK virus screening as part of a review for declining renal allograft function is a viable alternative to regular screening where there are limited resources. However, 2 cases alone are not enough to make any definitive conclusions and larger statistical studies and trials are required. Regular

screening for those identified to be at risk is another model that requires further consideration since both cases had at least 1 risk factor for BKN. Case 1 was advanced in age and had HLA mismatch while case 2 had very high BMI and long term DM. These could have further compromised their immune system. The serum tacrolimus level in the second case was as high as 14.4 ng/ml before it began to drop. This could have resulted in higher risk of BKVAN in the patient.

BK viraemia and viruria was noted during the period of intense immunosuppression in both patients. Although definite timeline from viruria and viraemia to biopsy confirmation could not be established, the findings do not contradict studies showing their use as a screening tool. [21,22] Detection of the virus in urine is thought to precede viremia by several weeks. According to KDIGO 2009 guidelines, [20] screening is recommended for BKV with quantitative nucleic acid testing at least monthly for the first 3–6 months and thereafter every 3 months until the end of the first year post-transplant, and whenever there is an unexplained rise in serum creatinine, or and after treatment for acute rejection. However, the usefulness of both modalities in clinical practice is questionable since BKN may not develop even with BK viraemia. [22]

The definitive diagnosis of BKN is made by histological examination of a kidney allograft biopsy. [1-3] In both our cases, the characteristic features of intracellular basophilic viral inclusions, interstitial mononuclear/polymorphonuclear cell infiltrates, tubular injury, and tubulitis 1-3 were seen. Special staining also confirmed the presence of BKN. Our experience of clinical features and diagnosis in this regard is not different from those described in other studies. [1-10,17-19]

There is no consensus on the best treatment approach to BKN. However, most researchers and clinicians agreed that a balance of immunosuppression that will safeguard the graft from both allograft rejection and BKN should be aimed for. Treatment of established BKN includes reduced immunosuppression, achieved with tacrolimus reduction or its replacement with cyclosporine, [24] reduced mycophenolate or replacement with leflunomide or azathioprine, and prednisolone pegged to 10 mg per day. Additional therapies included fluoroquinolones for 1 month and intravenous immunoglobulin. [24-26] The combination of low dose cyclosporine plus mammalian Target of Rapamycin (mTOR) inhibition appears to be safe and warrants further investigation. [27] However the fear of graft rejection has not made the use widespread.

For our 2 cases, treatment was approached by retaining tacrolimus at a reduced dose in the first, while replacing MMF with Sirolimus in the other patient and reducing drastically the dose of tacrolimus. Dose reduction of tacrolimus was between 25%-50% depending on serum concentration and clinical judgement. Both patients had improvements in renal function after the above measures and did not need further intervention.

## Conclusion

With newer and more potent immunosuppression, BK nephropathy has become a more common cause of allograft dysfunction. The reactivation of BK virus infection with the larger

effect on transplantation dynamics is a challenge for nephrologists until researches can establish an acceptable approach to its management. Reducing the dose of immunosuppressants is the main stay of treatment and management should be balanced against the risk of renal allograft rejection. From our experience, leflunomide and sirolimus combination is safe and should be considered early to manage graft dysfunction and reduce the risk of graft loss. The importance of programmed screening for early diagnosis is unclear. Therefore, BK virus testing as a review of declining allograft function could be a cost saving measure when resources are limited.

### Competing Interests

The authors report no competing (commercial/academic) interests.

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