CASE REPORT

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Transplant renal artery stenosis in a child with BK nephropathy

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Abstract

TRAS and BK nephropathy are known complications of RT, but the association between both has not been reported. A 2-year-old girl underwent a deceased donor renal transplant from a 20-year-old donor, along with bilateral native nephrectomies. She had a DGF due to a renal artery thrombus and required thrombectomy with re-anastomosis. Heparin and aspirin were used. Immunosuppressive agents included thymoglobulin, steroid, tacrolimus, and MMF. CMV and EBV DNA PCRs were negative, but she developed BK viremia at 2 months with stable allograft function. Immunosuppression was reduced, and leflunomide was initiated. Blood pressures were well controlled on low-dose amlodipine. Five months after RT, she presented with hypertensive emergency, following a respiratory infection, and required dialysis for oliguric acute kidney injury. Allograft biopsy showed evidence of BK nephropathy. Immunosuppression was further minimized. Doppler renal US and renal artery duplex studies were both suggestive of TRAS. Angiogram showed severe proximal anastomotic TRAS (>95% occlusion). PTA with stenting was done with immediate improvement in the blood flow and reduction in the pressure gradient. BPs and renal function normalized. Ten months post-RT, she remains normotensive with stable renal function and resolution of BK viremia. Although ureteral stenosis and nephropathy are known to occur with BK infection, TRAS is an interesting association and possibly suggest the tropism of BK virus to the vascular endothelial cells. Timely recognition and management of both is important to prevent uncontrolled hypertension and allograft dysfunction.

KEYWORDS
BK viremia, nephropathy, renal artery stenosis, renal transplant

1 | INTRODUCTION

Stenosis of the transplant renal artery is a well-known early complication of RT.[1] Early diagnosis and management is necessary to prevent allograft dysfunction and severe multi-system complications arising from severe hypertension. Post-RT surveillance of BK virus is commonly done at most transplant centers. BK viremia similarly is more common in the early post-RT period due to intense immunosuppression.[2] Untreated, BK viremia can progress to BKVAN, leading to transplant dysfunction.[3] Although CMV infection is known to occur in association with TRAS,[4] a concomitant BK viremia and TRAS has not been described. Here, we describe a 2-year-old girl who presented with such an association.

2 | CASE PRESENTATION

A 2-year-old Caucasian girl had ESRD secondary to hypoxic-ischemic injury at birth. She required temporary RRT in the form of PD from 2 weeks until 4 months of age. PD was discontinued at 4 months of age due to recurrent fungal peritonitis. She was able to maintain stable electrolytes with good urine output while off PD. At 2 years of age, she received a deceased donor kidney transplant from an adult donor. Donor kidney was 10 cm in length with a single renal artery and vein. KDPI was 33%. Her height was 80 cm (5th centile), and weight was 12 kg (50th centile) at the time of transplant. It was a five antigen mismatched kidney. Pretransplant hypercoagulable workup was negative. Allograft was placed intra-abdominally. The donor renal artery was anastomosed with the recipient's aorta and the donor renal vein with the recipient's IVC via end-to-side anastomosis, using # 6-0 prolene suture. Bilateral native nephrectomies (right kidney 4 cm and left kidney 4.5 cm in length) were performed at the time of transplant to prevent dehydration episodes post-RT as she was polyuric prior to transplant, and also, it was thought that the 10-cm donor kidney would be little difficult to fit in this small patient. Intra-operative event was otherwise unremarkable.

No peri-operative heparin was administered. Abdominal fascia was closed with # 2-0 PDS, and skin was closed with monocryl subcuticular suture. CIT was 8 hours and 38 minutes, and WIT was 49 minutes. There was an EBV and CMV mismatch (donor positive and recipient negative). She had an excision of her left parathyroid nodule 2 days prior to the transplant. A non-contrast MRI of neck done for persistent hypercalcemia and phosphaturia with normophosphatemia, suppressed serum intact PTH, elevated PTHrp (50-60 pg/mL), and FGF 23, had shown a left parathyroid nodule. Histology of the excised tissue showed the presence of thymic tissue. Induction was done with thymoglobulin (total 4.5 mg/kg) and methylprednisolone.

She had an excellent graft perfusion immediately after anastomosis with good urine output, but after an hour, she progressively became oligoanuric, and by 4 hours, she was anuric. Serum creatinine remained at pretransplant level (~2.5-3 mg/dL). Doppler US of renal transplant showed poor blood flow, leading to emergency abdominal re-exploration 6 hours post-RT. An early thrombus was found at the renal artery tip for which she underwent thrombectomy, while the kidney was kept cold at back bench. An end-to-side re-anastomosis of renal artery with the right common iliac artery was performed using # 6-0 prolene suture. Her abdomen was left open with a Gore-Tex patch with mesh, and ioband was placed over the mesh. Post-thrombectomy, she received heparin infusion and baby aspirin. Renal function remained deranged with dyselectrolytemias and elevated serum creatinine (peak 5 mg/dL), requiring initiation of HD. An open transplant kidney biopsy performed on POD 3 showed features of ATN without any rejection. MMF was started on POD 1 but initiation of tacrolimus was delayed due to DGF. Her urine output gradually improved, and by POD 14, dialysis was not required. On POD 19, the Gore-Tex patch was removed and fascia was closed with # 2-0 PDS and skin closed with monocryl in a subcuticular fashion. She was discharged home on POD 21 on tacrolimus, MMF, steroid, and aspirin. Anti-infective prophylaxis consisted of TMP-SMX, valganciclovir, and nystatin. At 1 month post-RT, she was started on amlodipine for mild asymptomatic hypertension. Ureteral stent was removed in 6 weeks.
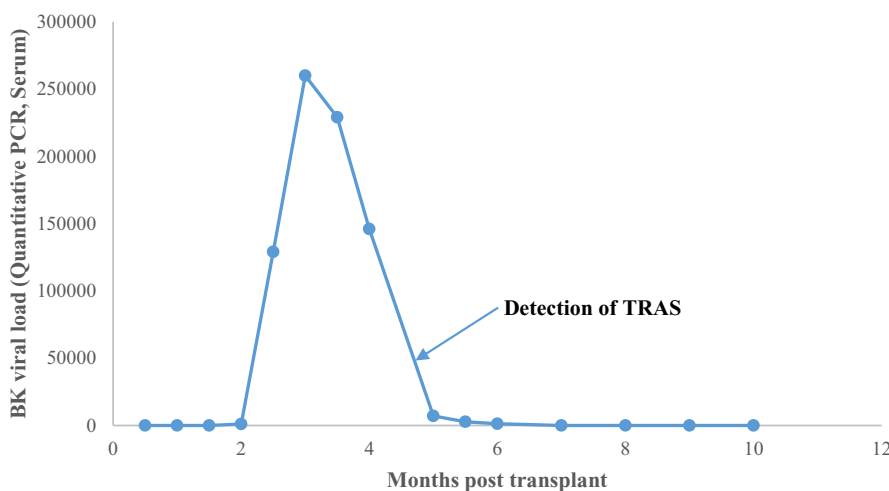

FIGURE 1 Association of BK viremia with transplant renal artery stenosis

Serum trough tacrolimus levels remained at goal (8-10 ng/mL, as per our center's protocol) with intermittent elevation, requiring dose reduction.

Later, her post-transplant course was complicated by multiple hospital admissions due to viral respiratory illness, UTI, and febrile neutropenia. These episodes were managed with appropriate antibiotics, reduced immunosuppression, G-CSF, and supportive measures. Aspirin was discontinued at 2 months due to development of spontaneous bruising. MMF was held at 2 months post-RT due to severe neutropenia and BK viremia; the latter started at 2 months and peaked at 260 000 copies/mL (ARUP laboratories; normal: <390 copies/mL; quantitative PCR, serum) at 3 months post-RT (Figure 1). Leflunomide 20 mg daily was started at 2 months. Renal function remained stable with baseline serum creatinine of 0.9-1 mg/dL. A transplant biopsy was not performed. There was no history of gross hematuria or hydronephrosis. CMV and EBV DNA PCR remained negative throughout. At 5 months post-RT, she presented with hypertensive emergency and PRES, apparently following another episode of respiratory illness which was later found to be secondary to coronavirus and parainfluenza infection. Her medications included tacrolimus, prednisolone, TMP-SMX, amlodipine, valganciclovir, and leflunomide. Serum trough tacrolimus level was 4 ng/mL, and serum creatinine was elevated at 1.4 mg/dL. Her average SBPs ranged from 160 to 180 mm Hg, despite multiple antihypertensives, including continuous nicardipine infusion. On the second day of admission, she developed generalized tonic-clonic seizure, with a BP of 190/100 mm Hg. MRI brain showed changes consistent with PRES. Antihypertensive therapy was augmented with the combination of nicardipine infusion, hydralazine, carvedilol, clonidine, furosemide, amlodipine, losartan, and minoxidil. Echocardiogram showed mild-to-moderate LVH with LVMI of 178.85 g/m$^{2.7}$. Doppler US of the allograft showed decreased resistive indices (0.4-0.5) with tardus parvus waveforms and no hydronephrosis. Duplex study of renal artery showed extremely elevated velocities at the proximal renal artery (ostial renal: 96, proximal renal: 720, mid renal: 128 and distal renal artery: 105 cm/s), confirming proximal TRAS. Renal function continued to worsen with peak serum creatinine of 3 mg/dL. Losartan was discontinued. Serum BK PCR load was 2510 copies/mL with negative CMV and EBV PCR. Urine BK PCR load was 3.1 million copies/mL. Urine cytology for decoy cells was not sent. Percutaneous transplant kidney biopsy showed mild but diffuse interstitial inflammation, heavier in medulla, with CD3-positive lymphocytes and CD68 mononuclear cells associated with mild lymphocytic tubulitis and moderate IF/TA. There was no hemorrhage, edema, or endotheliitis. Peritubular C4d staining was negative. No definitive intranuclear inclusion was seen. Immunohistochemical stain for SV40 was positive in the epithelial cells of distal and proximal tubules. These changes were consistent with BKVAN which was treated with IVIG, increase in the dose of leflunomide to 30 mg daily, and cessation of tacrolimus. The clinical course was complicated by diuretic-resistant oliguria and pulmonary edema, eventually requiring HD and mechanical ventilation. HD was discontinued a few days later with improved pulmonary function. However, the refractory hypertension persisted despite multiple antihypertensive agents. She underwent a conventional digital subtraction angiogram which showed a severe anastomotic stenosis (>95% occlusion) of the renal artery (Figure 2) and a preprocedural gradient of 50 mm Hg across the stenosis. Successful PTA with stenting (4 × 15 mm balloon mounted uncoated stent, Monorail Xience Sierra, Abbott laboratories) of the transplant renal artery was done, with immediate improvement of blood flow and gradient reduction to 18 mm Hg. BPs normalized within few hours with average SBPs of 100-110 mm Hg with intermittent elevation to 120-130 mm Hg. Repeat Doppler US showed normalization of resistive indices and normal-appearing vascular waveforms. She was maintained on aspirin following stenting of the transplant renal artery. At the time of discharge, her serum
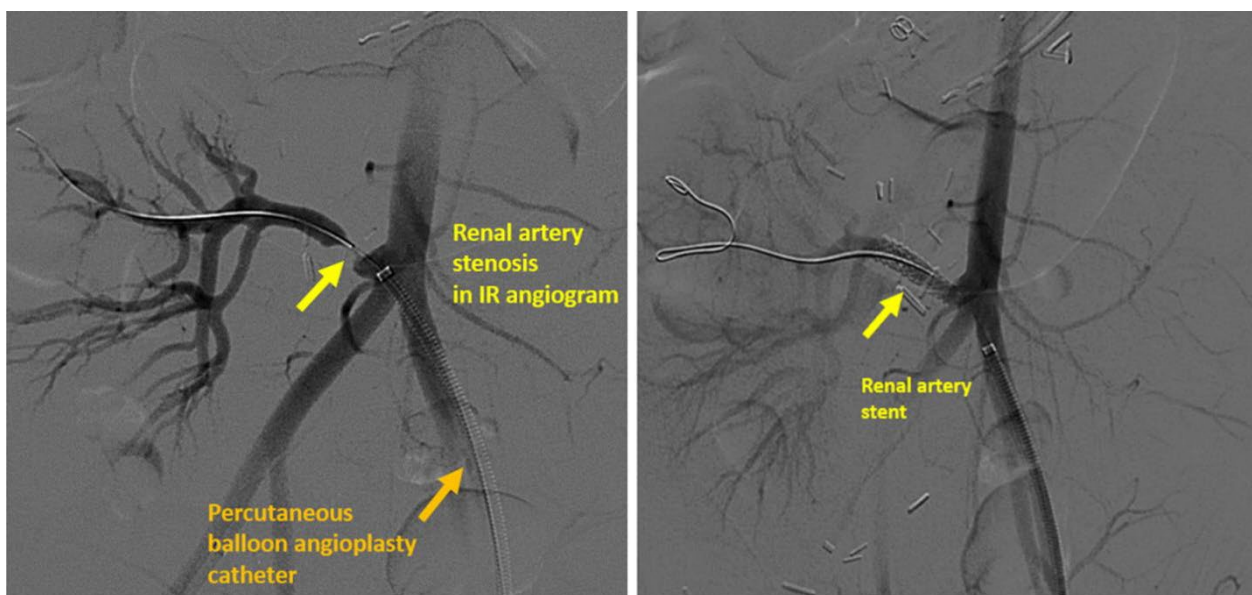
FIGURE 2 Angiogram showing a transplant renal artery stenosis, before and after PTA, and stent placement

creatinine was back to baseline at 1 mg/dL and BPs were controlled with 2 antihypertensives (amlodipine and clonidine). Other discharge medications included aspirin, prednisone, and low-dose tacrolimus. Repeat echocardiogram showed decrease in LVMI to 105.86 g/m[2.7]. Follow-up 10 months later showed stable baseline serum creatinine of 0.9-1 mg/dL and controlled BPs on two antihypertensive agents. Follow-up Doppler renal transplant sonograms and duplex study of the renal artery showed normal waveforms and velocities, respectively. BK viremia resolved at 7 months post-RT. Leflunomide was discontinued, and MMF was restarted.

3 | DISCUSSION

BK viremia and nephropathy are increasingly recognized as important causes of renal allograft dysfunction.[2,3] Incidence of BK viremia within the first year post-RT is about 13%-22%, and BKVAN has been reported in up to 10% of kidney transplant biopsies.[5,6] Generally, a high serum viral load is suggestive of BKVAN[7] and warrants very close follow-up of renal function. Although our patient had a high serum viral load, we did not initially perform a biopsy due to stable graft function. Performance of a renal biopsy is usually prompted by allograft dysfunction, but some studies suggest persistent BK viruria or viremia as appropriate indications as well.[8] On the other hand, a higher rate of false-negative biopsies may be encountered in the early stages of the disease when the parenchymal involvement is patchy.[9] Cytopathic changes were not obvious in our biopsy, mostly due to the focal nature of the nephropathy[10] and due to significant IF/TA.

In patients with renal transplants, ureteric stenosis and BKVAN are known complications of BK infection. However, the presence of BK infection along with TRAS has not been described. The widely accepted pathogenesis of BKVAN is characterized by an ascending infection from the uroepithelial cells to high-level viral replication in renal tubular epithelial cells leading to cellular loss and thereby denudation of the epithelial monolayer in the tubules. Virus then leaks into the tissue and bloodstream, and inflammatory cells infiltrate the interstitium leading to IF/TA.[11] The vascular spread of the virus may lead to the dissemination of virus to other tissues.

Historically, polyomaviruses (BK, JC virus, and SV40) are known to infect urorenal epithelial and neural cells. However, subsequent reports have described BK virus to infect and be reactivated in other large number of target cells, including the ones affected by inflammation or ischemia reperfusion injury, predominantly in the immunocompromised host. Some of these other target tissues or organ systems include liver, retina, lung, salivary gland, peripheral blood leukocytes, human umbilical cord vein umbilical cells, pancreatic cells, heart, and skeletal muscle.[12-14] BK virus has also been shown to have tropism for vascular endothelial cells and causes an immune response by upregulating the genes associated with cell proliferation.[15] BK infection also activates the interferon signaling in the endothelial cells by increasing the mRNA levels of many interferon-stimulated genes.[15] Uptake of blood-born BKV virus-like

particles by endothelial cells of liver sinusoids and renal vasa-recta has been shown in animal studies.[16] This indicates that endothelial cells might provide an initial immune defense against BKV infection. Furthermore, in vitro studies show that BK virus exhibits a prolonged viral protein expression (at least 2 months), low yield of infectious progeny, and delayed cell death and hence maintaining the antiviral defense in the endothelial cells.[15] This does raise the possibility of role of BK virus in inducing vascular stenosis, especially with prior history of renal artery thrombosis, thrombectomy, re-anastomosis, and possibly vascular injury, as in the case described in this report. Upregulation of cell proliferation genes from BK infection in the endothelial cells could lead to the production of granulation tissue, leading to stenosis of the renal artery. Indeed, ureteric stenosis is one of the known associations with BK infection, usually occurring 2-5 months post-RT,[17] which corresponds to the peak onset of BK virus reactivation in kidney transplant recipients. The most widely accepted theory is that the ureteric epithelium which is damaged by ischemia or inflammation supports the BK infection and then is replaced with a granulation tissue, leading to stenosis.[18,19] We are not able to provide a histological evidence of BK infection of the transplant renal artery due to the very invasive nature of the procedure and potential risks of procedure-related complications.

In contrast, infected renal proximal tubular epithelial cells do not elicit an efficient innate immune response against BKV as the infection leads to the release of many progeny virions and loss of cell monolayer viability.[20] Cytopathic effects of BK virus have also been demonstrated in podocytes, mesangial cells, and glomerular endothelial cells, along with the epithelial cells of bladder and urethra.[15] This suggests that these cells do not mount an effective antiviral response, and this may contribute to glomerular inflammation and hemorrhagic cystitis in BKV infection.[21] Due to the strong productive infection, the viral persistence is not maintained in these cells as opposed to the endothelial cells as described above. Hence, there seems to be a cell type-specific response to BKV infection. The simultaneous occurrence of BK nephropathy and TRAS in this patient may be an example of such cell-specific response (death of renal tubular cells and proliferation of renal artery endothelial cells).

BK tropism of vascular endothelial cells is well described in a clinical report which described disseminated BK vasculopathy in multiple organs including skeletal muscle, kidney, heart, and esophagus (all histologically proven) in an adult renal transplant recipient leading to death. Renal allograft biopsy showed an immunoreactivity to polyomavirus proteins in capillary endothelial cells and in tubular lumen. The study postulated that BK virus-induced endothelial-cell injury led to capillary leakage and massive edema, along with microthrombotic events causing tissue ischemia in multiple organs.[14] In this report, we describe a child with simultaneous occurrence of BK nephropathy and TRAS, the latter presumably due to spread of BK from renal tubular epithelial cells to the vascular endothelial cells.

TRAS is the most common vascular complication after RT.[1] It is a serious but potentially reversible cause of post-transplant hypertension and allograft dysfunction and usually presents 3 months to 2 years post-RT.[22] The reported incidence varies widely from 1%

to 23%[23,24] with recent studies showing lower incidence rates of 2%-5% within 3 years post-RT.[25] Risk factors include kinking of the artery, placement of vascular clamps during transplant, faulty retrieval or suturing, donor artery atherosclerosis, fibrosis and intimal hyperplasia from prior injury at the time of donation or anastomosis, prior thrombosis, older recipient age, marginal donor kidneys, DGF, prolonged CIT, acute rejection, and CMV infection, mainly in those who seroconvert after transplant.[25-31] CMV-induced vascular damage may occur through local infection and the mitogenic actions of viral gene products within cells of the vessel wall.[32] CMV infection is also thought to augment endothelial damage.[29] CMV-induced direct proliferative effect on vascular endothelial cells leading to TRAS is another possibility.[31] EBV-associated post-transplant B-cell lymphoma leading to TRAS secondary to extrinsic compression of the renal artery has been described in an adult patient.[33] Our patient did not have CMV or EBV viremia, and there was no extrinsic compression. She did have renal artery thrombus (thought to be secondary to two back-to-back surgeries leading to intravascular volume depletion due to being on NPO status for prolonged time in the setting of polyuria, this was supported by the evidence of ATN in the biopsy) for which she underwent end-to-side re-anastomosis after thrombectomy and that could have added further insult to the artery. End-to-side anastomosis has been reported in some studies as a risk factor for TRAS but has not been consistently demonstrated.[25,34] To the best of our knowledge, BK infection has not been shown to be a risk factor for TRAS but is possible given its effect on endothelial cells as outlined above. One of the drugs used in the treatment of BK infection, leflunomide, can cause cutaneous necrotizing vasculitis but its association with TRAS is unknown.[35]

Endovascular intervention with PTA with or without a bare-metal stent is usually the first-line therapy for TRAS. Increased risk of graft loss has been reported regardless of angioplasty or not,[25,29] but another retrospective study by Geddes et al[36] found no increased risk of graft loss in patients with TRAS who were treated with angioplasty vs those who did not receive angioplasty. Surgical repair is reserved for cases in which angioplasty is unamenable or unsuccessful.[37] Our patient had an excellent outcome with PTA and stent placement alone.

In our patient, there appears to be the development of clinically significant TRAS simultaneously with evidence of florid BKVAN during the resolution phase of BK viremia; however, the timing of biopsy could have caused this apparent observation. She had independent risk factors for the development of both TRAS and BKVAN, and hence, the definite causation cannot be established between the two solely from this report. It could be a mere "incidental finding." Rapid clinical improvement with PTA and stent placement also suggests that the stenosis may not be definitely due to BK infection only. The tissue histology of the renal artery demonstrating BK infection could have provided more definite answer but it was not obtained due to several potential risks of such procedure. Also, both hypertension and allograft dysfunction are multifactorial, and hence, we cannot attribute these post-RT complications due to TRAS and/or BK viremia only.

4 | SUMMARY

Both TRAS and BKVAN are serious complications after RT. Early diagnosis of both is necessary for improved allograft survival. In this report, we postulate that BK infection could be a risk factor for TRAS given the association. Further studies are necessary to determine any possible causal relationship between these two entities. Hence, it may be worthwhile to look at evidence of TRAS by non-invasive studies such as Doppler transplant sonogram and/or duplex renal artery study and if suggestive, invasive study such as angiogram, in patients with BK viremia and hypertension. Histological evidence of BK virus particles in the stenotic tissue may be very useful as well.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

AUTHORS' CONTRIBUTIONS
Sudha Mannemuddhu, Naile Pekkucuksen, Rachel Bush, and Felicia Johns: Collected data, drafted the initial manuscript, and reviewed and revised the manuscript; Kiran Upadhyay: Collected data, conceptualized the study, drafted the initial manuscript, and critically reviewed and revised the manuscript; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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