

BK Virus Nephropathy in the Native Kidney of a Liver Transplant Recipient



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INTRODUCTION

BK virus nephropathy (BKVN) develops from the reactivation of latent polyomavirus infection of urothelium and kidney tubular epithelium and is most prevalent in the allograft kidney.¹ Latent infection frequently occurs early in life without clinical significance in the immune competent host. Viral reactivation and spread into the permissive urothelium and kidney tubular epithelium, resulting in viremia, viremia, and less frequently renal dysfunction (i.e., BKVN), has been described in a multitude of immunosuppressed states, although most cases of BKVN occur in the renal allograft.^{2,3}

We present a liver transplant recipient with progressive rise of serum creatinine over a 1-year period. With a concern for potential chronic tacrolimus toxicity or acute tubular injury, a kidney biopsy specimen was obtained, and it unexpectedly revealed interstitial inflammation, tubulitis, and viral inclusions diagnostic of BKVN. After withholding immunosuppression, renal function progressively worsened, and a second kidney biopsy specimen obtained 1 month later revealed more prominent BKVN. The finding of BKVN in the native kidney, in the setting of liver transplantation, has only been rarely described.

CASE PRESENTATION

A 60-year-old white woman with history of hypertension and end-stage liver disease caused by Wilson disease who underwent a liver transplantation 5 years earlier presented with declining renal function (Table 1). From a baseline serum creatinine of 1.2 mg/dl 1 year prior, the patient's creatinine had increased to

3.9 mg/dl. Other laboratory values from the time of the initial biopsy procedure included serum albumin 3.9 g/dl, urinalysis notable for trace proteinuria, 1 red blood cell per high powered field (hpf), and 19 white blood cells per hpf, pancytopenia (hemoglobin 8.8 g/dl, white blood cell count $3.8 \times 10^9/l$, and platelet count $104 \times 10^9/l$), and tacrolimus <0.2 ng/mL (reflective of recently discontinuing tacrolimus). A kidney biopsy specimen was obtained to determine the etiology of the patient's acute kidney injury.

The specimen revealed patchy, mild to moderate interstitial inflammation involving approximately 30% of the cortex sampled and associated with multifocal tubulitis (Figure 1). The mononuclear inflammatory tubulointerstitial infiltrate was comprised of a mixture of CD3-positive T cells (~75% of the inflammatory cells), CD20-positive B cells (~20%), and rare plasma cells (~5%). Rare tubular epithelial cells contained enlarged nuclei with glassy intranuclear viral inclusions. Immunoperoxidase staining was positive for SV40 in the distribution of the intranuclear viral inclusions, and negative for cytomegalovirus. The findings were diagnostic of BKVN and were accompanied by mild to moderate tubular atrophy and interstitial fibrosis involving 30% of the cortex sampled. Mild arteriosclerosis was noted, and the glomeruli appeared unremarkable. Histopathologic changes of chronic tacrolimus toxicity, including isometric tubular vacuolization and beaded arteriolar hyalinosis, were absent. Immunofluorescence and electron microscopy were unremarkable.

Following the diagnosis of BKVN, treatment with tacrolimus did not resume. Subsequent studies showed BK virus in the serum (81,600 copies/ml) and urine

Table 1. Relevant laboratory parameters with clinical correlation over time

Time in relation to the first kidney biopsy procedure	5 months prior				Time of first kidney biopsy procedure	Time of second kidney biopsy (1 month after the 1st biopsy)	3 months after the 1st biopsy
	1 year prior	5 months prior	2 months prior	1 month prior			
Clinical situation/findings	Initial presentation to nephrology	Vomiting	Diarrhea	Elevated Cre even with resolution of diarrhea; tacrolimus held	Elevated Cre even after tacrolimus held	Cre progressively increasing; after the second biopsy's resulting IVIG added and tacrolimus resumed	BK virus not detected in the serum
Serum Cre, mg/dl	1.2	1.7	2.4	3.3	3.9	6.61	5.3
Proteinuria	—	—	Negative	—	Trace	—	Trace
UA	—	—	0 RBCs/hpf, 13 WBCs/hpf	—	1 RBC/hpf, 19 WBCs/hpf	—	1 RBC/hpf, 6 WBCs/hpf
Tacrolimus, ng/ml	2.1	2.5	2.1	2.1	<0.2	<0.2	<0.2

ATI, acute tubular injury; Cre, creatinine; hpf, high-powered field; IVIG, intravenous immunoglobulin; UA, urinalysis; RBC, red blood cell; WBC, white blood cell.

(>3.9 × 10⁸ copies/ml). Despite discontinuation of immunosuppression, the patient's creatinine increased to 6.61 mg/dl and serum BK virus rose to 1.0 × 10⁶ copies/ml 1 month later. A second kidney biopsy specimen revealed more extensive tubulointerstitial nephritis and more abundant intranuclear viral inclusions, which was confirmed by immunoperoxidase staining for SV40 (Figure 2). One dose of intravenous immunoglobulin was administered. Tacrolimus was resumed at low dosage (1 mg twice per day) with concern for the liver allograft. Three months after the first kidney biopsy procedure the patient's creatinine has remained stable at 5.3 mg/dl and BK virus is no longer detectable in the serum. The patient did not require dialysis support at any time.

DISCUSSION

BKVN is mediated by a polyomavirus capable of infecting the urothelium and renal tubular epithelium, with decreased host immunity augmenting kidney disease commonly in the form of a tubulointerstitial nephritis. Although BKVN is a common concern in the allograft kidney, viral infection of the native kidney can develop rarely in the setting of solid organ transplantation (e.g., heart, lung, and liver), hematologic malignancy (variably with bone marrow transplantation), and autoimmune disease.^{4,5}

Biopsy-proven BKVN in liver transplant recipients has been sparingly described. Lai *et al.*⁶ described a 59-year-old male who had a liver transplant 2 years earlier

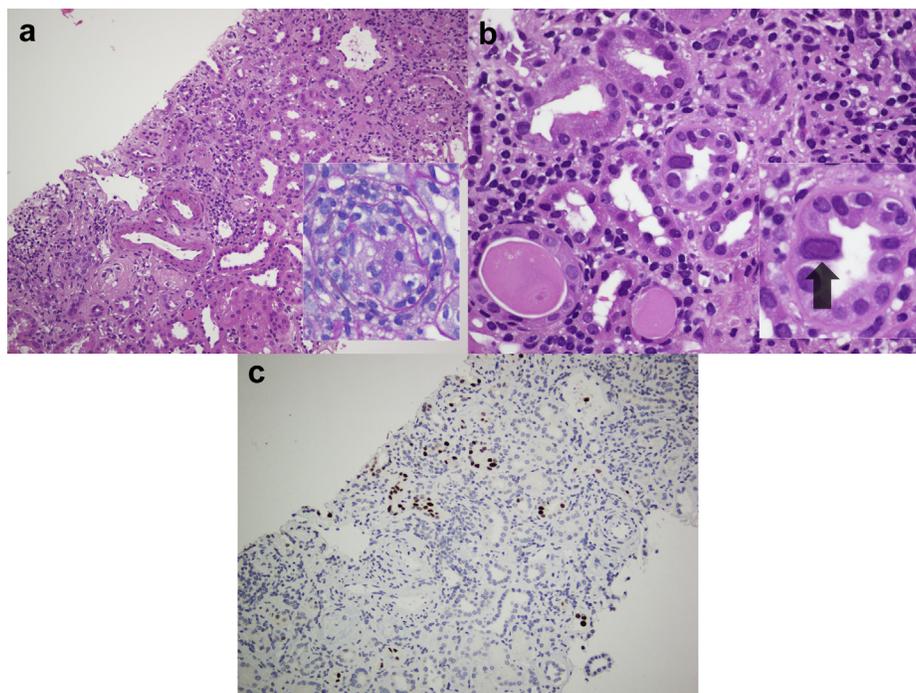


Figure 1. Initial renal biopsy specimen. (a and b) Light microscopy revealed mild to moderate interstitial inflammation and associated with foci of tubulitis (*inset*, a). The interstitial infiltrate was comprised of mononuclear inflammatory cells with a predominance of lymphocytes and interspersed plasma cells. Importantly, multiple interspersed tubular epithelia contained enlarged nuclei with intranuclear viral inclusions (*inset*, b, arrow). (c) Immunoperoxidase staining for SV40 T-antigen highlighted infected tubular epithelial cells. Original magnifications: a and c, ×200; a, *inset* and b, ×400; b, *inset* ×600.

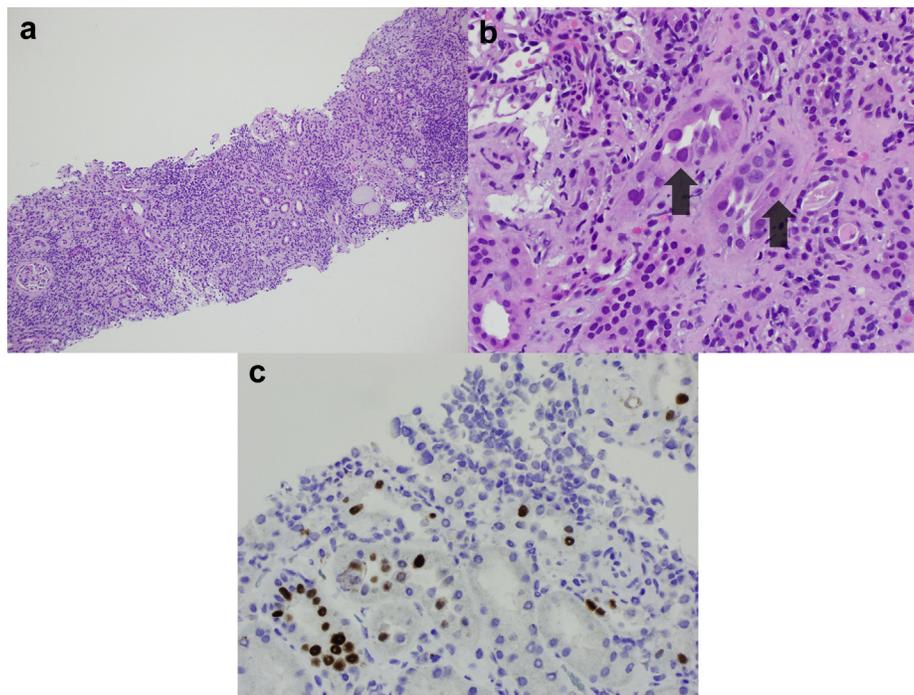


Figure 2. Repeat renal biopsy specimen. (a) The second kidney biopsy specimen revealed more severe interstitial inflammation and tubulitis compared with the first biopsy specimen (Figure 1). (b) A prominent viral cytopathic effect was still present (arrows) and immunoperoxidase staining for SV40 T-antigen again highlighted infected cells. Original magnifications: a, $\times 100$; b and c, $\times 400$.

and presented acutely with biopsy-proven cytomegalovirus colitis, acute kidney injury (serum creatinine of $280 \mu\text{mol/l}$), biopsy-proven BKVN, and 754,976 copies per milliliter of BK virus in his serum.⁶ Zeng *et al.*⁷ described a 59-year-old man who had a liver transplant 7 years earlier who had an increase in creatinine from $90 \mu\text{mol/l}$ to $165 \mu\text{mol/l}$ over 6 months which was initially ascribed to tacrolimus toxicity. When a dose reduction did not lead to improved renal function, a kidney biopsy specimen was obtained and revealed BKVN. The patient was subsequently found to have 2.4×10^6 copies/ml of BK virus in his serum.⁷ Follow-up data on these patients were not provided.

A few studies have investigated the prevalence of BK virus in serum or urine in liver transplant recipients, and its association with renal function, in the absence of a renal biopsy.^{8,9} BK viremia has been variably observed in $\leq 18\%$ of liver transplant recipients, and a comparison of patients with or without detectable serum BK virus showed no significant difference in time after transplantation, renal function, or immunosuppressive agents.^{8,9} While BK viremia was not observed by Salama *et al.*,⁹ BK viruria was detected in 24% of their liver transplant recipients. Loeches *et al.*⁸ noted that almost all detection of BK viremia occurs within the first 3 months after liver transplantation. No differences were observed in serum creatinine levels or estimated glomerular filtration rates among patients with BK viremia, BK viruria, or no detectable BK

virus.^{8,9} However, few patients with persistent viremia did develop renal insufficiency, suggesting that immunosuppressive modulation and even a kidney biopsy procedure may be warranted in rare instances.⁸

Biopsy-proven BKVN in the setting of solid organ transplantation also has been described rarely in recipients of heart, lung, and pancreas allografts, and these descriptions are limited to case reports. In a recent review of the literature by Shah *et al.*,⁵ biopsy-proven BKVN developing in the setting of solid organ transplantation accounted for approximately one third of all cases occurring in the native kidney. With respect to BKVN in the native kidney, review of the literature reveals 3 liver (including the case reported herein), 13 heart, 6 lung, and 1 pancreas transplant recipients. Cases are described in both pediatric and adult populations, men and women, affect differing races, with variable combinations of

Table 2. Teaching points regarding BK virus nephropathy in the native kidney

BK virus nephropathy (BKVN) can occur in the native kidney in immunosuppressed states, most notably hematologic malignancies and nonrenal solid organ transplantation

BKVN has been described in the native kidney in liver, lung, cardiac, and pancreas transplant recipients. In this setting, even with reduction in immunosuppression, BKVN has a poor prognosis with respect to renal functional recovery

Similar to the kidney allograft, BKVN in the native kidney is characterized by findings of tubulointerstitial nephritis with interstitial lymphocytes and plasma cells, accompanied by intranuclear viral inclusion

immunosuppression, and with differing antiviral management strategies. The mean time from solid organ transplantation to the biopsy-proven BKVN is 3.6 years ($n = 23$; the presented case's determination of BKVN was 5 years posttransplantation), mean serum creatinine at the time of diagnosis is 2.86 mg/dl ($n = 22$; was 3.9 mg/dl at the time of the biopsy procedure for the presented case), and the mean serum BK virus level is 3.97×10^7 copies/ml ($n = 18$; was 8.16×10^4 copies/ml at the time of the biopsy procedure for the presented case). When follow-up data were provided, outcomes were poor and varied from persistent renal dysfunction to eventual dialysis dependence. Based on the information available, similar to BKVN in the renal allograft and our described case, BKVN in the nonrenal solid organ transplant recipient has a poor prognosis, with optimal therapy not yet defined.

A unique case of a simultaneous liver and kidney transplant recipient reported by Ujire *et al.*^{S1} provides insight into the pathogenesis BKVN. A biopsy specimen of the kidney allograft revealed BKVN at 6 weeks posttransplant (with serum BK virus 15,000 copies/ml). A subsequent biopsy specimen of a native kidney at 3 months posttransplant (with serum BK virus 22,000 copies/ml) revealed no evidence of BKVN.^{S1} The reported findings suggest that the milieu of the allograft kidney augments the development of BKVN compared with the native kidney.

By light microscopy, BKVN is characterized by varying degrees of interstitial inflammation, tubulitis, tubular atrophy, and interstitial fibrosis, accompanied by characteristic, albeit not entirely specific, intranuclear viral inclusions.⁴ Confirmation of BKVN is attained via immunoperoxidase staining for the SV40 T-antigen or *in situ* hybridization to detect BK virus DNA. The interstitial infiltrate in BKVN is typically composed of lymphocytes, with more T cells than B cells, and a variable but often prominent component of plasma cells.⁴

CONCLUSION

We report the rare occurrence of BKVN in the native kidney in the setting of liver transplantation and provide a brief review of the literature on BKVN in the

native kidney in nonrenal solid organ transplant recipients (Table 2). While this is a rare occurrence, physician awareness of this rare entity is required for accurate diagnosis.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors received consent from the patient discussed herein.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References

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