

A case of polyomavirus-associated nephropathy presenting late after transplantation

Shweta Bansal, M Scott Lucia and Alexander Wiseman*

SUMMARY

Background A 36-year-old white female, who had received a deceased-donor kidney transplant for end-stage renal disease secondary to reflux nephropathy 8 years previously, was referred to a transplant clinic for evaluation following an increase in her serum creatinine level from 123.8 $\mu\text{mol/l}$ to 185.6 $\mu\text{mol/l}$ (1.4 mg/dl to 2.1 mg/dl) over the preceding 9 months. Her immunosuppression regimen included mycophenolate mofetil, ciclosporin and prednisone, with ciclosporin trough levels ranging from 100 ng/ml to 150 ng/ml, as detected by fluorescence polarization immunoassay, over the preceding year. The following possible causes of subacute renal failure were ruled out: post-obstructive nephropathy, altered hemodynamics (hypotension and renal artery stenosis), and toxicity from medications other than calcineurin inhibitors. Potential etiologies such as acute T-cell-mediated rejection, acute and chronic antibody-mediated rejection, polyomavirus-associated nephropathy, and calcineurin inhibitor nephrotoxicity were considered.

Investigations Physical examination, urine and blood analysis, analysis of human leukocyte antigen antibodies by flow cytometry (Luminex®, Luminex Corporation, Austin, TX), ultrasound of the transplanted kidney, polymerase chain reaction assay for the detection of BK virus in the serum, and biopsy of the transplanted kidney with staining for simian virus 40 antigen.

Diagnosis Polyomavirus-associated nephropathy with advanced nephrosclerosis and moderate to marked hyaline arteriolosclerosis.

Management Reduction of immunosuppression by discontinuation of mycophenolate mofetil, dose reduction of ciclosporin, and initiation of leflunomide.

KEYWORDS BK virus nephritis, immunosuppression, renal failure, SV40 staining, transplantation

CME

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Competing interests

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THE CASE

A 36-year-old white female who had received a deceased-donor renal transplant for reflux nephropathy 8 years previously was referred to a transplant clinic with an elevated serum creatinine level. Her initial transplantation course had been unremarkable. She had received induction with the non-depleting interleukin 2 receptor antagonist basiliximab 20 mg intravenously on day 0 and day 4 after transplantation, and an initial immunosuppression regimen of ciclosporin 250 mg orally twice daily, mycophenolate mofetil 1 g orally twice daily, and prednisone 20 mg orally daily, tapered to 5 mg daily by 1 year after transplantation. Ciclosporin treatment was gradually reduced over the next 4 years, to a stable dose of 100 mg in the morning and 125 mg in the evening, to maintain the ciclosporin trough level at below 200 ng/ml. The mycophenolate mofetil dose was reduced to 750 mg twice daily after 7 years because of diarrhea. Throughout the patient's post-transplantation course, her renal function remained stable with no episodes of rejection; her serum creatinine level was in the range 88.4–106.1 $\mu\text{mol/l}$ (1.0–1.2 mg/dl) over the first 6 years. Mild renal insufficiency (serum creatinine level 123.8 $\mu\text{mol/l}$ [1.4 mg/dl]) developed in the seventh year after transplantation, and was attributed to calcineurin inhibitor nephrotoxicity. Over the next 8 months, the patient's serum creatinine level increased to 150.3 $\mu\text{mol/l}$ (1.7 mg/dl), which prompted referral to the transplant clinic. At the time of her presentation to the transplant clinic, within 1 month after referral, the patient's serum creatinine level had increased further to 185.6 $\mu\text{mol/l}$ (2.1 mg/dl).

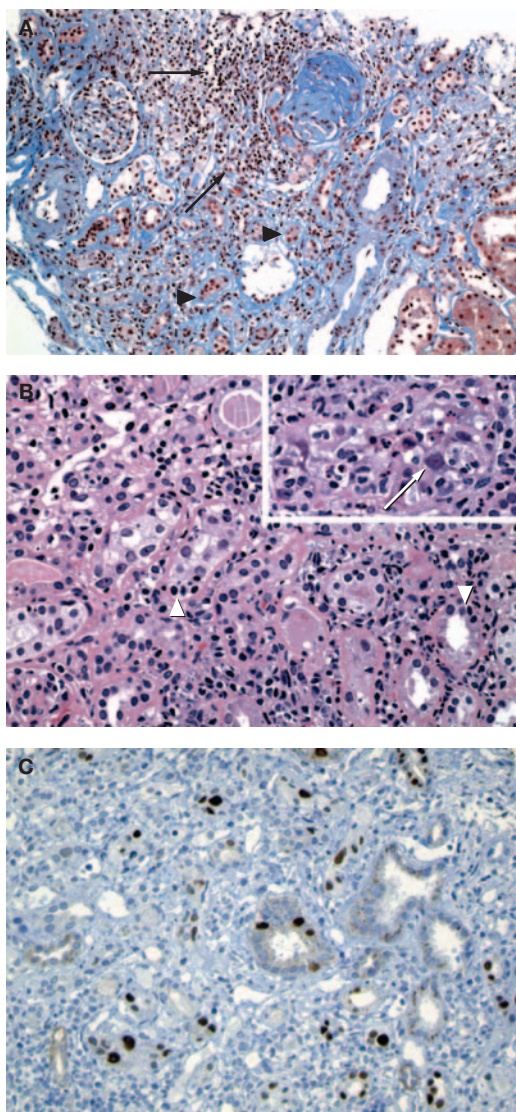


Figure 1 Light microscopy of the patient's kidney biopsy sample. **(A)** Renal biopsy sample showing glomerular sclerosis, interstitial fibrosis, tubular atrophy (arrowheads), and ongoing interstitial inflammation (arrows; trichrome stain, magnification $\times 200$). **(B)** Renal parenchyma with interstitial nephritis and tubulitis (arrowheads; hematoxylin and eosin stain, magnification $\times 400$). Inset showing tubular inflammation with lymphocytes and neutrophils in a tubule with striking polyomavirus nuclear inclusions (arrow; hematoxylin and eosin stain, magnification $\times 600$). **(C)** Immunohistochemistry for simian virus 40 (SV40) antigen showing staining of numerous nuclear viral inclusions (staining for SV40 antigen, magnification $\times 400$).

The patient's ciclosporin trough level had been within the range 100–150 ng/ml over the previous year.

Potential etiologies of subacute renal failure such as hydronephrosis, altered hemodynamics (from hypotension or renal artery stenosis), and toxicity from medications other than calcineurin inhibitors were considered and excluded via the patient's history, physical examination, and ultrasound of the transplanted kidney. Other potential etiologies such as acute T-cell-mediated rejection, acute and chronic antibody-mediated rejection, polyomavirus-associated nephropathy (PVAN), and calcineurin inhibitor nephrotoxicity were also considered. Analysis of human leukocyte antigen (HLA) antibodies by flow cytometry (Luminex®, Luminex Corporation, Austin, TX) showed weakly positive activity for class I HLA antibodies, but negative activity for donor-specific HLA antibodies. Serum BK viral load determined by polymerase chain reaction (PCR) was 127,600 copies/ml. A renal biopsy was performed 1 week after the patient's presentation to the transplant clinic.

On renal biopsy examination, up to 12 glomeruli per section were seen, a third of which were globally sclerotic. The remaining glomeruli showed collapsing lesions, thickening of the Bowman's capsule, and focal visceral epithelial hypertrophy. There was severe interstitial nephritis that involved the majority of the renal cortex. The infiltrates were composed of lymphocytes, histiocytes, plasma cells, and scattered polymorphonuclear leukocytes. Advanced interstitial fibrosis and tubular atrophy were present (Figure 1A). There was focal tubular cuffing and tubulitis, predominantly in atrophic tubules, as well as enlarged, smudged tubular epithelial cell nuclei (nuclear inclusions; Figure 1B). The arterioles showed moderate to severe arteriolosclerosis and no evidence of calcineurin inhibitor toxicity. A diagnosis of PVAN with advanced nephrosclerosis and moderate to marked hyaline arteriolosclerosis was made on the basis of the renal biopsy findings.

Following the renal biopsy, mycophenolate mofetil was discontinued, the ciclosporin dose was reduced to 100 mg twice daily, and oral leflunomide was started at 20 mg daily. Two months later, the patient's leflunomide and ciclosporin trough levels were 156 $\mu\text{g/ml}$ and 142 ng/ml, respectively. Serum BK viral load determined by PCR gradually fell to 30,320 copies/ml at 2 months, 7,034 copies/ml at 6 months, and less

than 600 copies/ml at 7 months after diagnosis. The patient's renal function remained stable throughout this period, with a serum creatinine level of 185.6 $\mu\text{mol/l}$ (2.1 mg/dl; Figure 2). At the time of her most recent follow-up examination, 12 months after diagnosis, the patient remained free of BK viremia with a serum creatinine level of 185.6 $\mu\text{mol/l}$ (2.1 mg/dl).

DISCUSSION OF DIAGNOSIS

PVAN is now recognized as an important cause of allograft failure in renal transplant recipients, requiring active surveillance and aggressive immunosuppression reduction. Two types of polyomaviruses commonly remain latent in the kidney after primary infection early in life—JC virus and BK virus. BK virus nephropathy occurs with a prevalence of 1–10% in renal transplant recipients; JC virus nephropathy is less common (prevalence <1% in renal transplant recipients) and less destructive than BK virus nephropathy.¹ Graft loss occurs within 6 months in about half of the cases of PVAN, a prognosis worse than acute rejection.² The usual onset of PVAN is reported to be between 1.5 months and 53 months after transplantation (median 12 months after transplantation).^{2,3} All nephrologists must be aware of the diagnostic and therapeutic approaches to PVAN, as they often participate in the management of transplant patients at this stage. The present case highlights the fact that PVAN can occur late after transplantation (>80 months in this patient) and must be considered in any renal transplant recipient who experiences a change in renal function.

In the immunocompetent host, primary polyomavirus infections occur early in life and are usually asymptomatic. Approximately 50% of healthy native kidneys harbor latent BK virus.² In the presence of immunosuppression, BK virus replication is unmasked and progresses to interstitial nephritis without clinical signs or symptoms, except for diminished renal function over a period of weeks to months. Occasionally, patients with polyomavirus present with a ureteral stricture or hemorrhagic cystitis. Histological findings on renal biopsy are the gold standard for diagnosis, with typical findings of focal interstitial mononuclear inflammatory cell infiltrates, the presence of plasma cells, necrotic tubular epithelium, and the presence of homogeneous intranuclear inclusion bodies.³ Immunohistochemistry staining for SV40 antigen is used to confirm the presence of

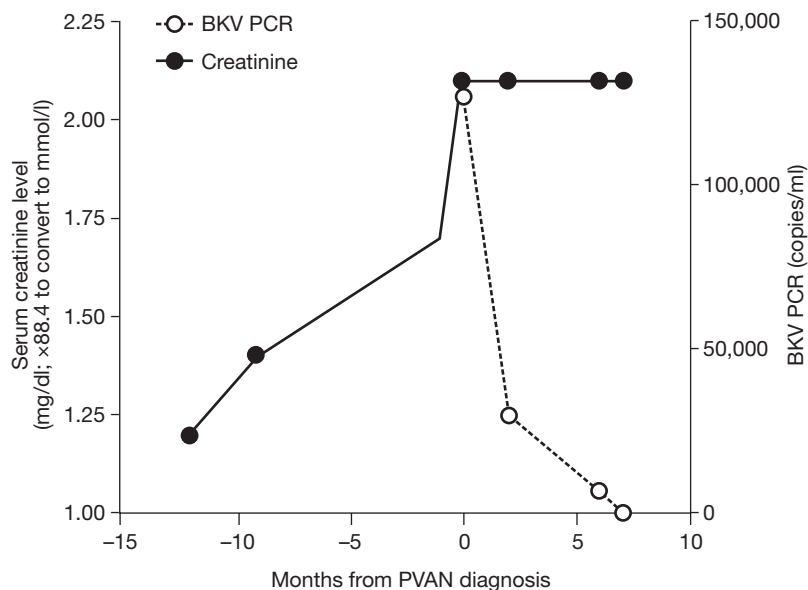


Figure 2 Trend in the patient's serum creatinine level before diagnosis and following treatment of the BK virus nephropathy, together with serial serum BK viral load determined by polymerase chain reaction. Abbreviations: BKV, BK virus; PCR, polymerase chain reaction; PVAN, polyomavirus-associated nephropathy.

polyomavirus in renal tissue. Additional methods for the detection of polyomavirus include *in situ* hybridization to identify polyomavirus genomes and electron microscopy to demonstrate the presence of virions of compatible morphology (i.e. nonenveloped, icosahedral particles, 40 nm in diameter).² In biopsies for renal dysfunction, distinct histological patterns of PVAN can be defined on the basis of the degree of viral cytopathic changes, tubulitis, tubular atrophy, and interstitial fibrosis, and these patterns can be predictive of outcome.³ In the patient presented here, the severe tubulointerstitial inflammation and extensive tubular atrophy on index biopsy would be predicted to result in a graft loss rate of more than 75% within 2 years.

A number of noninvasive tests for predicting which patients are at risk for PVAN development following kidney transplantation have been evaluated. Urinalysis might reveal decoy cells, which are suggestive of BK virus replication in the renourinary tract; decoy cells are not, however, a specific marker of PVAN (positive predictive value 20%).⁴ BK viremia detected by quantitative PCR is present in 30–40% of renal transplant recipients, with viral quantities in urine often 100-fold greater than in blood, but, like urinalysis for decoy cells, testing for urinary BK

virus DNA has a high negative predictive value but a poor positive predictive value for the diagnosis of PVAN.⁵ The most accurate screening test for PVAN is the assessment of polyomavirus viremia by quantitative PCR. BK virus viremia is seen in 10–40% of renal transplant recipients and in nearly 100% of PVAN cases, and has a positive predictive value for PVAN of 60%.⁶

Given the generally poor outcomes when PVAN is diagnosed in the setting of renal dysfunction, the transplant community has accepted screening for BK virus replication as a standard approach with which to identify patients at a higher risk of developing PVAN and to permit earlier interventions. Several screening strategies have been proposed to assist in the detection and treatment of PVAN, with an interdisciplinary recommendation to screen for viruria every 3 months during the first 2 years after renal transplantation, then annually until the fifth year after transplantation or until an event of renal allograft dysfunction.⁷ A cost-effectiveness analysis confirms the utility of PCR-based screening in transplant populations that have a PVAN prevalence of more than 2.1%.⁸ If high levels of viruria ($>10^7$ viral copies/ml)⁹ or viremia ($>10^4$ viral copies/ml) persist for more than 3 weeks, a diagnosis of presumptive PVAN can be made and immunosuppression should be reduced. In a recent large prospective study, pre-emptive reduction of immunosuppression (via elimination of antimetabolites) resulted in the clearance of BK virus, with no acute rejection or PVAN after a mean of 32 ± 6 months.⁶ If BK viruria and viremia is associated with renal dysfunction, a biopsy should be performed to quantify the presence and degree of injury and to rule out rejection. At least two cores should be obtained for polyomavirus-specific histological analysis, since biopsy findings of PVAN can be patchy and difficult to distinguish from acute rejection.³

TREATMENT AND MANAGEMENT

Management of PVAN is directed at eliminating the virus, avoiding acute rejection, and preserving renal function. Interventions include the reduction of immunosuppression, with or without provision of antiviral therapy. Methods for reducing immunosuppression vary greatly, but can be generally categorized as follows: reduction in the dose of two agents; discontinuation of one agent; or transition from one agent to another. No randomized trial has compared

reduction strategies, although in a retrospective, nonrandomized trial, Wadei *et al.*¹⁰ found no difference in graft outcomes when patients who were switched from a tacrolimus-based regimen to a low-dose ciclosporin-based regimen were compared to those who underwent tacrolimus dose reduction. Various case series have suggested additional interventions to be of benefit in PVAN. Leflunomide, an immunosuppressive agent commonly used in rheumatoid arthritis, has antiviral activity against polyomavirus *in vitro* and in animals. One case series reported a marked reduction in viremia and viruria with stabilization of renal function in patients who tolerated leflunomide (dosed to a target trough level of 50–100 µg/ml),¹¹ but these outcomes have not been universally noted. Cidofovir, an antiviral agent approved for the treatment of cytomegalovirus, has been reported to be of benefit in selected patients who did not respond to a reduction in immunosuppression alone,¹² but it has modest mechanistic effect against BK virus *in vitro*,¹³ and its clinical utility is uncertain because of its potential to cause nephrotoxic effects. In the setting of PVAN, the dose of cidofovir is 10–20% of that used for the treatment of cytomegalovirus. Similar to cidofovir, fluoroquinolones such as ciprofloxacin have a modest *in vitro* anti-BK-virus effect and may have a role in polyomavirus suppression.¹⁴ Finally, intravenous immunoglobulin has been proposed to be both a treatment for PVAN and a preventative strategy to avoid acute rejection during immunosuppression reduction in renal transplant recipients.¹⁵ In the patient presented here, aggressive immunosuppression reduction was combined with the addition of leflunomide, and plasma viral load was monitored to document clearance of viremia. At 7 months, BK viremia was undetectable and the patient had stable renal function. An improved outcome, with renal function recovery to a greater extent than was achieved in this case, might have been achieved if polyomavirus screening had been performed in the months before biopsy, and if viremia could have been cleared more rapidly, potentially via loading doses of leflunomide, addition of cidofovir, or further reduction in ciclosporin dose. Following the initial management of PVAN, it is imperative that a patient's glomerular filtration rate and BK viremia are monitored serially, and that a repeat biopsy is performed in the event of deterioration of either parameter. Retransplantation remains an option in cases of graft loss.¹⁶

CONCLUSIONS

Although typically diagnosed within 12 months of renal transplantation, PVAN can present up to 80 months after transplantation, as demonstrated by this case report. The key steps for the successful management of PVAN include an increased awareness of the condition among physicians, use of polyomavirus screening strategies, the ability to recognize viral inclusion bodies in biopsy samples, and the provision of appropriate immunosuppressive therapy reduction with judicious use of antiviral agents.

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Competing interests

The authors declared no competing interests.