Native BK virus nephropathy in lung transplant: a case report and literature review

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ABSTRACT

Classically described in renal allografts, BK virus nephropathy is increasingly recognized in native kidneys of other non-renal solid organ transplants. We discuss a 68-year-old woman with a history of bilateral lung transplant referred for worsening renal function, confirmed to have BK virus nephropathy by biopsy with a serum BK virus polymerase chain reaction of over 59 million copies/mL. She was managed with a reduction in immunosuppression and intravenous cidofovir with no improvement in her clinical parameters. The seven prior reported cases of polyoma virus nephropathy in lung transplant recipients are reviewed, and the challenges of screening and management are discussed.

Keywords: BK nephropathy, lung transplant, polyomavirus

BACKGROUND

The BK virus is a human polyoma virus and shares similar features to the simian virus 40 (SV40) and JC virus. Infection is endemic, and 80–90% of adults are seropositive. After infection, the virus remains dormant within the genitourinary epithelium, and up to 10% of healthy adults can have asymptomatic viruria [1, 2]. In immunocompromised individuals, BK virus infection can lead to progressive renal dysfunction and is well described in kidney transplantation. Up to half of renal allograft recipients with a high urine load will progress to viremia, and 1–10% of viremic patients develop BK virus nephropathy [1]. There is no ‘cut off’ level of viremia, which predicts nephropathy. However, in non-renal solid organ transplants (NRSOTs) with BK virus nephropathy, the mean serum BK viral load of $5.2 \times 10^{10}$ copies/mL and urine viral load was greater than $7 \times 10^{10}$ copies/mL [3].

There is growing awareness that BK virus nephropathy can occur in native kidneys of patients with other NRSOTs [3]. In lung transplant patients, 66% of patients will have evidence of polyoma detected at least once in the serum or urine, but the incidence of BK virus nephropathy is very low [4].

CASE PRESENTATION

We describe a 68-year-old woman with a history of idiopathic pulmonary fibrosis who underwent bilateral lung transplant 2 years prior to nephrology evaluation. After induction with basiliximab and methylprednisolone, she was maintained on...
tacrolimus (goal trough 8–12 ng/dL), mycophenolate mofetil (MMF), prednisone and monthly intravenous immunoglobulin (IVIG). In her first-year post-transplant, her creatinine increased from a baseline of 0.6 mg/dL to 1.6 mg/dL. This was attributed to calcineurin inhibitor toxicity, and her tacrolimus and MMF were changed to sirolimus. However, her creatinine continued to increase. Work-up revealed a random urine protein/creatinine ratio 696 mg/g, trace blood on urinalysis and a serum BK virus polymerase chain reaction (PCR) of 28 381 300 copies/mL. Kidney biopsy demonstrated tubular epithelial cells with enlarged nuclei and intranuclear inclusions staining positive for SV40 confirming BK nephropathy (Figure 1).

Our patient was already on the lowest immunosuppression afforded by her lung transplant team, so she was offered a trial of intravenous (IV) cidofovir. At the start of therapy, her creatinine was 2.2 mg/dL with a serum BK virus PCR of 59 225 688 copies/mL, and she was started on IV cidofovir at a dose of 0.5 mg/kg/day for 2 days. The dose was then increased to IV cidofovir 1 mg/kg/day, but unfortunately, her creatinine worsened, and treatment was discontinued after days. Two weeks after cessation of cidofovir, her creatinine was 4.67 mg/dL [estimated glomerular filtration rate (eGFR) 9 mL/min] and serum BK virus PCR remained elevated at 47 666 091 copies/mL. Four months later, she started hemodialysis for uremic symptoms and hypervolemia.

**DISCUSSION AND CONCLUSIONS**

Native BK virus nephropathy is more common than previously recognized in NRSOTs, especially in lung transplant recipients; however, it is still rare. A retrospective case series of 30 lung transplant patients over 5 years revealed only one case of BK virus nephropathy, and this is the eighth published case of polyomavirus nephropathy in lung transplant recipients (Table 1) [4–11]. The low incidence of BK nephropathy in NSROT compared with renal allografts may be because of a ‘second hit hypothesis’. Irritation of the genitourinary epithelium in kidney transplantation may increase the risk of viremia and subsequent nephropathy [3, 13]. Despite being at particular risk for severe BK virus nephropathy given the intensive immunotherapy and high incidence of hypogammaglobulinemia, at this time, experts currently do not recommend routine screening the serum for BK viral loads in lung transplantation [1]. But, a delay in diagnosis can lead to very high serum levels and increase the risk for renal dysfunction [1, 3, 14]. Every 10-fold increase in serum BK viral load was associated with a 0.8 mL/min decline in creatinine clearance in lung transplant recipients [14].

Reduction of immunosuppression is the mainstay of therapy, but particularly in lung transplantation, this may not be feasible especially given that chronic rejection within the first-year post-transplant is the leading cause of lung allograft dysfunction [15]. Therapies such as cidofovir, leflunomide and IVIG are available but not routinely recommended because evidence is equivocal [3, 9, 16]. Low-dose cidofovir may be effective, but given its nephrotoxicity, it should be used with caution [17]. Leflunomide may reduce levels of BK viremia, but its use was associated with increased rates of renal allograft rejection and allograft function [18]. Studies with IVIG are small and do not consistently show positive effect [19, 20]. Brincidofovir, a produg of cidofovir, is less nephrotoxic than cidofovir and led to improved renal function in pediatric kidney transplant patients, but, it is too early to make solid conclusions on this drug [21, 22].

Now that our patient is on dialysis, there is discussion about her eligibility for kidney transplantation; however, there are no clear guidelines or guidelines about therapies to lower BK viremia in order to allow candidacy for kidney transplantation. Consensus is that viral load should be undetectable to reduce recurrence post-renal transplant [23]. We highlight a concern in delayed diagnosis and advocate routine assessment for BK viremia in NSROT recipients and timely renal biopsy if there is concern about reduction of immunosuppression or uncertainty in the cause of renal dysfunction.

**PATIENT CONSENT**

Written consent for publication obtained from the patient.

**CONFLICT OF INTEREST STATEMENT**

None of the authors has any pertinent conflicts of interests. A.A.Y. is a paid consultant for Natera Renasight.
Table 1. Published case reports of polyoma virus nephropathy in lung transplant [5–11]

| Author, publication year | Age at report (years) | Gender | Primary lung disease | Time post-transplant | IS regimen at the time of biopsy | Cr at time of transplant | Cr at time of biopsy | Peak serum BK viral load (copies/mL) | Peak urine BK viral load (copies/mL) | Therapy | Outcome |
|--------------------------|-----------------------|--------|----------------------|----------------------|---------------------------------|------------------------|---------------------|-----------------------------------|----------------------------------|----------|---------|
| Milstone, 2004a [5]      | 32                    | Male   | Cystic fibrosis      | 3 years             | Cyclosporine, azathioprine, prednisone | 1.7–2.1 mg/dL          | ND                  | ND                               | ND                               | Reduction of IS, cidofovir pre-kidney transplant | Continued on hemodialysis, then underwent living related renal transplant (urine negative for BK virus pre-transplant) |
| Schwarz, 2005 [6]        | 40                    | Male   | Pulmonary fibrosis and pulmonary hypertension | 15 months Tacrolimus, MMF, steroids | ND                              | 89 μmol/L             | 380 μmol/L          | 1 600 000                         | ND                               | No change in IS, cidofovir, leflunomide | Serum BK viral load reduced, progressive renal decline, initiated on dialysis |
| Egli, 2010 [7]           | 67                    | Female | Centrilobular emphysema | 67 months Tacrolimus, sirolimus, prednisone | ND                              | 51 μmol/L             | 220 μmol/L          | 48 500 000 000                   | >1 000 000 000                   | Reduction of IS, cidofovir | Cleared viremia, improved creatinine |
| Dufek, 2013 [8]          | 8                     | Male   | Bronchiolitis obliterans | 2 years Cyclosporine, MMF, prednisone | ND                              | ND                    | ND                  | 140 000 000                        | >10 000 000 000                  | Reduction of IS, cidofovir | No change in serum BK viral load, progressive renal decline, initiated on dialysis, ductal Bellini carcinoma of native kidney |
| Vigil, 2016 [9]          | 70                    | Male   | Pulmonary fibrosis (usual interstitial pneumonitis) | 2 years Tacrolimus, MMF, prednisone | ND                              | ND                    | ND                  | 10 000 000                         | ND                               | Reduction of IS, leflunomide, IVIG | Serum BK viral load reduced, stable renal function |
| Kuppachi, 2017 [10]      | 63                    | Male   | COPD                | 2 years Tacrolimus, azathioprine, prednisone | ND                              | 0.7–0.9 mg/dL         | ND                  | 87 900                            | ND                               | Reduction of IS, leflunomide, ciprofloxacin | Serum BK viral load reduced, stable renal function |
| Crowhurst, 2020 [11]     | 58                    | Male   | COPD                | 9 months Tacrolimus, MMF, prednisone | ND                              | 0.6 mg/dL             | ND                  | 358 copies/mL                     | >10 million copies/mL            | Reduction of IS, IVIG | Serum BK viral load increased, progressive renal decline, initiated on dialysis |
| Our case                | 68                    | Female | Pulmonary fibrosis  | 13 months Tacrolimus, sirolimus, prednisone, IVIG | ND                              | 1.9 mg/dL             | ND                  | 59 225 688 copies/mL             | ND                               | No change in IS, cidofovir | Serum BK viral load reduced, progressive renal decline, initiated on dialysis |

*aThis case is often mislabeled as a case of BK virus nephropathy; however, authors conclude this is a case of SV40 nephropathy confirmed by DNA sequence analysis and is patient 7 in the article by Sharma et al. [12]. COPD, chronic obstructive pulmonary disease; Cr, creatinine; IS, immunosuppression; ND, not described.
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REFERENCES

1. Barten MJ, Zuckermann A. BK virus: a cause for concern in thoracic transplantation? Ann Transplant 2018; 23: 310–321
2. Davies SI, Muranski P. T cell therapies for human polyomavirus diseases. Cytotherapu 2017; 19: 1302–1316
3. Kuppachi S, Kaur D, Holanda DG et al. BK polyoma virus infection and renal disease in non-renal solid organ transplantation. Clin Kidney J 2016; 9: 310–318
4. Schwarz A, Haller H, Schmitt R et al. Biopsy-diagnosed renal disease in patients after transplantation of other organs and tissues: renal disease after other transplants. Am J Transplant 2010; 10: 2017–2025
5. Milstone A, Vilchez RA, Geiger X et al. Polyomavirus simian virus 40 infection associated with nephropathy in a lung transplant recipient. Transplantation 2004; 77: 1019–1024
6. Schwarz A, Mengel M, Haller H et al. Polyoma virus nephropathy in native kidneys after lung transplantation. Am J Transplant 2005; 5: 2582–2585
7. Egli A, Helmersen DS, Taub K et al. Renal failure five years after lung transplantation due to polyomavirus BK-associated nephropathy: BKV nephropathy in native kidneys after lung transplantation. Am J Transplant 2010; 10: 2324–2330
8. Dufek S, Haitel A, Müller-Sacherer T et al. Duct Bellini carcinoma in association with BK virus nephropathy after lung transplantation. J Heart Lung Transplant 2013; 32: 378–379
9. Vigil D, Konstantinov NK, Barry M et al. BK nephropathy in the native kidneys of patients with organ transplants: clinical spectrum of BK infection. World J Transplant 2016; 6: 472.
10. Kuppachi S, Holanda D, Eberlein M et al. An unexpected surge in plasma BKPyV viral load heralds the development of BKPyV-associated metastatic bladder cancer in a lung transplant recipient with BKPyV nephropathy. Am J Transplant 2017; 17 813–818
11. Crowhurst T, Nolan J, Faul R et al. BK virus-associated nephropathy in a lung transplant patient: case report and literature review. BMC Infect Dis 2020; 20: 600.
12. Sharma SG, Nickeleit V, Hertlitz LC et al. BK polyoma virus nephropathy in the native kidney. Nephrol Dial Transplant 2013; 28: 620–631.
13. Wingate JT, Brandenberger J, Weiss A et al. Ureteral stent duration and the risk of BK polyomavirus viremia or bacteriuria after kidney transplantation. Transpl Infect Dis 2017; 19: e12644.
14. Thomas LD, Milstone AP, Vilchez RA et al. Polyomavirus infection and its impact on renal function and long-term outcomes after lung transplantation. Transplantation 2009; 88: 360–366
15. Witt CA, Puri V, Gelman AE et al. Lung transplant immunosuppression – time for a new approach? Expert Rev Clin Immunol 2014; 10: 1419–1421
16. Johnston O, Jaswal D, Gill JS et al. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation 2010; 89: 1057–1070
17. Kuypers DRJ, Vandooren AK, Lerut E et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant 2005; 5: 1997–2004
18. Guasch A, Roy-Chaudhury P, Woodle ES et al. Assessment of efficacy and safety of FK778 in comparison with standard care in renal transplant recipients with untreated BK nephropathy. Transplantation 2010; 90: 891–897
19. Sener A, House AA, Jevnikar AM et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. Transplantation 2006; 81: 117–120
20. Wadei HM, Rule AD, Lewin M et al. Kidney transplant function and histological clearance of virus following diagnosis of polyomavirus-associated nephropathy (PVAN): outcome of polyomavirus nephropathy. Am J Transplant 2006; 6: 1025–1032
21. Lanier R, Trost L, Tippin T et al. Development of CMX001 for the treatment of poxvirus infections. Viruses 2010; 2: 2740–2762
22. Reisman L, Habib S, McClure GB et al. Treatment of BK virus-associated nephropathy with CMX001 after kidney transplantation in a young child. Pediatr Transplant 2014; 18: E227–E231
23. Sawinski D, Trofe-Clark J. BK virus nephropathy. Clin J Am Soc Nephrol 2018; 13: 1893–1896