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Exceptional Case

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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 × 10^{10} copies/mL and urine viral load was greater than 7 × 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

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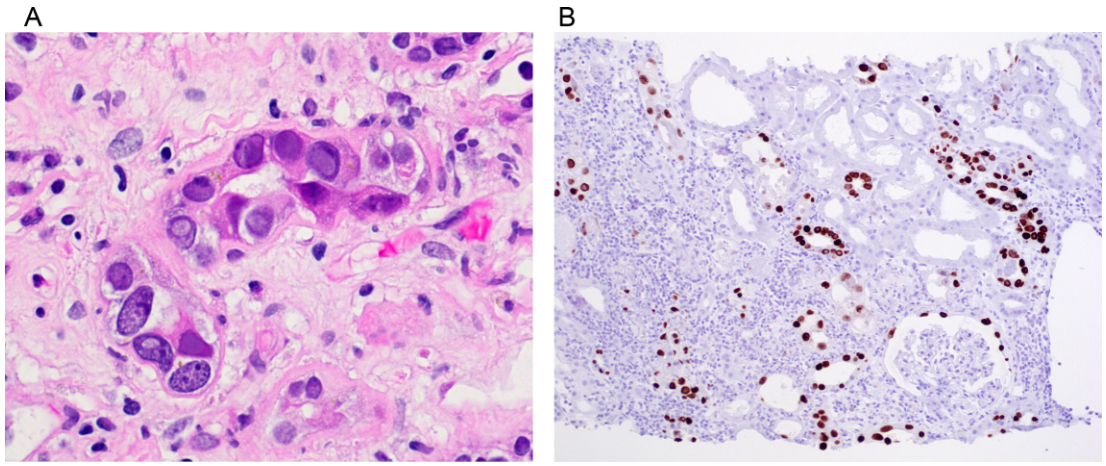

FIGURE 1: Kidney biopsy. **(A)** Hematoxylin and eosin staining showing tubular epithelial cells with enlarged nuclei and intranuclear inclusions and 40–50% interstitial fibrosis. **(B)** SV40 staining positive in the nuclei of tubular epithelial cells.

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 prodrug 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	Milstone, 2004[a] [5]	Schwarz, 2005 [6]	Egli, 2010 [7]	Dufek, 2013 [8]	Vigil, 2016 [9]	Kuppachi, 2017 [10]	Crowhurst, 2020 [11]	Our case
Age at report (years)	32	40	67	8	70	63	58	68
Gender	Male	Male	Female	Male	Male	Male	Male	Female
Primary lung disease	Cystic fibrosis	Pulmonary fibrosis and pulmonary hypertension	Centrilobular emphysema	Bronchiolitis obliterans	Pulmonary fibrosis (usual interstitial pneumonitis)	COPD	COPD	Pulmonary fibrosis
Time post-transplant	3 years	15 months	67 months	2 years	2 years	2 years	9 months	13 months
IS regimen at the time of biopsy	Cyclosporine, azathioprine, prednisone	Tacrolimus, MMF, steroids	Tacrolimus, sirolimus, prednisone	Cyclosporine, MMF, prednisone	Tacrolimus, MMF, prednisone	Tacrolimus, azathioprine, prednisone	Tacrolimus, MMF, prednisolone	Tacrolimus, sirolimus, prednisone, IVIG
Cr at time of transplant	1.7–2.1 mg/dL	89 µmol/L	51 µmol/L	ND	1.0–1.1 mg/dL	0.7–0.9 mg/dL	ND (eGFR of 85 mL/min)	0.6 mg/dL
Cr at time of biopsy	ND (on hemodialysis)	380 µmol/L	220 µmol/L	ND	3.0 mg/dL	3.0–3.4 mg/dL	ND (eGFR of 35 mL/min)	1.9 mg/dL
Peak serum BK viral load (copies/mL)	ND	1 600 000	48 500 000 000	140 000 000	10 000 000	87 900	358 copies/mL	59 225 688 copies/mL
Peak urine BK viral load (copies/mL)	ND	>1 000 000	98 500 000 000	>10 000 000 000	ND	ND	>10 million copies/mL	ND
Therapy	Reduction of IS, cidofovir pre-kidney transplant	No change in IS, cidofovir, leflunomide	Reduction of IS, leflunomide	Reduction of IS, cidofovir	Reduction of IS, leflunomide, IVIG	Reduction of IS, leflunomide, ciprofloxacin	Reduction of IS, IVIG	No change in IS, cidofovir
Outcome	Continued on hemodialysis, then underwent living related renal transplant (urine negative for BK virus pre-transplant)	Serum BK viral load reduced, progressive renal decline, initiated on dialysis	Cleared viremia, improved creatinine	No change in serum BK viral load, progressive renal decline, initiated on dialysis, ductal Bellini carcinoma of native kidney	Serum BK viral load reduced, stable renal function	Serum BK viral load reduced, stable renal function	Serum BK viral load increased, progressive renal decline, initiated on dialysis	Serum BK viral load reduced, progressive renal decline, initiated on dialysis

[a]This 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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