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Case Report

BK virus-associated viruria and viremia in a patient with lymphangioleiomyomatosis after lung re-transplantation: A case report and review of the literature on BK virus infection post-lung transplantation☆

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ABSTRACT

The BK virus (BKV) is a member of the polyomaviridae family of DNA viruses. BKV reactivates under a highly immunosuppressed state and causes renal dysfunction. In renal transplant patients, BKV infection leads to tubular impairment and loss of transplanted kidney grafts. However, few studies have reported on the relationship between BKV and lung transplantation. Adjustment of the dosage of immunosuppressants is needed in some cases, but the treatment method has not been established.

Here, we report a case of BKV-associated viruria and viremia in a patient with lymphangioleiomyomatosis (LAM) after lung re-transplantation. A 44-year-old female refractory LAM patient who had undergone lung re-transplantation 3 months earlier was diagnosed with BKV-associated viruria and viremia. Urine cytology indicated decoy cells and the urine and serum polymerase chain reaction test was positive for BKV. As scheduled after re-transplantation surgery, immunosuppressive drugs were progressively reduced. This patient was considered to have experienced spontaneous BKV-associated viremia and viruria. Review of the literature suggested that 17%–42% of BKV-associated viruria cases have been reported after lung transplantation, but cases of BKV-associated nephropathy are rarely reported. Based on the present case, doctors involved in lung transplantation should monitor patients for BKV infection. Decoy cell monitoring by urine cytology is a useful screening method in the follow-up observation after lung transplantation. Early-stage interventions may prevent BKV-associated nephropathy even in patients who have developed BKV viremia, and sirolimus can be administered to patients with histories of BKV infection if they are carefully monitored.

1. Introduction

The BK virus (BKV) is a member of the polyomaviridae family of DNA viruses. It was first isolated from the urine of a renal transplant patient with ureteral stenosis in 1971 [1]. After primary infection during early childhood, the latency of the virus in the urogenital tract appears to remain asymptomatic. The rate of seroprevalence is 60–80% in the general adult population [2–4].

Renal dysfunction and renal transplant graft loss due to BKV reactivation after renal transplantation are clinical problems. Approximately 1–10% of kidney transplant recipients develop BKV

Abbreviations: AZA, azathioprine; BKV, BK virus; CyA, Cyclophosphamide; LAM, lymphangioleiomyomatosis; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; PSL, prednisolone; TAC, tacrolimus.

☆ All authors meet the ICMJE authorship criteria.

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nephropathy [4,5]. Typical cases of BKV infection first lead to viruria and progress to viremia, followed by nephropathy [6,7]. BKV infected cells appearing in the urine, termed 'decoy cells,' show a specific morphology and they are an indicator of polyoma virus reactivation [5,7]. It is specifically diagnosed by detection of BKV in the urine or serum by polymerase chain reaction (PCR).

Lung transplantation may be required in some cases due to the progression of lymphangioleiomyomatosis (LAM). After lung transplantation, immunosuppressive treatment is necessary, which may increase the risk of immunosuppression associated infection. Studies on BKV and lung transplantation are scarce. Here, we present the case of a patient diagnosed with BKV-associated viruria and viremia after lung re-transplantation due to LAM and review the associated literature.

2. Case report

A 44-year-old woman with LAM underwent lung transplantation twice (Fig. 1). In the year XX-16, she was diagnosed with sporadic LAM and in the year XX-14, she underwent a bilateral living-donor lobar lung transplantation. Since then, she had been receiving immunosuppressive treatment. In the year.

XX-13, she was diagnosed with obstructive bronchiolitis by spirometry due to progressive mixed ventilatory disorder. In the year XX-9, chest computed tomography showed recurrence of LAM that was clinically diagnosed due to bilateral pulmonary cystification. The respiratory condition gradually worsened and, in the year XX, lung re-transplantation was performed. Three months after re-transplantation, on the day after she was discharged, she visited our hospital. Decoy cells were observed in urine cytology screening (Fig. 2), and BKV infection was suspected. At the onset, she was on immunosuppressant treatment, prednisolone (14 mg/day), tacrolimus (TAC) (2.6 mg/day), and mycophenolate mofetil (250 mg/day). Other medications included sulfamethoxazole (400 mg/twice/week), trimethoprim (80 mg/twice/week), rabeprazole (10 mg/day), itraconazole (100 mg/day), valganciclovir (450 mg/day). Administration of these medications continued without dosage changes. At the same time, a rapid and abnormal increase in TAC trough value was observed. The patient was hospitalized for strict monitoring of renal function and normalization of TAC values. During the course of hospitalization, although the patients' condition was asymptomatic, adjustment of TAC trough concentration was difficult. More than 2 weeks were required to achieve the target trough value of 8–10 mg/dl. The immunosuppressant dosage was reduced to the maintenance dosage as planned after re-transplantation surgery. Urine decoy cells diminished, and virus titer in the serum below the measurement limit was achieved by the 5th month from onset (Table 1). Six months after surgery, sirolimus administration was resumed as a treatment for recurrent LAM. Since then, no decoy cells in urine cytology were observed, and the general condition was stable 2 years after surgery (Fig. 1).

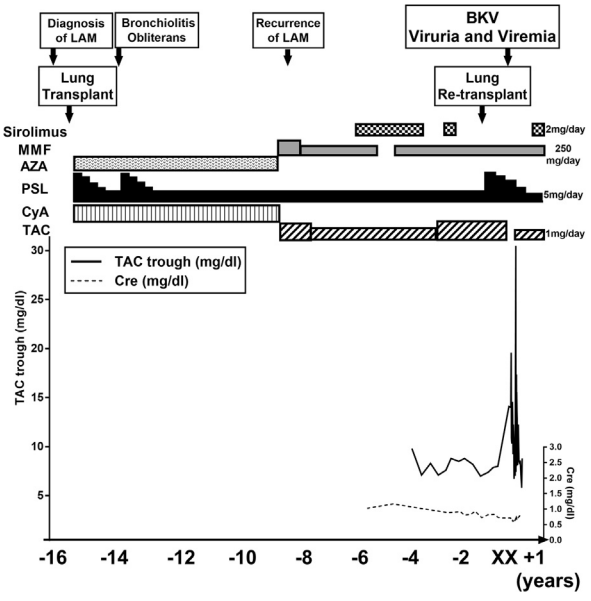

Fig. 1. Clinical course, tacrolimus trough, and serum creatinine level. LAM, lymphangioleiomyomatosis; BKV, BK virus; MMF, mycophenolate mofetil; CyA, Cyclophosphamide; PSL, prednisolone; TAC, tacrolimus; Cre, creatinine.

3. Discussion

Since BKV infection is commonly associated with graft loss in kidney transplants, testing for BKV infection is recommended in case of renal transplants [8]. However, studies exploring the mechanism of BKV infection in non-renal transplants are rare [8,9]. To the best of our knowledge, this case is the first to report BKV-associated viruria and viremia after lung re-transplantation. We believe that we successfully avoided the development of BKV-associated nephropathy in this case. We also demonstrated successful add-on sirolimus treatment to a LAM patient with history of BKV infection.

Clinical studies and case reports on BKV infection after lung transplantation [10–15] have been summarized in Tables 2 and 3. Based on the studies reviewed, the incidence of BKV infection in lung transplantation cases is 17.4%–42.2%. Two cases with BK viremia after lung transplantation showed BKV-associated nephropathy [10,15]. Renal biopsy was not performed in the present case. However, PCR for BKV in the serum was negative in a short period of time, urine decoy cells disappeared, and serum creatinine and urine test results were also within the normal range. Thus, we suspect that this is the first case of BK viremia that did not result in BKV nephropathy after lung transplantation. We consider three reasons why the case did not progress to BKV-associated nephropathy. First, the viral blood concentration was lower compared than those in past reports (Table 3). Second, we suspected BKV infection in screening test during the asymptomatic phase before there was elevation of serum creatinine. In the present case, BKV infection was suspected because of the appearance of decoy cells in urine cytology screening. At the same time, an abnormal increase of TAC trough value was observed (Fig. 1). It has been reported that TAC trough elevation is associated with suppression of BKV specific T cells [16]. Drugs that could have altered the TAC concentration were not modified, and the TAC levels were within acceptable ranges one week before abnormal TAC elevation. This timeframe is the transition period from hospitalization to the outpatient treatment, during which improvement in activity of daily living or changes in fluid and food intake can lead to changes in the amount of patient's body fluid. As a consequence, the blood levels of TAC could have been relatively increased. The third reason is that the re-hospitalization treatment aimed at strict monitoring and adjustment of TAC concentration and renal function may have shortened the duration of viremia, which was shorter than that reported in previous reports (Table 3). BKV-associated viremia lasting for 14 months has been reported [15], but in this case, the viremia lasted for only 5 months (Table 1, Table 3).

Studies have reported the use of cidofovir as a specific treatment for BKV [10,17]. Since it is not available in Japan, we could not use it in clinical practice. Several studies have reported the effectiveness of ciprofloxacin as an alternative treatment for BKV-associated hemorrhagic cystitis [18], and the neutralizing action of γ-globulin [19]. However, a consensus on BKV treatment has not been

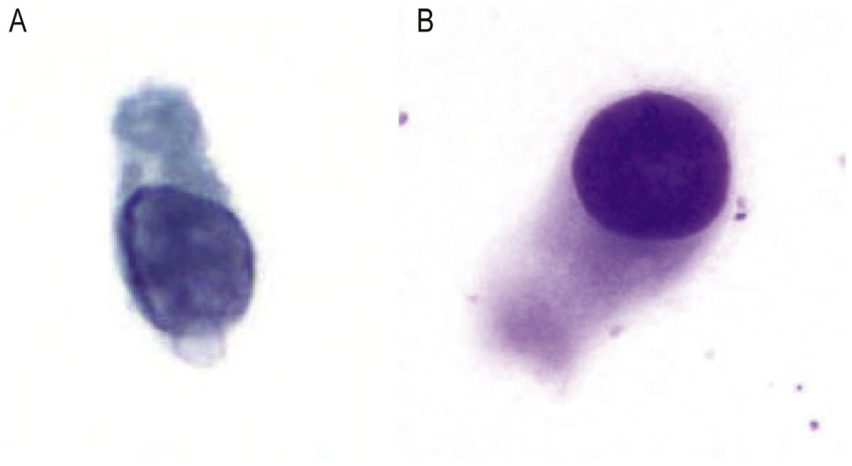

Fig. 2. Decoy cells in urine cytology show enlarged nuclei with ground glass appearance (A: Papanicolaou staining, B: Giemsa staining).

Table 1
BKV viral load in urine and serum.

Time from diagnosis of BKV infection (days)	0	13	54	75	152
BKV viral load in urine (copies/mL)	1×10^9			4×10^5	
BKV viral load in serum (copies/mL)		8×10^2	4×10^2		Below the detection limit

Detection limit: 2×10^2 copies/ml.
BKV: BK virus.

Table 2
Summary of clinical studies including patients with BKV infection following lung transplantation.

Reference	Year	Type of lung transplantation	Patients with BK viruria, n, (%)	Patients with BK viremia, n	Time after lung transplantation (months)	Type of immuno-suppressant	Renal dysfunction	Conclusion
Barton et al. [11]	2006	Unknown	4/23 (17.4)	0/23	median 65	PSL, MMF, TAC, CyA, AZA, Sirolimus	Unexplained chronic renal dysfunction of at least 3 months duration	BKV might have contributed to chronic renal dysfunction
Thomas at al. [12]	2007	Single, Double, Heart-lung	16/50 (32.0)	0/50	mean 44	PSL, MMF, TAC, CyA, AZA, Sirolimus, Everolimus	No association	BKV infection was not associated with renal dysfunction
Doucette et al. [13]	2008	Unknown	5/28 (17.9)	0/28	within 9	PSL, MMF, TAC, CyA,	No association	No association between BK uremia and renal dysfunction
Thomas et al. [14]	2009	Single, Double, Heart-lung	38/90 (42.2)	Unknown	mean 31	PSL, MMF, TAC, CyA, AZA, Sirolimus, Everolimus	Lower creatinine clearances (4.2 ml/min)	BKV infection was associated with increased mortality

BKV: BK virus, PSL: prednisolone, MMF: mycophenolate mofetil, TAC: tacrolimus, CyA: Cyclophosphamide, AZA: azathioprine.

established. For the recovery of host immune function, we attempted to control the immunosuppressant dosage. Since the calcineurin inhibitor is one of the key drugs used as an immunosuppressant post-organ transplantation and the BKV infection occurred only 3 months after transplantation, we decided to reduce the immunosuppressant post-transplantation as originally planned. We decided not to replace TAC but to decrease its dosage, hoping for a gradual improvement in the host immune system. Whether treatment by decreasing the dosage of immunosuppressive agents can be generalized depends on each case.

In this case, sirolimus was required for the treatment of recurrent LAM. The drug label documents for sirolimus warn that the activation of latent viral infections, including BKV-associated nephropathy, are potential adverse events, but these risks have not been thoroughly characterized [20]. There was no association between BKV onset and sirolimus because sirolimus had been withdrawn more than 2 years before lung re-transplantation. Six months after re-transplantation, add-on sirolimus administration was started. Urine decoy cells were not observed for 1 year after re-starting sirolimus. This case showed the possibility of add-on sirolimus therapy to LAM patients who have history of BKV infection.

Although the cause is unknown, it was reported that presence of BKV infection was associated with an increased risk of death [14]. Because there is a possibility of recurrence of BKV infection according to the change in the immunosuppressed state, we continued to carefully monitor the TAC trough level and decoy cells by urine cytology. Further studies to clarify the mechanism of BKV onset and progression are needed.

In conclusion, based on the course of this case, it is necessary to pay attention to BKV reactivation even in post-lung transplantation patients. Urine cytology may be useful for monitoring the course of treatment. Early-stage interventions may prevent BKV-associated nephropathy even in patients who have developed BKV viremia,

Table 3
Summary of case reports concerning patients with BKV infection following lung transplantation.

Reference	Year	Age Sex	Type of lung transplantation	Time after lung transplantation (months)	Type of immunosuppressant at the onset of BKV infection (per day)	Serum max BKV load (copies/ml)	Urine max BKV load (copies/ml)	Therapy	Duration of BK viremia (months)	Renal dysfunction	Others
Schwarz et al. [10]	2005	40 M	Double	15	PSL 7.5 mg, MMF 1500 mg, TAC 2.5 mg	1.6×10^6	$>1 \times 10^8$	Cidofovir 250mg	8	Elevation of serum creatinine, BKV nephropathy	Need to continue hemodialysis after 3 months of BKV infection, Recurrence with BKV due to high dose PSL for acute lung rejection
Egli et al. [15]	2010	67 F	Double	60	PSL 15 mg, MMF 500 mg, TAC 3.0 mg,	7.1×10^4	7.1×10^9	Step-wise reduction of immunosuppressant	14	Elevation of serum creatinine, BKV nephropathy	Add-on leflunomide was discontinued for anemia and diarrhea
Present case	2018	44 F	First:Double (living-donor lobar) Second: Double	3	PSL 14 mg, MMF 250 mg, TAC 2.6 mg,	8×10^2	1×10^9	Step-wise reduction of immunosuppressant	5	None	Elevation of TAC trough onset of BKV infection, Success with add-on sirolimus after BKV viremia

M: Male, F: Female, BKV: BK virus, PSL: prednisolone, MMF: mycophenolate mofetil, TAC: tacrolimus.

and sirolimus can be administered to patients with histories of BKV infection if they are carefully monitored.

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Ethics statement

Informed consent and permission for publication were obtained from the patient.

Conflicts of interest

None.

Author contributions

J.O.: This author contributed to the concept and review of the case report.

Y.N., Y.S., T.H., K.W., N.H., Y.H.: These authors contributed to the concept, writing, and critical revision of the article.

N.M.: This author assisted in the review of the case report and pathological findings.

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