OPEN

BK Viremia Exacerbation With Adalimumab Coadministration

Erik L. Lum, MD[1] and Suphamai Bunnapradist, MD[1]

INTRODUCTION

BK polyomavirus (BKV) is a common complication of kidney transplantation, which may result in allograft dysfunction and premature graft loss. Reduction in immunosuppression is the cornerstone of management in transplant recipients with BK viremia. Tumor necrosis factor alpha (TNFα) inhibitors are a class of mediations used to treat a variety of nonrenal inflammatory conditions. Use of TNFα inhibitor has been associated with reactivation of fungal and viral infections. The impact of TNFα inhibitors on BK viremia is unknown. Herein, we describe a case of persistent BK viremia related to maintenance adalimumab use for rheumatoid arthritis in a kidney transplant recipient.

CASE STUDY

A 73-y-old woman with end-stage renal disease ascribed to hypertension received a deceased-donor kidney transplant after spending 8 y on dialysis. She had a history of rheumatoid arthritis on maintenance adalimumab monthly, which she received 11 d before transplant, and a gastrointestinal bleed 15 y prior requiring transfusion of red blood cells. Her donor was in their teens and had a kidney donor profile index of 11%. She was very highly sensitized with a calculated panel reactive assay of 100%, and no donor-specific HLA antibodies, at the time of transplant and received a total of 4.5 mg/kg of antithymocyte globulin. Her maintenance immunosuppression regimen consisted of prednisone, tacrolimus, and mycophenolate mofetil. Her initial hospital course was uncomplicated, and she was discharged on postoperative day 4 with a serum creatinine of 0.7 mg/dL.

She had an uneventful first month post–kidney transplant and received a dose of adalimumab 40 mg 3 wk post–kidney transplant from her rheumatologist. She reported no side effects from the medication, and future infusions were discontinued. On routine screening for BK viremia 6 wk posttransplant, she was noted to have a BK blood polymerase chain reaction (PCR) of 1273 copies, a repeat test 1 wk later showed BK viremia at 63 000 copies. Her mycophenolate mofetil was subsequently held, and her BK viremia continued to worsen to a peak of 2.7 million copies (Figure 1). At the time, she was also noted to have a low-level class II donor-specific antibody (DSA) and received IVIG 2 g/kg total over 2 d, and her viremia improved to 245 000 copies 1 mo after her IVIG infusion. DSA testing was performed per center protocol given her highly sensitized status at the time of transplantation. Her testing at 2 wk, 4 wk, and 2 mo post–kidney transplantation were negative. Her DSA persisted and received a second dose of IVIG, following which quarterly DSA testing remained negative. A kidney transplant biopsy was recommended, but the patient refused because of concerns for complications. Her renal function remained excellent with a creatinine between 0.6 and 0.8 mg/dL, while on dual therapy with prednisone and tacrolimus with a trough between 2.9 and 7.3 ng/L throughout the remainder of the transplant course.

Her viremia continued to improve to a nadir of 8000 copies until 8 mo posttransplant when she was given a prednisone pulse by her rheumatologist for worsening joint pain. Two weeks after her prednisone pulse, her BK was noted to increase and she underwent another treatment with IVIG with improvement in her BK viremia.

At 11 mo posttransplant, her rheumatologist restarted monthly administration of adalimumab. Her dose was increased to every 2 wk to 13 mo posttransplant. Her BK viral load increased modestly during the initial exposure and then to a much higher degree with the dose increase. She went on to receive additional doses of IVIG with transient decreases in viral load after IVIG administration. Her kidney transplant function remained stable throughout this period. After discussion with her rheumatologist, her adalimumab was discontinued. To treat her arthritis symptoms, her prednisone was increased to a maintenance of 10 mg daily and she was started on low-dose methotrexate. Following these changes, her BKV load markedly improved.

Received 30 January 2020. Revision received 11 March 2020.

Accepted 26 March 2020.

[1]Division of Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, CA.

The authors declare no funding or conflicts of interest.

E.L.L. participated in writing the article and collected the figure. S.B. participated in writing the article.

Correspondence: Erik L. Lum, MD, Connie Frank Kidney Transplant Center, 200 Medical Plaza, Ste 565, Los Angeles, CA 90095. (elum@mednet.ucla.edu).

ISSN: 2373-8731

Transplantation Direct 2020;6: e557; doi: 10.1097/TXD.0000000000001000. Published online 22 May, 2020.

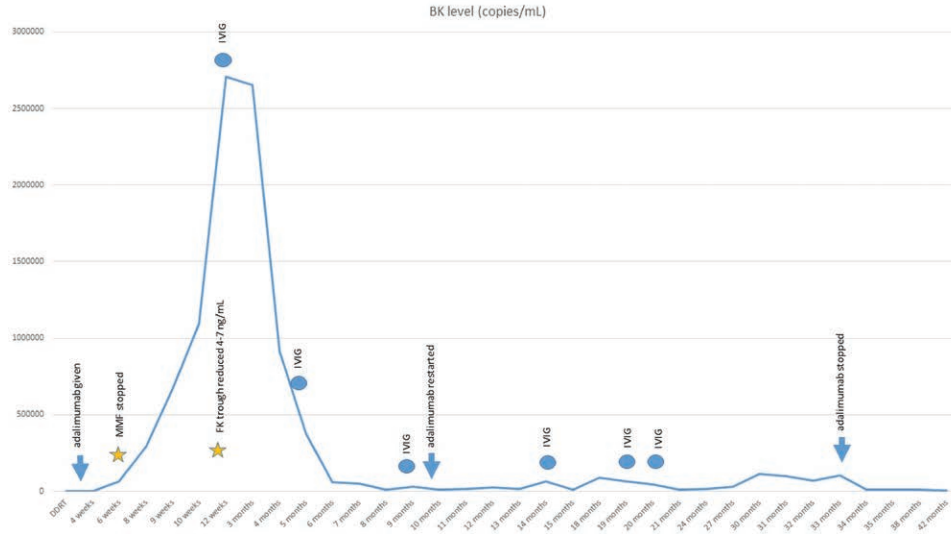

FIGURE 1. BKV PCR trend over time for patient posttransplantation. Arrows for adalimumab administration times. Stars indicate significant changes to maintenance immunosuppression. Circles indicate the administration of IVIG. BKV, BK polyomavirus; PCR, polymerase chain reaction.

DISCUSSION

BKV infection is common, with studies indicating >70% of children infected by the age of 10 y.[1] Following primary infection, the virus remains latent within the renal tubular epithelial and urothelial cells. Exposure to immunosuppression may result in reactivation of BKV from these cells. BKV reactivation results in the spread of infection toward adjacent cells with subsequent cell lysis. Lysis results in viruria and spread of the virus to the tubular capillary wall, where viral particles are transmitted into the blood and can be detected as viremia. The incidence of BK viremia in solid organ transplants is highest in kidney transplant recipients, with an estimated incidence of 10%–30%.[2]

Advanced infections may lead to interstitial inflammation and tubulitis, the hallmarks of BKV-associated nephropathy (BKVAN), hemorrhagic cystitis, and ureteric obstruction. An estimated 3%–10% of transplant recipients with BKV will progress to BKVAN. BKVAN may result in accelerated allograft loss and urinary strictures, which may compromise the allograft. A recent analysis identified tacrolimus-based regimens, a deceased donor, a male recipient, a history of previous transplant, age at transplantation, ureteral stent use, delayed graft function, and acute rejection episodes as risk factors for BK viremia post–kidney transplant.[3]

Despite the potential complications associated with BK nephropathy, no prophylaxis regimen or antiviral therapy has been shown to be effective. Reduction in immunosuppression and serial monitoring of BK viremia by PCR has become the mainstay of BKV management. There is also retrospective observational data suggesting that use of mammalian target of rapamycin inhibitors, such as sirolimus and everolimus, reduce the incidence of BK viremia. When approached about a potential immunosuppression regimen change, our patient opted to remain on tacrolimus as her kidney function has remained stable and DSAs had disappeared. Other agents that have been used the treat BKVAN include ciprofloxacin, leflunomide, cidofovir, rapamycin, and IVIG. However, the data on the use of these agents for BK viremia are limited by small study sizes and often the lack of a control group and in some cases may cause significant morbidity.[4,5] In the case presented, IVIG was also used to treat the patient's DSA.

The TNFα system is a major component of the immune system's control of viral infections. TNFα is a cell-signaling molecule that is secreted by activated macrophages and T cells that aid in macrophage activation, phagosome activation, differentiation of monocytes into macrophages, and granuloma formation. Decreased local TNFα expression in renal tubular epithelial cells has been in individuals with BKVAN, a process thought to permit local viral replication.[6]

TNFα inhibitors are a class of medications used to treat chronic inflammatory conditions. Currently, 5 such drugs have been approved by the Food and Drug Administration, including infliximab, adalimumab, etanercept, certolizumab, and golimumab. These medications are effective at treating chronic inflammatory conditions but are associated with an increased risk of infections. TNFα inhibitors have been associated with a decrease in hepatitis B clearance, increase in liver injury in patients with hepatitis C, and increase in zoster.[7] IVIG has been reported to counteract the effects of adalimumab, which may explain the transient decrease in BK virus copies after administration of IVIG in our patient.[8]

In kidney transplant recipients, the concurrent use of TNFα inhibitors results in an increased risk of infection.[9] BKV has been shown to increase in patients receiving TNFα inhibitor therapy for inflammatory bowel disease. In a prospective study by Flores et al, 53 patients with IBD on TNFα inhibitor therapy were studied for BKV. A control group of patients with IBD not on TNFα inhibitor therapy was used. TNFα inhibitor therapy was associated with an increase in BKV viruria (54.7% versus 11.3%). No BKV viremia was detected in these patients. Two kidney transplant were lost in this cohort, 1 from recurrent amyloidosis and the other from antibody-mediated rejection. In the remaining 51 patients, renal allograft function remained stable over a 24-mo period.

In this case, the recipient developed high levels of BK viremia following antithymocyte globulin induction. She received doses of adalimumab 11 d before transplant and

3 wk posttransplant, which were followed by a marked rise in BKV viremia to a peak of 2.7 million copies. She received IVIG for concurrent BK viremia and a de novo class II DSA, and her viremia improved over the course of 11 mo, following which she was restarted on adalimumab for worsening arthritis. She remained on adalimumab for a year and a half with persistent BK viremia. Her BK viremia improved transiently with IVIG administration; however, it was not until discontinuation of her adalimumab that her BKV markedly improved. Our center's current recommendation is to avoid TNFα inhibitors posttransplant unless their symptoms cannot be controlled with another agent. If TNFα medications are used, then increased BK screening is indicated. For candidates already on TNFα inhibitors, we ask that they can be converted before transplant if possible.

CONCLUSION

BKV is an important complication of kidney transplantation. TNFα inhibitor use following transplantation may result in an increased risk for BK reactivation and persistent infection as demonstrated in this case. Assessment of non-transplant-related medications, especially those with immune-modulating properties, is essential in limiting complications from transplantation.

REFERENCES

1. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). *Adv Exp Med Biol.* 2006;577:19–45. doi:10.1007/0-387-32957-9_2
2. Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. *Clin J Am Soc Nephrol*. 2007;2(Suppl 1):S36–S46. doi:10.2215/CJN.00920207
3. Demey B, Tinez C, François C, et al. Risk factors for BK virus viremia and nephropathy after kidney transplantation: a systematic review. *J Clin Virol.* 2018;109:6–12. doi:10.1016/j.jcv.2018.10.002
4. Sawinksi D, Goral S. BK virus infection: an update on diagnosis and treatment. *Nephrol Dial Transplant*. 2015;30:209–217. doi:10.1093/ndt/gfu023
5. Huang J, Danovitch G, Pham PT, et al. Kidney retransplantation for BK virus nephropathy with active viremia without allograft nephrectomy. *J Nephrol.* 2015;28:773–777. doi:10.1007/s40620-015-0200-6
6. Ribeiro A, Merkle M, Motamedi N, et al. BK virus infection activates the TNFα/TNF receptor system in polyomavirus-associated nephropathy. *Mol Cell Biochem.* 2016;411:191–199. doi:10.1007/s11010-015-2581-1
7. Kim SY, Solomon DH. Tumor necrosis factor blockade and the risk of viral infection. *Nat Rev Rheumatol.* 2010;6:165–174. doi:10.1038/nrrheum.2009.279
8. Sharma T, Riedl MA. Beneficial effects of adalimumab counteracted in patient with common variable immunodeficiency disorder (CVID) receiving IVIG: case report. *J Allergy Clin Immunol*. 2017;139:AB21. doi:10.1016/j.jaci.2016.12.025
9. Garrouste C, Anglicheau D, Kamar N, et al. Anti-TNFα therapy for chronic inflammatory disease in kidney transplant recipients: clinical outcomes. *Medicine (Baltimore).* 2016;95:e5108. doi:10.1097/MD.0000000000005108