

Adenovirus Nephritis in Kidney Allograft Recipients: An Important Differential Diagnosis

By Krishna Kumar Agrawaal and Priti Meena

Viral infections are an important cause of morbidity and mortality in kidney transplant recipients. Adenovirus, a double-stranded DNA virus, is a rare cause of infection in this group of patients. The prevalence of asymptomatic adenovirus viremia in kidney transplant recipients is estimated to be approximately 6.0%–6.5% (1). Research on adenovirus as the source of nephritis has been limited, making it an understudied cause. Nevertheless, a recent study by Jagannathan et al. (2) has provided an in-depth look at the issue.

This study was a retrospective, multicenter analysis of 11 kidney transplant recipients with adenovirus nephritis from 2010 to 2021. The authors compared the pathologic and transcriptomic characteristics of adenovirus nephritis cases with that of BK virus nephropathy. Because these were all “for cause” kidney biopsies, the entire cohort had elevations in serum creatinine. A majority of the individuals also exhibited fever and hematuria. The adenovirus DNA levels were all high. The median adenovirus DNA levels were 28,250 (interquartile ranges [IQRs]: 3525–75,550) copies/mL in the plasma and 1,900,000 (IQRs: 468,000–15,000,000) copies/mL in the urine. Histopathology findings revealed tubulointerstitial inflammation composed

of a mixture of mononuclear leukocytes, neutrophils, and eosinophils involving cortex and medulla. All adenovirus nephritis cases showed scattered, smudgy nuclear viral inclusions. Immunohistochemistry for adenovirus in the tubular epithelial cells was positive.

The distinguishing characteristics of adenovirus nephritis compared with BK virus nephritis were more granulomas and less tubulointerstitial scarring in adenovirus nephritis; furthermore, adenovirus nephritis cases showed more rapid clearance of viral DNA from plasma (Table 1). Although adenovirus nephritis showed a more aggressive inflammatory response compared with BK virus nephropathy, it rarely resulted in allograft failure. Adenovirus infection mainly occurs in the first year of transplant when the doses of immunosuppression are high, although it can present after 1 year also, as demonstrated in another study (3). Hemorrhagic cystitis is the most common presentation of adenovirus nephritis, but it can also present as mass lesion, obstructive uropathy (4). Currently, Kidney Disease: Improving Global Outcomes (KDIGO) does not recommend routine screening in kidney transplant recipients, but based on this study, in kidney allograft recipients who present with fever and hematuria, adenovirus nephritis is an important differential

diagnosis. Treatment of adenovirus nephritis in this case series included reduction in immunosuppression, intravenous immunoglobulin, and less commonly antiviral agents, like cidofovir or valganciclovir. Thus, this study showed that there is improved allograft survival in kidney transplant recipients with adenovirus nephritis despite aggressive neutrophil-rich infiltrates. ■

Krishna Kumar Agrawaal, MBBS, MD, DM, FACP, FASN, is an associate professor with the Universal College of Medical Sciences, Nepal. Priti Meena, MBBS, MD, DNB, FASN, is an assistant professor with the All India Institute of Medical Sciences, Bhubaneswar, India.

The authors report no conflicts of interest.

References

- Humar A, et al. PV16000 Study Group. A surveillance study of adenovirus infection in adult solid organ transplant recipients. *Am J Transplant* 2005; 5:2555–2559. doi: 10.1111/j.1600-6143.2005.01033.x
- Jagannathan G, et al. The pathologic spectrum of adenovirus nephritis in the kidney allograft. *Kidney Int* 2023; 103:378–390. doi: 10.1016/j.kint.2022.10.025
- Seralathan G, Kurien AA. Adenovirus interstitial nephritis: An unusual cause for early graft dysfunction. *Indian J Nephrol* 2018; 28:385–388. doi: 10.4103/ijn.IJN_218_16
- Watanabe M, et al. Literature review of allograft adenovirus nephritis and a case presenting as mass lesions in a transplanted kidney without symptoms of urinary tract infection or acute kidney injury. *Transpl Infect Dis* 2021; 23:e13468. doi: 10.1111/tid.13468

Table 1. Differences in characteristics of adenovirus nephritis and BK virus nephropathy

Characteristics	Adenovirus nephritis (n = 11)	BK virus nephropathy (n = 33)	p value
Microhematuria	10 (91%)	4 of 21 (19%)	<0.001
Granulomas	9 (82%)	0	<0.001
Pure tubulointerstitial nephritis	1 (9%)	32 (97%)	<0.001

The pathologic spectrum of adenovirus nephritis in kidney allograft recipients

KidneyNews

Methods and Cohort

- KTR with adenovirus nephritis
- Retrospective study
- N = 11
- North American Medical Centers
- Control biopsy: BKVN (n = 33)

- Fever (73%)
- Hematuria (91%)
- Increased serum creatinine (100%)
- Median ADV DNA levels: 28,250 copies/mL (plasma) and 1,900,000 (urine)
- Granulomas (82%)
- Tubulo-centric inflammation (73%)
- Intranuclear viral inclusions (100%)
- Tubular degenerative changes consistent with ATN (73%)
- Increased expression of pro-inflammatory innate immunity transcriptomes
- Higher enrichment with neutrophils, which can cause aggressive but short-lasting damage

Conclusions: Compared with BK virus nephritis (BKVN), adenovirus (ADV) nephritis is associated with aggressive neutrophil-rich inflammation and increased expression of innate immunity-related transcripts with faster viral clearance but similar allograft survival. ATN, acute tubular necrosis; KTR, kidney transplant recipients.

Reference: Jagannathan G, Weins A, Daniel E, Crew RJ, Swanson SJ, Markowitz GS, D'Agati VD, Andeen NK, Remke HG, Batal I. The pathologic spectrum of adenovirus nephritis in the kidney allograft. *Kidney Int*. 2022. Nov 24;50085-2558(2):00968-1. Visual abstract by Krishna K Agrawaal, MD, DM, FACP, FASN @agrawalkris Priti Meena, MD, DNB, FASN @priti899

Comparison of adenovirus nephritis (ADV) with BK virus nephropathy (BKVN) in the kidney allograft

- Clinical comparison** Patients with ADVN had higher incidences of hematuria.
- Histological comparison** Biopsies with ADVN characteristically demonstrate smudgy and basophilic nuclear viral inclusions. Higher granulomas and lower Banff scores for interstitial fibrosis and tubular atrophy and tubular atrophy present in ADVN.
- Outcome** Allograft survival was similar in patients with ADVN and those with BKVN. ADVN had more rapid clearance of viral DNA from the plasma.
- Immunological response** ADVN is associated with increased expression of immunologic cascades, mainly involving innate immunity, defense against pathogens, cytokine and interferon signaling, and antigen presentation.
- Leukocyte profiling** Compared with BKVN, our cases of ADVN were characterized by a higher burden of total infiltrating leukocytes. ADVN is characterized by relatively fewer mast cells than BKVN.



Want to learn even more about how changes in health care policy, the kidney workforce, and new research will affect you?

Check out Kidney News Online at www.kidneynews.org