Adenovirus Nephritis in Kidney Allograft Recipients: An Important Differential Diagnosis

By Krishna Kumar Agrawaal and Priti Meena

Vir al 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 under-studied 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 cases showed scattered, smudgy viral nuclear 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 antiviral-rich infiltrates.

Krishna Kumar Agrawal, 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

The pathologic spectrum of adenovirus nephritis in kidney allograft recipients

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adenovirus nephritis (n = 11)</th>
<th>BK virus nephropathy (n = 33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microhematuria</td>
<td>10 (91%)</td>
<td>4 of 21 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Granulomas</td>
<td>9 (82%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pure tubulointerstitial nephritis</td>
<td>1 (9%)</td>
<td>32 (97%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Comparison of adenovirus nephritis (ADVN) 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 compared to BKVN.

Outcome
- Allograft survival was similar in patients with ADVN and those with BKVN.
- ADVN had more rapid clearance of viral DNA from the plasma.

Immunosuppressive 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 innate infiltrating leukocytes.