Background

- Adenoviruses (AdV) are double-stranded DNA viruses that are rare, but well recognized causes of morbidity and allograft dysfunction.
- We have previously shown that adenovirus nephritis (AdVN) can present with granulomatous or neutrophilic tubulointerstitial nephritis in kidney biopsies (See Figure).
- In kidney transplant recipients, certain clinical and histologic features should raise concern for adenovirus nephritis (AdVN).
- There are many options to management, ranging from supportive therapy to the use of AdV-directed therapy.
- Here we report eight cases of AdVN in kidney transplant recipients and their clinical course, management, and outcomes.

Methods

- A retrospective search to identify cases of AdVN in renal transplant recipients from 2009-2016 at the Emory Transplant Center was performed.
- The diagnosis of AdVN was confirmed by immunostaining on kidney transplant biopsy in 7/8 cases.
- The diagnosis was made clinically in case 8 due to inadequate sampling of the biopsy.
- The following information was collected and recorded on all patients (see Table): Demographic data (age and gender) Number of days between transplantation and biopsy showing AdVN Serum creatinine level at time of biopsy Baseline immune level Serum urine AdV level at time of biopsy Evidence of concurrent rejection Evidence of concurrent infection Treatment regimen

Results

- Median time from transplant to development of adenovirus infection: 50 days.
- All patients presented with constitutional symptoms: dysuria, hematuria, and proteinuria.
- 5/8 patients presented with fever, 5/8 with diarrhea and 2/8 with diarrhea and respiratory symptoms.
- Of the 2 that did not receive AdV-directed therapy, 1 had resolution of the viremia after 42 days. There was no documentation of viremia clearance for the second, although they had a benign clinical course.
- The 4 who received ribavirin cleared the virus at a median of 78 days.
- The 1 who received brincidofovir cleared the virus at 22 days.
- Proteinuria and hematuria improved or resolved in all patients irrespective of treatment regimen.
- All patients were noted to have a concurrent viral or bacterial complication (see Table) at the time of management for AdV.

Conclusions

- This case series summarizes the range of clinical features and management of AdVN.
- Treatment regimen varied, but clinical resolution was noted in all cases and was most profound with brincidofovir.
- Despite the morbidity of AdVN, if managed and monitored closely, resolution can be achieved with good outcomes in renal function in kidney transplant recipients.
- Additional study of cases of AdVN without AdV-directed therapy are required before supportive therapy can be considered a universally viable option.
- Overall, our study demonstrates the need to account for the management of simultaneous rejections, other viremias, and potential side effects of the therapeutics.

Table: All eight patients had a concurrent infection with AdVN. 2 of 4 patients had a prior biopsy showing cell mediated rejection. All eight patients had macroscopic hematuria. CR:creatinine, TX:transplant, AMR:antibody mediated rejection, IS=immunosuppression, SNR=site not recorded.

<table>
<thead>
<tr>
<th>CASE</th>
<th>PATIENT</th>
<th>GENDER</th>
<th>AGE</th>
<th>DAYS POST TX</th>
<th>DAYS PRIOR TO BIOPSY</th>
<th>REACTION (CURRENT/PRIOR BIOPSY)</th>
<th>SERUM/URINE ADENOVIRUS LEVEL</th>
<th>% RISEMEN PRIOR TO BIOPSY</th>
<th>HISTOLOGIC PATTERN</th>
<th>TREATMENT</th>
<th>OTHER INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Male</td>
<td>74</td>
<td>307</td>
<td>None/Prior Biopsy</td>
<td>MACROSCOPIC</td>
<td>&quot;Detected&quot; in virus only</td>
<td>MACROSCOPIC</td>
<td>&quot;Positive&quot; (&gt;2,000,000 copies/mL)</td>
<td>PROGRESSIVE, CELLECTIC</td>
<td>RIBAVIRIN</td>
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<td>2</td>
<td>2</td>
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<td>19</td>
<td>50</td>
<td>None/Prior Biopsy</td>
<td>MACROSCOPIC</td>
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<td>DETERMINATE, TUBULAR NECROSIS WITH NECTROSIS AND NEUTROPHILIC INTERSTITIAL INFLAMMATION, VAGUE GRANULOMATOUS FORMATION, &quot;SMUDGE CELLS&quot;</td>
<td>RIBAVIRIN</td>
<td>EV AND PARVIVORUS VIREMA</td>
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<tr>
<td>3</td>
<td>3</td>
<td>Male</td>
<td>63</td>
<td>13</td>
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<td>PROGRESSIVE, CELLECTIC</td>
<td>DETERMINATE, TUBULAR NECROSIS WITH NECTROSIS AND NEUTROPHILIC INTERSTITIAL INFLAMMATION, VAGUE GRANULOMATOUS FORMATION, &quot;SMUDGE CELLS&quot;</td>
<td>RIBAVIRIN</td>
<td>EV AND PARVIVORUS VIREMA</td>
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<tr>
<td>4</td>
<td>4</td>
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<td>63</td>
<td>33</td>
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<td>&quot;Positive&quot; (&gt;2,000,000 copies/mL)</td>
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<td>DETERMINATE, TUBULAR NECROSIS WITH NECTROSIS AND NEUTROPHILIC INTERSTITIAL INFLAMMATION, VAGUE GRANULOMATOUS FORMATION, &quot;SMUDGE CELLS&quot;</td>
<td>RIBAVIRIN</td>
<td>EV AND PARVIVORUS VIREMA</td>
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<tr>
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<td>5</td>
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<td>42</td>
<td>1,414</td>
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<td>DETERMINATE, TUBULAR NECROSIS WITH NECTROSIS AND NEUTROPHILIC INTERSTITIAL INFLAMMATION, VAGUE GRANULOMATOUS FORMATION, &quot;SMUDGE CELLS&quot;</td>
<td>SUPPORTIVE CARE</td>
<td>S. AUREUS IN SERUM AND URINE, E. COLI UTI</td>
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<tr>
<td>6</td>
<td>6</td>
<td>Female</td>
<td>24</td>
<td>52</td>
<td>Post Biopsy</td>
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<td>PROGRESSIVE, CELLECTIC</td>
<td>NEUTROPHILIC TUBULAR NECROSIS AND NEUTROPHILIC INTERSTITIAL INFLAMMATION, VAGUE GRANULOMATOUS FORMATION, &quot;SMUDGE CELLS&quot;</td>
<td>RIBAVIRIN</td>
<td>EV AND PARVIVORUS VIREMA</td>
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<tr>
<td>8</td>
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<td>&quot;Positive&quot; (&gt;2,000,000 copies/mL)</td>
<td>PROGRESSIVE, CELLECTIC</td>
<td>DETERMINATE, TUBULAR NECROSIS WITH NECTROSIS AND NEUTROPHILIC INTERSTITIAL INFLAMMATION, VAGUE GRANULOMATOUS FORMATION, &quot;SMUDGE CELLS&quot;</td>
<td>BRINDIDOFOIR REDUCED DO</td>
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FIGURE: A:B: Hematoxylin and eosin (H&E) and corresponding AdV immunohistochemistry (IHC) showing necrotizing, granulomatous AdV. C: Electron microscopy showing an AdV particle. D: H&E showing severe neutrophilic tubulitis with reactive HC for AdV. E: "Smudge cells" in a granulomatous focus of the AdV.

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