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# Fever and Gross Hematuria in a Kidney Transplant Recipient

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## Clinical Images in Nephrology and Dialysis

### Case Description

A 61-year-old man presented, 7 months after deceased donor kidney transplantation, with 4 days of fever, hematuria, and dysuria. His immunosuppression regimen included tacrolimus 1.5 mg twice daily, prednisone 5 mg daily, and mycophenolate mofetil 500 mg twice daily. He was febrile to 101.6 and had tenderness to palpation in the right lower quadrant over his graft site. His serum creatinine on admission was 1.4 mg/dl from a baseline of 1.0 mg/dl. White blood cell count was $4.4\times10^3/\mu$l with 85.9% neutrophils. Tacrolimus trough level was 13.3 ng/ml. Urinalysis demonstrated 100 mg/dl protein, 109 white blood cells per high-power field, 344 isomorphic red blood cells per high-power field, and hyaline casts. Urine and blood cultures were negative. Renal ultrasound was unremarkable. Kidney biopsy was ultimately performed that demonstrated multifocal tubulocentric necrotizing granulomatous tubulointerstitial nephritis and enlarged nucleoli (Figure 1A). Immunohistochemical staining was positive for adenovirus (Figure 1B). The patient's immunosuppression regimen was reduced and kidney function returned to baseline over the next 6 weeks.

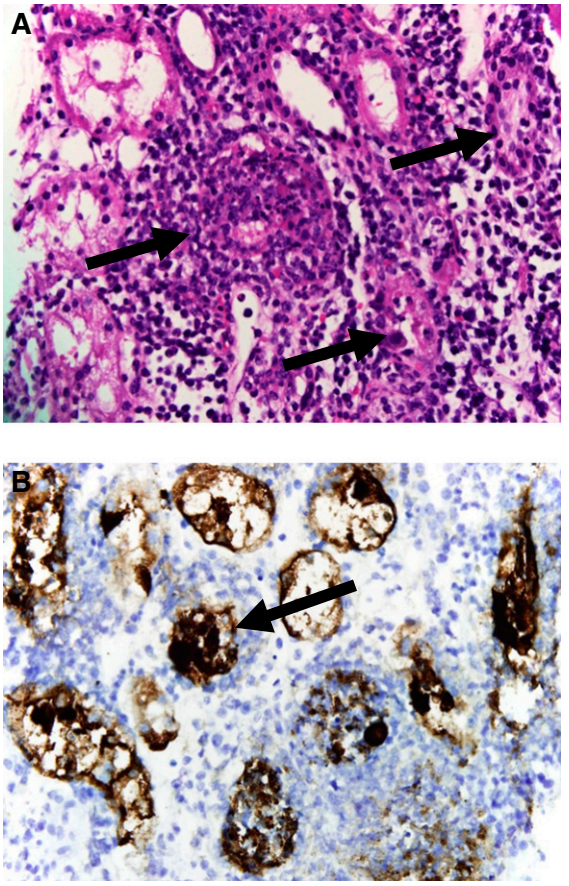


**Figure 1. | Kidney Biopsy.** (A) Hematoxylin and eosin staining demonstrating multifocal necrotizing tubulocentic granulomatous inflammation (arrows). (B) Immunohistochemical staining of kidney biopsy positive for adenovirus (arrow).

Members of the Adenoviridae family are nonenveloped, lytic, double-stranded DNA viruses that can cause significant morbidity and mortality. Infections can range from asymptomatic with detection of adenovirus in the urine, blood, stool, or upper airway specimens to disseminated with organ-specific involvement of two or more organs. Among solid organ recipients, most infections occur within the first year after transplant. Immunosuppression increases the risk of developing adenovirus infection in transplant patients. Among adult solid organ transplant recipients, 6.5%–22% will have asymptomatic viremia at some point with an unclear risk of progression to adenoviral disease. Routine screening for adenovirus viremia has limited utility and it is currently not recommended.

Adenovirus infection of the transplanted kidney frequently presents with hemorrhagic cystitis, fever, and dysuria. Hemorrhagic cystitis is usually accompanied by allograft dysfunction. This presents a challenge for clinicians who must try to differentiate adenovirus infection from BK polyomavirus nephropathy and allograft rejection. Histologic changes seen in adenovirus infection consist of acute tubular injury and necrosis, interstitial nephritis, and viral cytopathic changes including nuclear enlargement, peripheral condensed chromatin, and basophilic nuclear inclusions, which represent viral particles. Granulomatous inflammation has also been observed.

Adenovirus infection is treated with immunosuppression reduction. Cidofovir, a cytosine nucleoside analog that inhibits viral DNA polymerase, has been used in kidney transplant patients with disseminated

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adenovirus that have not responded to reduction in immunosuppression. Cidofovir therapy is associated with significant nephrotoxicity and its use in this setting is only supported by a limited number of case studies.

## Teaching Points

- Adenovirus infection in solid organ transplant patients ranges from asymptomatic to disseminated with multiorgan involvement. Kidney involvement frequently manifests with dysuria, fever, and hemorrhagic cystitis.
- Treatment with reduction in immunosuppression is vital to promote viral clearance. The antiviral agent cidofovir is nephrotoxic and its use in this patient population has not been extensively studied.
- Characteristic changes on light microscopy include acute tubular injury and necrosis, interstitial nephritis often with a pleiomorphic infiltrate, and viral cytopathic changes. Infection can be demonstrated through immunohistochemical staining for adenovirus of biopsy samples (1–5).

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**Author Contributions**

P. Thorne wrote the original draft of the manuscript; all authors were responsible for conceptualization, and review and editing the manuscript.

**Disclosures**

All authors have nothing to disclose.

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