KI REPORTS
KIReports.org

Disseminated Adenovirus Nephritis After Kidney Transplantation

Timothy Hatlen[1,2], Henry Mroch[3], Katherine Tuttle[3,4], Okechukwu Ojogho[5], Michele Rooney[6], Sara Desmond[7] and Samer Bani-Hani[7]

[1]Department of Medicine, Providence Sacred Heart Medical Center, Spokane, Washington, USA; [2]Department of Infectious Diseases, Harbor-UCLA Medical Center, Torrance, California, USA; [3]Department of Nephrology, Providence Kidney Care Spokane, Spokane, Washington, USA; [4]Institute of Translational Health Sciences, Kidney Research Institute, and Nephrology Division, University of Washington, Seattle, Washington, USA; [5]Department of Transplant Surgery, Providence Transplant Surgery, Spokane, Washington, USA; [6]Department of Pathology, Incyte Diagnostics, Spokane, Washington, USA; and [7]Department of Nephrology–Transplant Medicine, Providence Kidney Transplant, Spokane, Washington, USA

Correspondence: Timothy Hatlen, 1000 West Carson Street, Box 466, Torrance, California 90502, USA. E-mail: hatlentj@gmail.com

Kidney Int Rep (2017) ■, ■–■; http://dx.doi.org/10.1016/j.ekir.2017.08.004

INTRODUCTION

Human adenovirus (HAdV) is a linear, non-enveloped, double-stranded DNA virus that typically causes a mild respiratory, gastrointestinal, and conjunctival illnesses in healthy persons.[1] However, HAdV may cause more severe infection in immunocompromised patients, especially those who have received organ transplants. In kidney transplant recipients, urinary tract infection is the most frequently reported manifestation at 4.8%, with rare dissemination.[2,3] In a surveillance study, 6.5% of kidney transplant recipients will have a positive polymerase chain reaction (PCR) viremia within the first year, without significant symptoms, that is self-limited.[4] Disseminated HAdV, defined as symptomatic disease of multiple organ systems and associated viremia, is infrequently reported and is associated with transplant rejection, failure, and mortality.[5–10] A case of disseminated HAdV in a kidney transplant recipient is reported, including a review of management and outcomes in disseminated disease with the goal to guide clinical decision making.

CASE REPORT

A 45-year-old man with a history of end-stage kidney disease, secondary to chronic reflux nephropathy, received a deceased donor kidney transplant. Induction immunosuppression comprised anti–thymocyte globulin and methylprednisolone. Maintenance therapy included tacrolimus, mycophenolate mofetil, and prednisone. His clinical course was complicated by delayed allograft function that required ongoing hemodialysis for 4 weeks.

At his 6-week posttransplantation follow-up visit, he reported a 2-day history of fever, fatigue, cough, and hematuria. He was admitted to the hospital with tachycardia, hypoxemia, and hypotension. He had lymphopenia, thrombocytopenia, and a serum creatinine level of 1.73 mg/dl, compared to his baseline of 1.58 mg/dl. Urinalysis had sterile pyuria and hematuria. Computed tomography of his chest showed an opacity consistent with pneumonia. Vancomycin, piperacillin–tazobactam, and levofloxacin were empirically administered.

Over the next 3 days, he had nightly fevers. His serum creatinine level increased to 2.4 mg/dl. Blood cultures were negative. Studies for serum fungal–(1,3)-B-D-glucan and Aspergillus galactomannan EIA, as well as serum viral PCR cytomegalovirus and human herpesvirus 6 infections, were negative. Urine BK viral particles were not detected by PCR. A nasal swab was positive for HAdV (PCR). Kidney ultrasound demonstrated a 12.6-cm allograft without evidence of renal artery stenosis and with high resistive indices of the upper pole. The 24-hour urine protein was 0.5 g/d at admission and increased to 3.3 g/d by hospital day 7.

A biopsy was performed on the kidney allograft. Paraffin sections showed an edematous parenchyma with a histiocyte-predominant nodular inflammatory infiltrate resembling granulomatous tubulointerstitial nephritis. In place of the epithelioid histiocytes characteristic of granulomas, the predominant cell type in the infiltrate was an atypical monocyte with an eccentrically located, elongated, curved, and crinkled nucleus. These cells infiltrated and distended the tubules, many of which contained epithelial cells with

nuclear viral inclusions as well as apoptic cells (Figure 1). Inflammation with rupture of the tubule appeared to give rise to nodules that, in areas, coalesced into solid inflammatory infiltrate. Remnants of the ruptured tubular basement membranes could be found within the pseudogranulomas on periodic acid–Schiff staining. Strong nuclear staining for adenovirus antigen by cytopathic tubular epithelial cells confirmed adenovirus infection (Arkana Laboratories, Little Rock, AR). No histologic features of acute T-cell or antibody-mediated rejection were found, and the immunofluorescence stain for complement factor C4d was negative. Testing for serum and urine HAdV by PCR returned at 102,801 copies/ml and > 2,000,000 copies/ml, respectively.

Initial treatment consisted of reduction of the patient's immunosuppression by discontinuing mycophenolate mofetil and targeting a serum tacrolimus trough level of 3 to 7 ng/ml. The prednisone dose was increased from 5 mg to 10 mg daily. Because of the ongoing severity of his allograft dysfunction and associated respiratory illness, he was given i.v. Ig dosed at 0.5 g/kg for 2 days. Symptomatic improvement was reported by the second day after completion of i.v. Ig. Serum creatinine and urine PCR HAdV DNA levels declined steadily, with return to baseline and resolution, respectively (Figure 2). The transplant team was subsequently notified that the recipient of the donor's other kidney also developed disseminated HAdV.

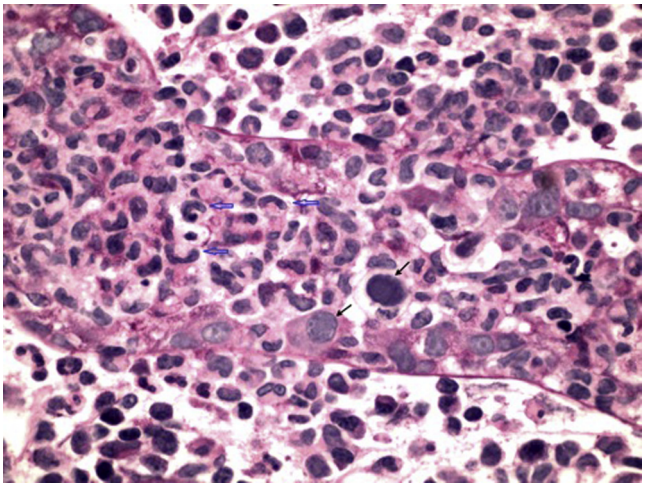

Figure 1. Kidney biopsy sample containing a virus-infected renal tubule. Most of the renal tubular epithelial cells are lost or damaged beyond recognition. Two of the residual epithelial cells contain "smudged" intranuclear viral inclusions typical of adenovirus, with nuclear enlargement and peripheral displacement of nuclear chromatin (black arrows). There is an associated intratubular and peritubular infiltrate consisting predominantly of distinct histiocytes with elongated, curved, and crinkled nuclei (open blue arrows). Periodic acid–Schiff stain, original magnification ×600.

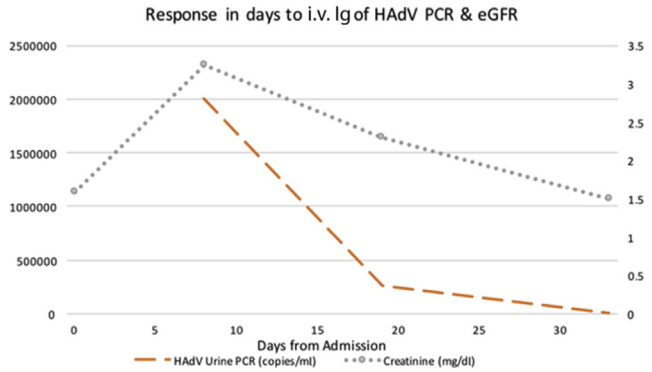

Figure 2. Temporal trend of human adenovirus (HAdV) urine polymerase chain reaction (PCR), serum creatinine, and inception of immunotherapy. Discontinuation of mycophenolate mofetil and reduction of tacrolimus goal trough initiated at day 0, i.v. Ig 0.5 g/kg received on days 8 and 9.

DISCUSSION

Kidney transplant recipients are at high risk over the first 6 months after transplantation for infectious complications, with bacterial cystitis as 1 of the most common culprits.[11] HAdV is well recognized in the healthy population to be associated with self-limited respiratory, gastroenteritis, and conjunctivitis illness. However, in kidney transplant recipients, the spectrum of HAdV activity ranges from asymptomatic viremia to hemorrhagic cystitis to allograft loss and mortality.[1,4-10] In the largest case series to date following 349 kidney transplant recipients over a 3-year period, the incidence of HAdV urinary infection and disseminated disease was 4.8% and 3.1%, respectively. Onset of disease was within the first 3 months in 75% of the patients, and 97% were reported within 1 year.[3,12] A 10-year review of 170 kidney transplant recipients reported an incidence of 4.7% for hemorrhagic cystitis with median time to onset of 1 year.[2] In comparison, recipients post–allogenic stem cell transplantation have a median time of diagnosis of adenovirus hemorrhagic cystitis and dissemination within the first few weeks and month, respectively.[13] Asymptomatic HAdV viremia was reported as 6.5% from a surveillance study, over a 1-year period, of 92 kidney transplant recipients.[4]

HAdV in kidney transplant recipients may be secondary to reactivation of latent disease, but infection also has been reported to be *de novo* from environmental sources or from endogenous transmission through a donor organ.[1,5] The most frequent signs and symptoms at presentation include dysuria, fever, hematuria, sterile (bacterial) pyuriam and acute kidney injury.[2,3,12,14] Given the lack of specificity, a broad differential for the etiology of nephritis must be maintained.[15] Common extrakidney manifestations