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Timothy Hatlen
Department of Medicine, Providence Sacred Heart Medical Center, Spokane, Washington, USA.

Henry Mroch
Department of Medicine, Providence Sacred Heart Medical Center, Spokane, Washington, USA.

Katherine Tuttle
Department of Nephrology, Providence Kidney Care Spokane, Spokane, Washington, USA; Institute of Translational Health Sciences, Kidney Research Institute, and Nephrology Division, University of Washington, Seattle, Washington, USA.

Okechukwu Ojogho
Department of Transplant Surgery, Providence Transplant Surgery, Spokane, Washington, USA.

Michele Rooney

See next page for additional authors

Authors
Timothy Hatlen, Henry Mroch, Katherine Tuttle, Okechukwu Ojogho, Michele Rooney, Sara Desmond, and Samer Bani-Hani

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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

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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.

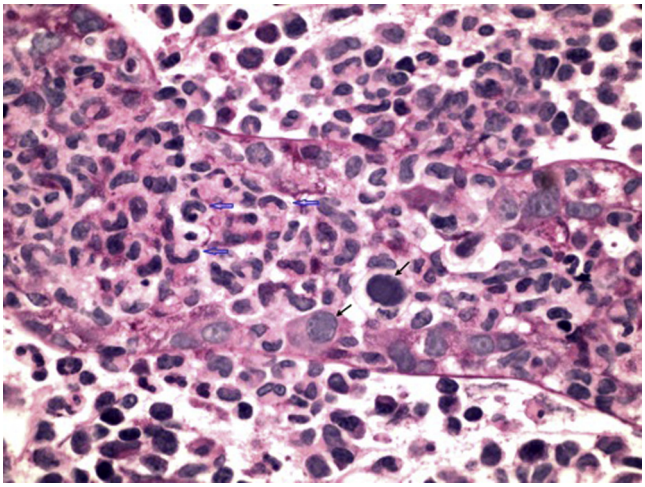

Figure 1. Kidney biopsy sample containing a virus-infected renal tubule. Most of the renal tubular epithelial cells are lost or damaged beyond recognition. Two of the residual epithelial cells contain "smudged" intranuclear viral inclusions typical of adenovirus, with nuclear enlargement and peripheral 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.

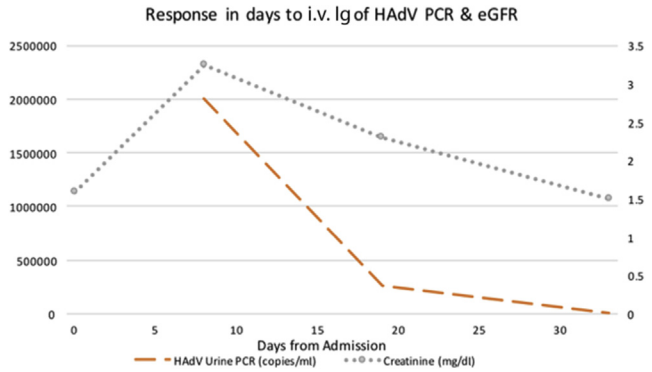

Figure 2. Temporal trend of human adenovirus (HAdV) urine polymerase chain reaction (PCR), serum creatinine, and inception of immunotherapy. Discontinuation of mycophenolate mofetil and reduction of tacrolimus goal trough initiated at day 0, i.v. Ig 0.5 g/kg received on days 8 and 9.

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

among kidney transplant recipients with disseminated disease include orchitis, lymphopenia, gastroenteritis, and pneumonitis.[3,16–18] Confirmatory diagnostic testing is predominantly through HAdV PCR quantification and tissue biopsy histopathological assessments. Viral culture may be conducted in some cases.[12] PCR is sensitive to all known serotypes of HAdV, and has the benefit of serial monitoring for response to treatment. PCR testing for HAdV prognostication has been reported in groups receiving hematopoietic stem cell therapy and solid organ transplants.[9,19,20]

In the present case, this patient had a classically defined presentation of disseminated HAdV. His kidney biopsy findings of inclusion-bearing proximal tubular cells and adjacent noncaseating granulomas in the tubulointerstitium were consistent with HAdV infection and confirmed by immunohistochemical staining.[21] Given the severity of his acute kidney injury and progressive pneumonia, he was treated with i.v. Ig based on reports for hematopoietic stem cell transplant recipients.[19,22–24] Cidofovir was not used because of concerns about additional nephrotoxicity in the setting of severe acute kidney injury in the transplanted kidney.

Clinically symptomatic patients with HAdV viremia and 2 or more organ systems involved is considered disseminated disease. Little has been published about clinical management, and current recommendations for treatment are lacking.[10,25] Overall, 29 cases of disseminated HAdV disease have been reported, including the present case (Table 1). Adverse outcomes have been reported in 6 cases (20%), including 4 deaths and 2

Table 1. Reported cases of disseminated adenovirus in patients post kidney transplantation

Case no.	Author (reference)	Year	Transplant organ	Age (yr)/sex, onset post transplantation	Organ or disease condition	Diagnostic testing	Additional antiviral	Outcome
1	Myerowitz (34)	1975	Kidney	61/F, 40 days	Nephritis, pneumonitis, leukopenia	Unavailable, histological confirmation	None	Dead
2	Ardehali (35)	2001	Kidney	45/M, 6 yr	Nephritis, pneumonitis, gastritis, cardiac arrest	No PCR done, histological confirmation	None	Dead
3	Emovon (31)	2003	Kidney-Pancreas	46/F, 540 days	HC, nephritis, septic shock	No PCR, histopathology confirmation	RBV + i.v. Ig	Alive, graft intact
4	Rosario (36)	2006	Kidney	58/M, 22 days	Multiorgan failure, colitis	PCR: +blood, +stool	None; died prior to dx	Dead
5	Alsaad (37)	2007	Kidney	19/M, 12 yr	HC, pneumonia	PCR: +urine/no serum testing	CDV	Alive, graft intact
6	Keswani (38)	2007	Kidney	5/M, 65 days	HC, gastroenteritis	PCR: +urine, +serum	CDV	Alive, graft intact
7	Saquib (39)	2009	Kidney	51/F, 6 yr	Pneumonitis, diarrhea, HA, no nephritis/HC	PCR: +urine, serum, stool, BAL	CDV + i.v. Ig	Alive, graft intact
8			Kidney	62/M, 29 days	PNA, colitis	PCR: −urine, +serum, +stool	CDV + i.v. Ig	Alive, graft intact
9	Barraclough (26)	2009	Kidney	68/M, 14 days	HC, nephritis, severe sepsis with respiratory compromise	PCR: +urine, +serum, −CSF	CDV + i.v. Ig	Alive, graft intact
10	Gaspert (6)	2009	Kidney	64/M, 60 days	HC, nephritis, pneumonitis	PCR: +urine, +serum, +BAL	None	Alive, graft loss
11	Kozlowski (5)	2010	Kidney	44/M, 20 days	HC, nephritis, pneumonitis	PCR: +BAL	GCV	Alive, graft loss
12	Watcharananan (3)	2011	Kidney	unkn	HC, nephritis	PCR: +serum	None	Alive, graft intact
13			Kidney	unkn	HC, orchitis, diarrhea	PCR: +serum	CDV + i.v. Ig	Alive, graft intact
14			Kidney	unkn	HC, pneumonitis, orchitis	PCR: +serum	CDV	Dead
15			Kidney	unkn	HC, URI, orchitis	PCR: +serum	CDV	Alive, graft intact
16			Kidney	unkn	HC, orchitis, graft rejection	PCR: +serum	CDV + i.v. Ig	Alive, graft intact
17			Kidney	unkn	HC, nephritis, enteritis	PCR: +serum	None	Alive, graft intact
18			Kidney	unkn	HC, nephritis enteritis	PCR: +serum	None	Alive, graft intact
19			Kidney	unkn	HC, leukopenia, enteritis	PCR: +serum	None	Alive, graft intact
20	Varma (20)	2011	Kidney-Pancrease	57/M, 11 days	Fever, neutropenia/leukopenia, nephritis	PCR: +serum	i.v. Ig	Alive, graft intact
21	Sujeet (40)	2011	Kidney	65/F, 3 yr	HC, nephritis, enteritis, respiratory symptoms	PCR: +serum	CDV	Alive, graft intact
22	Parasuraman (18)	2013	Kidney	44/M, 22 days	HC, nephritis, pneumonitis, gastroenteritis	PCR: +urine, +serum	CDV, i.v. Ig	Alive, graft intact
23	Dawood (16)	2014	Kidney	70/F, 810 days	HC, nephritis, gastroenteritis	PCR: +urine, +serum, +stool	CDV, i.v. Ig	Alive, graft intact
24			Kidney	60/F, 28 days	HC, nephritis, gastroenteritis	PCR: +blood, +urine, +stool	CDV, i.v. Ig	Alive, graft intact
25	Lachiewicz (17)	2014	Kidney	20/F, 2 yr	Nephritis, URI	PCR: +urine, +serum	CDV, i.v. Ig	Alive, graft intact
26	Rady (41)	2014	Kidney	63/M, 42 days	HC, nephritis, gastroenteritis	PCR: +urine, serum not performed	GCV, i.v. Ig	Alive, graft intact
27	Park (42)	2015	Kidney	32/F, 180 days	HC, nephritis, pneumonitis	PCR: +urine, +serum	RBV, i.v. Ig	Alive, graft intact
28	Index case	2016	Kidney	45/M, 42 days	HC, nephritis, pneumonitis	PCR: +urine, +serum	i.v. Ig	Alive, graft intact
29	Veer (43)	2017	Kidney	75/F, 365 days	HC, nephritis	PCR: +urine, +serum	i.v. Ig	Alive, graft intact

BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; CDV, cidofovir; dx, diagnosis; F, female; GCV, ganciclovir; HA, headache; HC, hemorrhagic cystitis; M, male; PCR, polymerase chain reaction; PNA, pneumonia; RBV, ribavirin; unkn, unknown; URI, upper respiratory infection; +, positive; −, negative.

kidney allograft losses. In all, 21 case patients (72%) received additional drug interventions along with reduction of their immunosuppressive regimen. Cidofovir, used in 14 of 20 cases, was the most commonly used antiviral agent, either alone or in combination with i.v. Ig.

The first step in standard-of-care for HAdV in transplant recipients is reduction of the immunosuppressive regimen. This intervention is often effective at resolving cases of hemorrhagic cystitis and nephritis.[3,14] The usual indication for additional therapies of antiviral or i.v. Ig is progressive disease despite immunosuppression reduction.[3,26] A PCR quantification of 1 log reduction within 2 to 3 weeks is considered a therapeutic response.[19] Antiviral therapies in kidney transplant recipients include cidofovir, ganciclovir, ribavirin, and brincidofovir and i.v. Ig.[27,28] Cidofovir, the most commonly used antiviral agent, with activity against all serotypes of HAdV, is a cytosine purine analogue that leads to chain termination.[27,28] The primary adverse effect is hematological as well as kidney toxicity.[29] Cidofovir is not considered a preferred therapy in kidney transplant recipients owing to clearance by the kidney and risk of nephrotoxicity. Brincidofovir (formally CMX101) is a new lipid derivative of cidofovir. The lipid formulation allows increased intracellular penetration that minimizes proximal tubular accumulation, and as such, may reduce the risk of nephrotoxicity.[28] The AdVise Study (NCT02087306), a currently completed phase III trial, is predominantly a study of hematopoietic stem cell recipients with small subset of solid organ transplant recipients, evaluating brincidofovir for HAdV disease. Results are expected to be reported soon.[28,30] Ganciclovir, a 1-phoshorylated purine analog, has limited effectiveness in HAdV, but there are case reports of its use.[2,4,28] Ribavirin, a nucleoside analogue of guanosine, is also not generally recommended due to *in vitro* activity against only subgroup C of HAdV. However, in the posttransplantation population, subgroup C is a common cause of disease.[1,27,31] Intravenous Ig is proposed to promote antiviral activity or to provide passive immunotherapy.[32,33] Intravenous Ig has been used in combination with cidofovir or as a single agent.

In conclusion, in kidney transplant recipients, HAdV is an uncommonly recognized, but potentially serious, infectious complication. This case reaffirms the clinical context in which to consider such a viral source of infection in kidney transplant recipients. We report the successful management of disseminated HAdV with i.v. Ig as a single agent along with reduction of immunosuppressive therapy. Ongoing prospective studies of HAdV surveillance and antiviral strategies are needed to improve outcomes in this high-risk group.

DISCLOSURE

All the authors declared no competing interests.

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