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NOVEL ID CASES

Human Adenovirus 11 in 2 Renal Transplant Recipients: Suspected Donor-Derived Infection

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Background. Human adenovirus (HAdV) infections can lead to high mortality in solid organ transplant (SOT) recipients, with rare reports of donor-derived infection.

Methods. Two renal transplant recipients with HAdV-11 infection who received kidneys from the same donor are described. Whole-genome sequencing (WGS) was performed.

Results. WGS showed 100% nucleotide sequence identity for the 2 HAdV-11 isolates. The patients presented with distinct clinical syndromes, and both were treated with brincidofovir.

Conclusions. Donor-derived HAdV infection is presumed to be low; however, disseminated HAdV in SOT recipients can be severe, and clinicians should be aware of the clinical course and treatment options.

Keywords. adenovirus; renal transplantation; brincidofovir.

Human adenovirus (HAdV) infections are usually mild and self-limited in immunocompetent patients, but can cause severe disease and even death in immunocompromised hosts [1, 2]. Severe HAdV disease has been best characterized in the hematopoietic stem cell transplant population, with more limited incidence data in the solid organ transplant (SOT) population [3]. Among all SOT patients, HAdV viremia has mostly been described as causing symptomatic disease in liver transplant recipients, pediatric SOT recipients, recipients with discordant donor-recipient HAdV serologic status, and recipients who require antilymphocyte globulin [2, 4]. Disease manifestations vary depending on the transplanted organ and the causative HAdV serotype.

In the renal transplant population, HAdV infection predominantly leads to genitourinary manifestations, including hemorrhagic cystitis (associated with HAdV-7, 11, 34, and 35) and tubulointerstitial nephritis (associated with HAdV-11, 35, 37) [5], although disseminated disease has also been described (associated with HAdV-11, 33, 34, 35, and 40) [6, 7]. Given limited data on HAdV latency in renal tissue, donor-derived infections can be difficult to distinguish in this population.

The following report describes 2 probable cases of donor-derived HAdV transmission in 2 patients who received renal transplants from the same donor. Both patients were diagnosed with disseminated infection with HAdV-11 in the early post-transplant period, the clinical syndrome differed between the 2 patients, and both patients had unique features compared with prior literature reports describing HAdV-11 infection.

METHODS

We completed a retrospective chart review for 2 transplant recipients who were diagnosed with disseminated HAdV infection. Information including the clinical course, key laboratory features, and pathology results were extracted from the electronic medical record. This report did not require approval from an ethics board.

HAdV identification was performed on donor and both renal transplant recipient samples. HAdV-positive specimens obtained from recipients including serum, stool, and nasopharyngeal (NP) swab as well as fixed, paraffin-embedded (FFPE) tissue specimens from the donor and recipients were sent to the Centers for Disease Control and Prevention (CDC) for further characterization. Total nucleic acid was extracted from 200 µL of the serum, stool, and NP swab specimens using the NucliSENS easyMAG (BioMerieux, Durham, NC, USA) following the manufacturer's instructions, and HAdVs were typed by polymerase chain reaction (PCR) and sequencing of a partial region of the hexon gene [8]. HAdV was isolated from stool and NP specimens on A549 cells, and whole-genome sequencing (WGS) was performed on the virus isolates as previously described [9]. WGS obtained from this study and sequences from GenBank were aligned using MAFFT in Geneious 10.0.9 (Biomatters, Auckland, New Zealand). DNA was extracted

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from FFPE renal tissue biopsy specimens using the QIAamp DNA Mini Kit (Qiagen Inc., Valencia, CA, USA) and amplified and sequenced by a PCR assay targeting the hexon gene [10].

RESULTS

Clinical Course

Donor

The organ donor was a young woman who progressed to brain death after a drug overdose. There were no documented respiratory, ophthalmic, or gastrointestinal symptoms during the week before her death. All standard screening before organ procurement was negative. HAdV real-time PCR (rPCR) was negative on both the serum collected on the date of death and banked serum during a retrospective analysis. The biopsy samples that had been obtained from the right and left kidneys before organ procurement were re-examined, and immunohistochemical (IHC) staining and PCR for HAdV were negative.

Once HAdV infections were identified in the 2 kidney recipients, there was concern for the source being the organ donor, and thus organ procurement organization (OPO) was notified. A third organ (heart) had been allocated to a different institution; the heart transplant recipient remained asymptomatic, and no further testing was performed.

Renal Transplant Patient 1

A 67-year-old man with a medical history of end-stage renal disease (ESRD) due to chronic hypertensive nephropathy underwent deceased donor renal transplant (DDRT), donor cytomegalovirus (CMV) immunoglobulin G (IgG)+/recipient IgG+, and donor Epstein-Barr virus (EBV) IgG-/recipient IgG+, with an initial post-transplant course complicated by delayed graft function and early borderline rejection requiring 5 days of high-dose prednisone (100 mg per os [PO] daily). His renal function subsequently improved, and he was discharged to a facility for post-transplant care on postoperative day (POD) 6 on an immunosuppressive regimen of belatacept, tacrolimus, prednisone, and mycophenolate mofetil. Starting on POD 20, he developed diarrhea (5–6 watery bowel movements daily), poor oral intake, fevers (39°C), and malaise. Initial infectious workup of the diarrhea on POD 24 was negative. However, he re-presented to the hospital on POD 32 with continued diarrhea, fevers, weakness, dehydration, and a 19-kg weight loss since transplant. His laboratory findings were significant for acute kidney injury without hematuria and transaminitis (Supplementary Table 1). Routine blood and urine cultures, serum CMV, EBV, BK, HAdV rPCR, and hepatitis A and B serologies were all negative. On POD 34, his serum was HAdV positive (cycle threshold [Ct], 24.5). Given the severity of his symptoms with evidence of disseminated HAdV infection, he was treated with brincidofovir on POD 36 via a clinical trial regimen (NCT02596997).

Following initiation of brincidofovir, he defervesced slowly with fever resolution on POD 46 and liver enzyme normalization around POD 55. An endoscopic retrograde cholangiopancreatography was performed without significant findings, and the consulting biliary team proposed that his hepatitis was likely secondary to HAdV infection. Weekly to biweekly HAdV rPCRs were performed from collected sera, with 2 negative results documented (POD 102 and POD 123) before brincidofovir discontinuation. At the conclusion of treatment, he was asymptomatic with no further diarrhea and improved appetite, and his renal graft was functioning well.

Renal Transplant Patient 2

A 64-year-old woman with a medical history of ESRD secondary to hypertension, diabetes, and systemic lupus erythematosus underwent DDRT on the same day as Patient 1 and received a kidney from the same donor. She initially did well in the postoperative period and was discharged to a facility specifically for post-transplant care on an immunosuppression regimen of belatacept, tacrolimus, mycophenolate mofetil, and prednisone. She subsequently developed hematuria on POD 33, which was initially attributed to a double-J ureteral stent that was then removed on POD 37. However, she continued to experience persistent, painless hematuria and developed new acute kidney injury (Supplementary Table 1). On POD 42, she was admitted for further evaluation including a renal biopsy, which had positive HAdV IHC staining (Figure 1). A serum was HAdV positive (Ct 37.0) on the same day. Given evidence of HAdV nephritis and worsening renal function, brincidofovir via the same clinical trial protocol regimen (NCT02596997) was initiated on POD 47.

The patient's hematuria resolved shortly after starting therapy, and the renal graft was functioning well. She had a HAdV-negative serum on POD 102 and a subsequent serum that was weakly positive on POD 116 (Ct 40.0). She completed brincidofovir, although she continued to have positive HAdV with high Ct's (>40).

Identification and Sequencing of HAdV

Renal Transplant Patient 1

Renal transplant patient 1 had several specimens tested for HAdV (Table 1). A renal biopsy was performed on POD 5 due to concern for early rejection, which was positive for HAdV by tissue-based conventional PCR, although IHC staining was negative. Sequencing showed highest nucleotide identities with HAdV-11. A clinical laboratory multiplex PCR panel on a stool sample on POD 53 was negative for HAdV-40 and -41; however, HAdV-11 was later identified at the CDC. The serum sample was also identified as HAdV-11. HAdV-11 WGS was obtained from the virus isolated from the stool specimen and submitted to GenBank (accession no. MT505438).

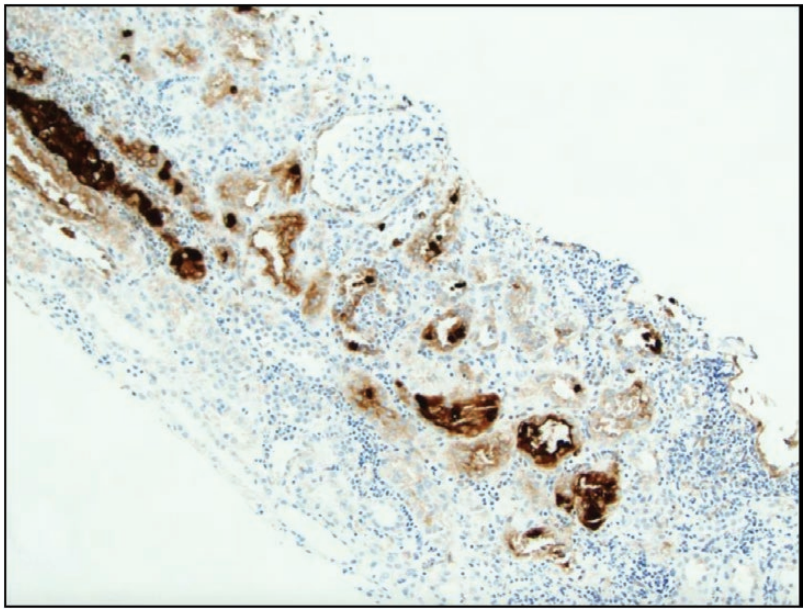

Figure 1. Renal biopsy from renal transplant patient 2. The image at 20x magnification shows immunohistochemical staining with the adenovirus antibody. There is positive reactivity (brown staining) within tubular lumens, and the nuclei of the tubular epithelial cells are labeled. The glomerulus is at the top, and the center of the core is negative for reactivity, indicating the tubules as the primary site of infection.

Renal Transplant Patient 2

Renal transplant patient 2 also had several specimens that were tested for HAdV (Table 1). Both IHC and tissue-based PCR were positive from the renal biopsy on POD 42 when she presented with symptoms of hematuria (although initial post-transplant renal biopsies were negative), and sequencing showed highest identities with HAdV-11. Her POD 42 serum and NP swab were identified as HAdV-11 (HAdV-11 WGS, GenBank accession no. MT505439), with 100% nucleotide sequence identity compared with the stool isolate from patient 1.

DISCUSSION

Disseminated HAdV has been described in the SOT population and can present due to de novo infection, reactivation, or donor-derived infection [11–13]. De novo infections can be identified based on seasonality of HAdV and surveillance data for respiratory viruses for a given geographical region. Cases

Table 1. Human Adenovirus Detection and Identification for Renal Transplant Patient 1 and Patient 2

Detection and Identification Method	Renal Transplant Patient 1 Result	Renal Transplant Patient 2 Result
Serum HAdV real-time PCR and typing[a]	Positive, Ct 24.5 HAdV-11 (POD 34)	Positive, Ct 37.9 HAdV-11 (POD 42)
IHC staining, renal allograft biopsy	Negative (POD 5)	Immunoreactive for HAdV (POD 42)
PCR and sequencing,[b] renal allograft biopsy	Positive for HAdV HAdV-11 (POD 5)	Positive for HAdV HAdV-11 (POD 42)
Stool multiplex PCR panel (HAdV types 40/41), clinical laboratory	Not detected (POD 53)	Not performed
Stool HAdV real-time PCR, typing and whole-genome sequencing	Positive, Ct 22.0 HAdV-11 GenBank accession no. MT505438[c] (POD 53)	Not performed
Nasopharyngeal swab real-time PCR, typing and whole-genome sequencing	Not performed	Positive, Ct 36.3 HAdV-11 GenBank accession no. MT505439[c] (POD 42)

Abbreviations: Ct, cycle threshold; HAdV, human adenovirus; PCR, polymerase chain reaction; POD, postop day.

[a]Adenoviruses were typed by PCR and sequencing of a partial region of the hexon gene [8].

[b]Renal tissue biopsy specimens were amplified and sequenced by an HAdV PCR assay [10].

[c]Virus isolates showed 100% nucleotide sequence identity.

can be linked to reactivation when the surrounding environment and situation make a de novo infection unlikely, including cases that have occurred in the hospital setting with no concurrent nosocomial outbreaks or sick contacts identified [14]. Pettengill et al. described a probable donor-derived HAdV infection in 2 renal transplant recipients from the same donor who were infected with HAdV-34 shortly after transplant [15]. HAdV-34 infections have been demonstrated to cause persistent shedding in the urine of renal transplant recipients in the absence of symptoms, which supports the possibility of HAdV latency and donor-derived infection.

In the 2 patients described, there was 100% nucleotide sequence identity between the stool HAdV-11 virus isolate from patient 1 (GenBank accession no. MT505438) and the NP HAdV-11 virus isolate from patient 2 (GenBank accession no. MT505439). Both isolates had 99.3% nucleotide sequence identity with HAdV-11 prototype strain genome sequence (accession no. AY163756.1) available in GenBank. The timing of infection and the 100% nucleotide sequence identity of HAdV-11 in the 2 renal transplant patients provide evidence that the donor is the likely source. HAdV-11 is relatively rare in the environment [16]. The 2 case patients did briefly overlap at the post-transplant facility, but no patients or health care workers at the facility were reported to have HAdV infection. Most of the guests at the facility were immunocompromised; thus, the other residents would be potentially high risk to acquire HAdV as well if transmission occurred at the facility. The 2 patients also overlapped in the hospital during the time of transplantation; however, none of the transplant surgeons, surgical staff, or nurses and technicians were noted to have HAdV infection or symptoms (although asymptomatic infection cannot be ruled out). In terms of the donor, the HAdV rPCR was negative from the sera and renal biopsy samples. These findings indicate that the donor was not overtly viremic at the time of organ procurement; however, it is possible that she had viremia below the limit of detection. The negative staining and PCR from the renal biopsies may indicate that she had limited infection or latency in the renal tissue, or that the tissue biopsied did not contain HAdV (although it may have been present in other geographical areas of the kidneys).

Interestingly, the 2 patients described presented with distinct and dissimilar clinical syndromes, despite infection with the same HAdV-11. Possible explanations include differences in host factors, varying inoculums of HAdV transmitted from the donor kidney, and/or varying levels of immunosuppression. A unique feature of this report was the successful use of brincidofovir, which is a lipid conjugate of the nucleotide analog cidofovir and is active against all types of HAdV [17]. Brincidofovir is not nephrotoxic like cidofovir and achieves high intracellular drug levels. Although brincidofovir has been shown to prevent adenovirus-induced mortality in animal models and was associated with sustained adenovirus viral load decrease and survival advantage in pediatric HSCT patients with severe or disseminated adenovirus, it is not currently Food and Drug Administration–approved for treatment of disseminated adenovirus [17, 18]. In the cases described here, both patients were treated successfully with brincidofovir as part of the clinical trial. Future studies should address use of brincidofovir for disseminated and severe adenovirus infections, especially in the SOT population.

Although HAdV infections in the SOT population are rare, infections are associated with severe disease and high mortality. There are no specific guidelines currently that recommend screening either donors or recipients in the post-transplant period. Screening may not be a valuable tool as many patients may be viremic but are asymptomatic [19]. However, given the possibility of severe disease that could potentially lead to graft failure and/or death, HAdV infection should be considered in the post-transplant period in the context of fevers, diarrhea, and/or hemorrhagic cystitis or tubulointerstitial nephritis. Clinicians must maintain a high index of suspicion and consider disseminated HAdV in the differential for solid organ transplant recipients.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. Patient consent was obtained from both patients. Institutional Review Board and ethics' board were not required for this work, since, as a case report, it does not produce generalizable knowledge.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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