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MAJOR ARTICLE

Epidemiology and Outcomes of Early-Onset and Late-Onset Adenovirus Infections in Kidney Transplant Recipients

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Objective. Adenovirus (ADV) infection after kidney transplantation (KT) causes significant morbidity. Patient characteristics and outcomes of ADV infection in KT recipients were investigated.

Method. All adult KT recipients with ADV infection between January 2015 and June 2019 were included. ADV infection/disease was defined as detection of ADV DNA in clinical specimens/plus symptoms. Clinical and laboratory findings, treatments, and outcomes were assessed.

Results. Adenovirus infection was diagnosed in 24 of 751 (3.2%) KT recipients. Twenty (83%) were male with a median age of 47 years (interquartile range [IQR], 36–58). Fifteen (63%) underwent deceased donor KT, and 13 (54%) received induction therapy. Twenty-one (88%) and 4 (17%) patients developed hemorrhagic cystitis and disseminated disease, respectively. There were equal distributions of early-onset (EOI) (≤3 months) and late-onset (LOI) (>3 months) infections. Patients who were diagnosed with EOI had lower median absolute lymphocyte counts compared with those with LOI (735/mm^3 [IQR, 543–1123] vs 1122/mm^3 [IQR, 784–1344], $P = .04$). All achieved resolution after reduction of their immunosuppression regimen and 13 (54%) received cidofovir therapy. Eighteen (75%) developed allograft dysfunction, of which 67% were transient. One (4%) underwent nephrectomy for allograft failure and 1 (4%) died (non-ADV–related). Patients with EOI were more likely to receive cidofovir therapy (75% vs 33%, $P = .04$) and develop other opportunistic infections (75% vs 8%, $P < .001$).

Conclusions. Adenovirus infection after KT typically involves a genitourinary system and transiently impairs an allograft function. Those who developed early infection tend to have more lymphopenia, coinfection, and receive antiviral therapy.

Keywords: absolute lymphocyte count; cidofovir; cytomegalovirus; hemorrhagic cystitis; human adenovirus; lymphopenia.

INTRODUCTION

Adenovirus (ADV) is a nonenveloped double-stranded DNA virus that can cause a wide variety of clinical symptoms in humans. Adenovirus infection usually is asymptomatic or mild in immunocompetent individuals, but it can cause substantial morbidity in immunocompromised individuals [1]. In kidney transplant (KT) patients, ADV can cause localized and invasive end-organ diseases, including hemorrhagic cystitis, nephritis, pneumonitis, hepatitis, and gastroenteritis, which occasionally result in severe disseminated infection affecting multiple organs [2]. Only a few published reports mention the epidemiology of ADV infection in adult KT recipients. Our team retrospectively reviewed the incidence of ADV infection in adult KT recipients, and it was approximately 4.9% [3, 4]. As well as clinical and histopathological findings, nucleic acid amplification testing (NAAT) has been utilized for the diagnosis and monitoring of ADV infection after KT [2]. Virus-specific immune monitoring has recently been explored in the management of solid organ transplant (SOT) recipients [5, 6]. A low absolute lymphocyte count (ALC) is associated with early ADV infection resulting in significant morbidity after KT [3]. In a recent study, the restoration of ALC and ADV-specific T-cell immunity was correlated with viral clearance in KT recipients [7]. The management of ADV infection in SOT recipients mainly involves the reduction of their immunosuppression regimen combined with cidofovir therapy. For the last few years, NAAT and cidofovir have been accessible more at our transplant center. In the present study, we investigated the incidence of ADV infection after KT, aspects of

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its epidemiology, diagnosis, and management, and patient outcomes during the study period. Severe or disseminated ADV infection can require cidofovir therapy, but clinicians may hesitate to administer it to KT recipients in view of potential drug-related nephrotoxicity. Herein, we report our experiences in the management of ADV infection in KT recipients using cidofovir, in terms of clinical and virological resolutions, adverse reactions, allograft outcomes, and rates of rejection after therapy.

METHODS

All adult KT recipients diagnosed with ADV infection between January 2015 and June 2019 at a single transplant center in Bangkok, Thailand, were included in the present study. At our center, trimethoprim/sulfamethoxazole for pneumocystis prophylaxis, acyclovir for herpes simplex virus prophylaxis, and isoniazid for latent tuberculous infection therapy (regardless of status) were prescribed in all patients. Surveillance testing for cytomegalovirus (CMV) infection was performed due to a high prevalence of CMV-seropositive recipients, except for those requiring antithymocyte globulin induction therapy when (val) ganciclovir prophylaxis was implemented. Instead, surveillance for ADV infection was not performed routinely. Only patients clinically suspected of ADV infection or exhibiting a consistent etiology underwent investigation, and other pathogens that were potentially responsible for their symptoms were excluded in the patients included in the study. Adenovirus infection was defined as detection of ADV by NAAT in plasma or organ-specific specimens. Adenovirus disease was defined as ADV infection combined with at least 1 specific organ symptom. Disseminated ADV disease was defined as ADV disease with the involvement of at least 2 specific organs. Early (EOI) and late (LOI) onset ADV infection was defined as the occurrence within and after 3 months, respectively. Adenovirus DNA loads in plasma and urine specimens were measured via quantitative real-time polymerase chain reaction (PCR) assays (Adenovirus R-Gene US Real-Time PCR kit, bioMérieux, Marcy l'Etoile, France, from January 2015 until August 2018, and Adenovirus ELITe MGB Kit, ELITech Group SpA, Turin, Italy, thereafter). Adenovirus DNA load was reported as log10 copies/mL with limits of quantification of 2.0–6.0 log10 copies/mL for the R-Gene kit and 2.4–6.0 log10 copies/mL for the ELITe MGB kit. Adenovirus DNA in respiratory specimens was measured via qualitative PCR assays (xTAG Respiratory Viral Panel, Luminex Corporation, Austin, TX). Imaging and histopathologic analyses were performed as appropriate based on clinical indications. Plasma ADV DNA loads were determined at the time of diagnosis and twice weekly after treatment until no ADV DNA load was detected in 2 consecutive tests. Clinical resolution was defined as resolution of all symptoms. Virological resolution was defined as undetectable ADV DNA load in plasma or urine on 2 consecutive occasions. Demographic, clinical, laboratory, and virological data pertaining to all patients were recorded, as were treatment details. Intravenous (IV) cidofovir at a dose of 5 mg/kg, 1 mg/kg 3 times weekly, or 0.5 mg/kg 3 times weekly (those with creatinine clearance <50 mL/min) and IV immunoglobulin (IVIG) therapy at doses ranging from 0.5–2.0 g/kg was prescribed based on current guidelines [8]. Outcomes were recorded, including clinical and virological resolution, patient survival, allograft function, and opportunistic infection other than ADV. Allograft function was calculated as the estimated glomerular filtration rate as determined via either the Cockcroft-Gault Formula, the Modification of Diet in Renal Disease Study Equation, or the Chronic Kidney Disease Epidemiology Collaboration equation. Transient allograft dysfunction was defined as any estimated glomerular filtration rate (eGFR) reduction compared to baseline that subsequently returned to baseline after the resolution of infection. Allograft failure and loss was defined as an irreversible estimated glomerular filtration rate reduction requiring chronic hemodialysis and/or retransplantation. The Institutional Review Board of the Faculty of Medicine of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, approved the study protocol and waived the requirement to obtain any informed consent.

Statistical Analyses

Patient demographic data and clinical characteristics were assessed via descriptive analysis. Categorical data were described as absolute and relative frequencies, and continuous data were described as medians with interquartile ranges (IQRs). Clinical and laboratory findings, treatments, and outcomes in those with EOI and LOI were compared via the Mann-Whitney test and χ^2 test for continuous and categorical data, respectively. *P* values <.05 determined via a 2-tailed test were considered statistically significant. Statistical analyses were performed with Stata statistical software (version 15, StataCorp, LLC, College Station, TX).

RESULTS

Epidemiology and Demographic Data

During the study period, 751 KTs were performed at our transplant center, and of these, 24 (3.2%) patients subsequently were diagnosed with ADV infection. Each and overall patient characteristics are shown in Table 1 and 2, respectively. Twenty (83%) patients were male and the median age was 47 years (IQR 36–58 years). Twenty-three (96%) patients received their first KT, and 15 patients (63%) received an allograft from a deceased donor. The most common etiology of end-stage renal disease was unknown (67%). Thirteen patients (54%) received induction therapy, including 12 (50%) who received antithymocyte globulin (ATG) and 1 (4%) who received interleukin-2 receptor antagonist. The majority was followed by maintenance therapy, including tacrolimus (75%), mycophenolate mofetil (83%), and prednisolone (100%). All donors and recipients were seropositive for CMV; hence, preemptive CMV monitoring was

Table 1. Baseline Characteristics of 24 Kidney Transplant Recipients

Characteristics, n (%)	N = 24
Age (median, IQR; years)	47 (36–58)
Male sex	20 (83)
Etiologies of end-stage renal disease	
- Diabetic nephropathy	2 (8)
- IgA nephritis	3 (13)
- Lupus nephritis	2 (8)
- Chronic glomerulonephritis	1 (4)
- Unknown etiology	16 (67)
Deceased-donor kidney transplantation	15 (63)
Immunosuppressive regimens	
Induction therapy	
- None	11 (46)
- Antithymocyte globulin	1 (4)
- Interleukin-2 receptor antagonist	12 (50)
Maintenance therapy	
- Tacrolimus	18 (75)
- Cyclosporine	6 (25)
- Mycophenolate mofetil	20 (83)
- Mycophenolate sodium	3 (13)
- Everolimus	1 (4)
- Prednisolone	24 (100)

Abbreviations: ADV, adenovirus; Ig, immunoglobulin; IQR, interquartile range.

undertaken after KT in the majority of cases. One patient underwent a second KT requiring ATG induction therapy and received IV ganciclovir prophylaxis during admission and subsequently was switched to preemptive approaches for 3 months after KT. Trimethoprim/sulfamethoxazole for pneumocystis prophylaxis, acyclovir for herpes simplex virus prophylaxis, and isoniazid for latent tuberculous infection therapy were prescribed in all patients.

Diagnosis of Adenovirus Infection

The distribution of ADV infection onset after KT included 7 (29%) patients who developed infection within 1 month after KT, 5 (21%) between 1 and 3 months, and 12 (50%) after 1 year. There were equal distributions of patients diagnosed with EOI and LOI. Seven (29%) and 17 (71%) patients developed infection during a wet season (June to October) and a dry season (November to May), respectively. Among 7 patients (no respiratory symptoms) who underwent an investigation for possible route of acquisition, nasopharyngeal (NP) swab for ADV PCR was detectable in 2 (29%) patients. Among the LOI group, there was no patients who developed rejection within 3 months prior to ADV infection.

The infections were classified as asymptomatic ADV (4%), ADV disease (4%), hemorrhagic cystitis (88%), upper respiratory tract infection (4%), lower respiratory tract infection (8%), gastroenteritis (4%), hepatitis (8%), interstitial nephritis (8%), epididymo-orchitis (8%), and disseminated disease (17%). Initial presentations included dysuria (83%), gross hematuria (83%), fever (46%), sore throat/runny nose (4%), shortness of breath (8%), reduced allograft function (8%), and testicular pain (8%). Urinalysis results included pyuria (n = 7), microscopic hematuria (n = 8), and proteinuria (n = 10). Twenty-two (92%) patients had a detectable plasma ADV DNA load. Among those, the median initial plasma ADV load was 5.3 log copies/mL (IQR, 3.5–6.0 log copies/mL), then it increased to a median peak plasma ADV load of 5.5 log copies/mL (IQR, 5.3–6.0 log copies/mL). Twenty (83%) patients had detectable ADV DNA in urine and the majority (85%) had a urine ADV load of 6.0 log copies/mL or more. Two (17%) had detectable ADV DNA in respiratory specimens. At diagnosis, the median total white blood cell count was 6255/mm^3 (IQR, 4208–10498/mm^3) and the median ALC was 883/mm^3 (IQR, 704–1398/mm^3). Probable ADV pneumonitis was diagnosed via the detection of ADV DNA from bronchoalveolar lavage fluid via PCR, histopathology revealed no viral cytopathic change, and ADV *in situ* hybridization was not detected. Adenovirus interstitial nephritis was defined as the detection of viral cytopathic changes in tubular cells; ADV *in situ* hybridization was detected in 1 patient (proven) and it was inconclusive in another. In 2 patients, a diagnosis of probable epididymo-orchitis was supported by compatible symptoms, Doppler ultrasonography, and detectable ADV DNA in urine without histopathological confirmation that was deemed to be invasive. Clinical, radiological, and histopathological findings of representative patients who were diagnosed with hemorrhagic cystitis, pneumonitis, epididymo-orchitis, and interstitial nephritis are shown in Figure 1.

Patients who were diagnosed with LOI were slightly more frequent to present with hemorrhagic cystitis compared to EOI (100% vs 75%, $P = .06$) Table 3. Patients who were diagnosed with EOI were more likely to be febrile compared with those with LOI, but this was not statistically significant (83% vs 58%, $P = .18$). Patients with EOI had lower median absolute lymphocyte counts (ALCs) than those with LOI (735/mm^3 [IQR, 543–1123] vs 1122/mm^3 [IQR, 784–1344], $P = .04$). There was no different in median peak plasma and urine ADV DNA load between 2 groups.

Management

After diagnosis the immunosuppression regimen was reduced in all patients. Mycophenolic acid was discontinued. The median dose reduction of mycophenolate mofetil was 1.5 g (IQR, 1.25–1.50 g). Calcineurin inhibitors were reduced to maintained trough levels of 3–5 ng/mL in patients who were on tacrolimus and 50–100 ng/mL in patients who were on cyclosporine. Prednisolone was maintained as tolerated, to a median dose of 7.5 mg/day (IQR, 5–15 mg/day). Thirteen (54%) patients received IV cidofovir with prehydration and posthydration with 1 L of 0.9% normal saline solution, and, of those patients, 10 (77%) received oral probenecid with dosing of a total of 4 g oral

Table 2. Patient Characteristics, Management, and Outcomes in 24 Kidney Transplant Recipients Diagnosed With Adenovirus Infection

Patient	Age (Years)	Sex	Type of KT	Induction Regimen	Maintenance Regimens	Onset After KT (Months)	Diagnosis	Plasma/urine Peak ADV DNA Load (Log Copies/mL)	Cidofovir	IVIG	Clinical Outcome/Other Infections	Allograft Outcome	Survived
1	37	M	LRKT	IL2RA	TAC Everolimus Pred	0.50	ADV-associated hemorrhagic cystitis	5.4/ > 6.0	Yes, 3 mg/kg/wk (divided as 3 times a wk) at wk 0 without oral probenecid	Yes, 0.5 g/kg at week 1	Resolved	Transient allograft dysfunction	Yes
2	45	M	DDKT	IL2RA	TAC MMF Pred	0.50	Disseminated ADV disease (hemorrhagic cystitis, right epididymo-orchitis)	> 6.0/> 6.0	Yes, 1.5–3.0 mg/kg/wk (divided as 3 times a wk) at wk 0,1 with oral probenecid	Yes, 2 g/kg (in 5 divided doses daily)	Resolved/ asymptomatic CMV infection	Transient allograft dysfunction	Yes
3	38	F	DDKT	IL2RA	TAC MMF Pred	0.50	ADV-associated hemorrhagic cystitis	4.2/> 6.0	Yes, 1.5–3.0 mg/kg/wk (divided as 3 times a wk) at wk 0,1 with oral probenecid	No	Resolved	Transient allograft dysfunction	Yes
4	58	M	LRKT	IL2RA	CsA MMF Pred	0.75	ADV-associated hemorrhagic cystitis	> 6.0/> 6.0	Yes, 5 mg/kg/wk at wk 0,1 with oral probenecid	No	Resolved/ asymptomatic CMV infection	Allograft dysfunction	Yes
5	42	M	LRKT	IL2RA	TAC MMF Pred	1	Asymptomatic ADV infection	3.6/4.6	No	No	Resolved/asymptomatic CMV infection	No allograft dysfunction	Yes
6	34	F	Re-DDKT	ATG	TAC MMF Pred	1	ADV-associated hemorrhagic cystitis, ADV interstitial nephritis	> 6.0/> 6.0	Yes, 1.5 mg/kg/wk (divided as 3 times a wk) at wk 0,1,2 with oral probenecid	Yes, 2.8 g/kg (in 7 divided doses daily)	Resolved, human parainfluenza URI, *E. coli* UTI	Allograft failure, acute antibody-mediated and T-cell–mediated rejection/graft loss	Yes
7	60	M	LRKT	None	CsA MMF Pred	1	ADV pneumonitis	< LLOQ/not detected	No	No	Organizing pneumonia, resolved/asymptomatic CMV infection	Transient allograft dysfunction	No (non-ADV – related)
8	56	M	LRKT	None	CsA MMF Pred	1.50	ADV-associated hemorrhagic cystitis	5.1/> 6.0	No	No	Resolved	Transient allograft dysfunction	Yes
9	42	M	LRKT	IL2RA	CsA MMF Pred	1.50	ADV-associated hemorrhagic cystitis	> 6.0/> 6.0	Yes, 5 mg/kg/wk at wk 0,1 without oral probenecid	No	Resolved/ESBL-producing *E. coli* UTI	Allograft dysfunction, acute T-cell–mediated rejection	Yes
10	36	M	DDKT	IL2RA	TAC MMF Pred	2	Disseminated ADV disease (hemorrhagic cystitis, left epididymo-orchitis, pneumonitis, hepatitis)	> 6.0/> 6.0	Yes, 3 mg/kg/wk (divided as 3 times a wk) at wk 0,1 with oral probenecid	Yes, 2 g/kg (in 5 divided doses daily)	Resolved/asymptomatic CMV infection	Transient allograft dysfunction	Yes
11	59	F	DDKT	IL2RA	TAC MMF Pred	2	ADV-associated hemorrhagic cystitis	5.7/> 6.0	Yes, 5 mg/kg/wk at wk 0,1 with oral probenecid	No	Resolved/*Enterococcus* spp. UTI, BKVAN	No allograft dysfunction	Yes
12	30	M	LRKT	None	CsA MMF Pred	3	ADV syndrome (fever with leukopenia)	5.5/N/A	Yes, 5 mg/kg/wk at wk 0, 1, 3, 5 with oral probenecid	No	Resolved/asymptomatic CMV infection	No allograft dysfunction	Yes

Table 2. Continued

Patient	Age (Years)	Sex	Type of KT	Induction Regimen	Maintenance Regimens	Onset After KT (Months)	Diagnosis	Plasma/urine Peak ADV DNA Load (Log Copies/mL)	Cidofovir	IVIG	Clinical Outcome/Other Infections	Allograft Outcome	Survived
13	53	M	DDKT	IL2RA	TAC MMF Pred	12	ADV-associated hemorrhagic cystitis, ADV interstitial nephritis	5.4/> 6.0	Yes, 3 mg/kg/wk (divided as 3 times a wk) at wk 0,1 without oral probenecid	Yes, 2 g/kg (in 5 divided doses daily)	Resolved	Allograft dysfunction	Yes
14	55	F	DDKT	None	TAC MMF Pred	16	ADV-associated hemorrhagic cystitis	> 6.0/5.0	Yes, 3 mg/kg/wk (divided as 3 times a wk) at wk 0, then 5 mg/kg/wk at wk 1, 3, 5 without oral probenecid	No	Resolved	No allograft dysfunction	Yes
15	29	M	LRKT	None	TAC MMF Pred	15	Disseminated ADV disease (hemorrhagic cystitis, hepatitis)	> 6.0/> 6.0	Yes, 5 mg/kg/wk at wk 0,1 with oral probenecid	No	Resolved	Transient allograft dysfunction	Yes
16	43	M	DDKT	None	CsA MMF Pred	22	Disseminated disease (hemorrhagic cystitis, gastroenteritis, upper respiratory tract infection)	5.7/> 6.0	No	Yes, 1 g/kg (in 3 divided doses daily)	Resolved/CMV syndrome, BKVAN	Transient allograft dysfunction	Yes
17	49	M	DDKT	IL2RA	TAC MMF Pred	22	ADV-associated hemorrhagic cystitis	< LLOQ/5.6	No	No	Resolved	Transient allograft dysfunction	Yes
18	62	M	DDKT	None	TAC MPS Pred	27	ADV-associated hemorrhagic cystitis	5.3/> 6.0	Yes, 3 mg/kg/wk (divided as 3 times a wk) at wk 0 with oral probenecid	No	Resolved	No allograft dysfunction	Yes
19	59	M	DDKT	None	TAC MMF Pred	36	ADV-associated hemorrhagic cystitis	> 6.0/> 6.0	No	No	Resolved	Transient allograft dysfunction	Yes
20	54	M	DDKT	IL2RA	TAC MPS Pred	39	ADV-associated hemorrhagic cystitis	5.0/> 6.0	No	No	Resolved	Allograft dysfunction	Yes
21	57	M	DDKT	None	TAC MMF Pred	40	ADV-associated hemorrhagic cystitis	> 6.0/> 6.0	No	No	Resolved	No allograft dysfunction	Yes
22	67	M	DDKT	None	TAC MPS Pred	47	ADV-associated hemorrhagic cystitis	3.9/> 6.0	No	No	Resolved	Transient allograft dysfunction	Yes
23	24	M	LRKT	None	TAC MMF Pred	59	ADV-associated hemorrhagic cystitis	5.1/> 6.0	No	No	Resolved	Transient allograft dysfunction	Yes
24	34	M	DDKT	IL2RA	TAC MMF Pred	63	ADV-associated hemorrhagic cystitis	5.3/> 6.0	No	No	Resolved	Allograft dysfunction, acute T-cell–mediated rejection	Yes

Abbreviations: ADV, adenovirus; ALC, absolute lymphocyte count; ATG, antithymocyte globulin; BKVAN, BK polyomavirus-associated nephropathy; CMV, cytomegalovirus; CsA, cyclosporine; DDKT, deceased-donor kidney transplantation; DNA, deoxyribonucleic acid; ESBL, extended-spectrum beta-lactamase; F, female; IL2RA, interleukin-2 receptor antagonist; IVIG, intravenous immunoglobulin; LLOQ, lower limit of quantification; M, male; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; LRKT, living-related kidney transplantation; N/A, not applicable; Pred, prednisolone; TAC, tacrolimus; UTI, urinary tract infection; wk, week.

probenecid,with 2 g 3 hours prior to infusion, 1 g 2 hours after infusion, and 1 g 8 hours after infusion. The details of cidofovir dosing are shown in Table 2. Five patients received weekly IV cidofovir at a dose of 5 mg/kg, 5 patients received 1 mg/kg 3 times per week, and 3 patients received 0.5 mg/kg 3 times per week (those with creatinine clearance <50 mL/min) for 2 consecutive weeks followed by every other week until clinical and viral clearance in most cases. Different doses of cidofovir was selected on clinician preference based on the doses that were recommended by an international guideline. Patients diagnosed with EOI were more likely to receive IV cidofovir therapy (75% vs 33%, $P = .04$) compared with those who diagnosed with LOI. Among 13 patients who received IV cidofovir, the creatinine increased in 9 (69%) patients after therapy and 5 (38%) returned to baseline. Allograft dysfunction occurred more frequently in patients who received IV cidofovir therapy compared with those withheld from therapy (38% vs 18%, $P = .66$) as well as those received once weekly (40%) compared with thrice-weekly regimen (40% vs 25%, $P = .57$), though the trends were not statistically significant. No patients developed uveitis, significant neutropenia, anemia, or proteinuria, or adverse reactions to probenecid, including fever, rash, headache, or nausea.

Six (25%) patients received IVIG at doses ranging from 0.5–2.0 g/kg as adjunctive therapy. After resolution, all patients were restarted gradually on mycophenolic acid closed to baseline dosing. Calcineurin inhibitors were kept at appropriate trough levels and low dose prednisolone was maintained.

Outcome

In all patients, the median time from diagnosis to clinical resolution of 9 days (IQR, 5–13 days) was significantly shorter than virological resolution of 46 days (IQR, 30–60 days) ($P < .001$). Infection completely resolved without complications in 23 patients (96%). One patient was diagnosed with probable ADV pneumonitis that was subsequently complicated by organizing pneumonia requiring a tapered course of prednisolone therapy. Recurrence with low-level ADV DNAemia that was not clinically significant occurred in 1 patient (4%) after the resumption of immunosuppressant. Ten patients (42%) developed opportunistic infections other than ADV, including CMV (including asymptomatic CMV infection; n=6), CMV syndrome (n=1), BK polyomavirus-associated nephropathy (n=2), human parainfluenza virus upper respiratory tract infection (n=1), urinary tract infection with *Enterococcus* spp. (n=1), *Escherichia coli* (n=1), and extended-spectrum beta-lactamase-producing *E. coli* (n=1). Patients diagnosed with EOI were more likely to develop opportunistic infection other than ADV (75% vs 8%, $P < .001$), including CMV coinfection (50% vs 8%, $P = .03$), compared with those diagnosed with LOI.

Eighteen (75%) patients developed allograft dysfunction, and 67% of these were transient. Three (13%) patients developed acute T-cell–mediated allograft rejection after therapy, and 1 (4%) of them developed concurrent antibody-mediated rejection. One patient (4%) underwent nephrectomy for allograft failure and 1 (4%) died from a non-ADV–related cause.

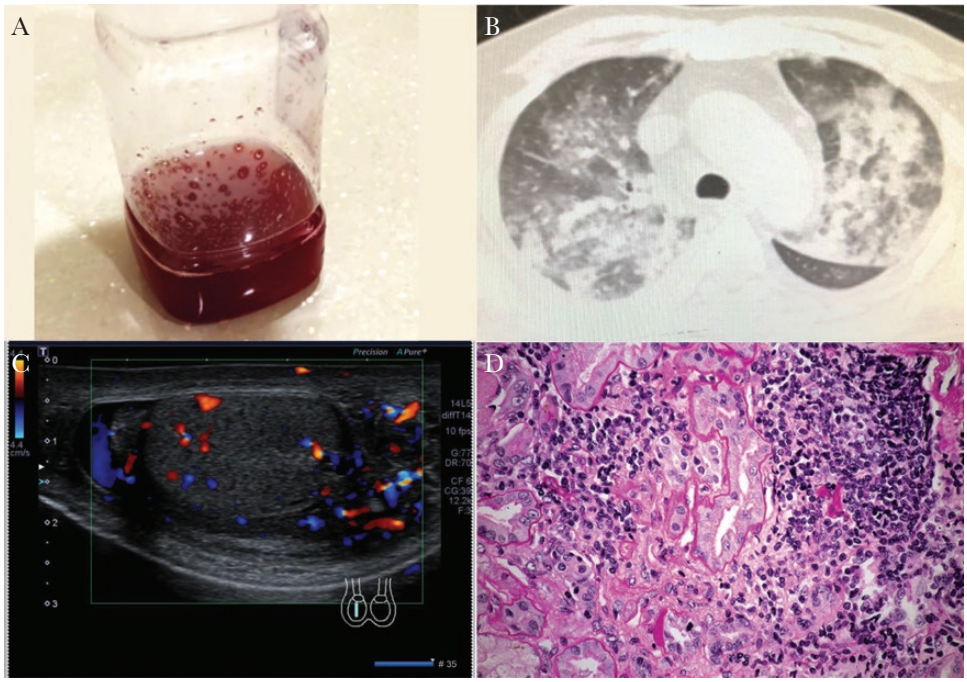

Figure 1. Clinical, Radiographic, and Histopathology Findings in Kidney Transplant Recipients Diagnosed With Adenovirus Infection A, Gross hematuria. B, computed tomography of the chest showed newly developed patchy ground glass opacities with overlying consolidation opacity as well as several scattering solid nodules in both lungs. C, Doppler ultrasonography of the testes showed relatively enlarged size and increased vascularity of the right testis without mass or abnormal echogenicity. D, histopathology findings of the renal allograft biopsy showed lymphoplasmacytic infiltration in the interstitium with tubular injury and focal tubulitis. (PAS X 400).

Table 3. Clinical, Laboratory, Management, and Outcome Data Derived From 24 Kidney Transplant Recipients Who Were Diagnosed with Early and Late Onset ADV Infection

	Early onset (n = 12)	Late onset (n = 12)	*P* value
ADV infection, n (%)			
- Asymptomatic infection	1 (8)	0	.30
- Hemorrhagic cystitis	9 (75)	12 (100)	.06
- Interstitial nephritis	1 (8)	1 (8)	>.999
- Hepatitis	1 (8)	1 (8)	>.999
- Upper respiratory tract infection	0	1 (8)	.30
- Pneumonitis	2 (17)	0	.14
- Gastroenteritis	0	1 (8)	.30
- Epididymo-orchitis	2 (17)	0	.14
- ADV syndrome	1 (8)	0	.30
- Disseminated infection	2 (17)	2 (17)	>.999
Clinical presentations, n (%)			
- Fever	10 (83)	7 (58)	.18
- Dysuria	9 (75)	11 (92)	.27
- Gross hematuria	9 (75)	11 (92)	.27
- Testicular pain	2 (17)	0	.14
- Shortness of breath	2 (17)	0	.14
Laboratory findings at diagnosis, median (IQR)			
- Total white blood cell count (cells/mm^3)	7670 (4013–10658)	6050 (4208–7423)	.37
- Absolute lymphocyte count (cells/mm^3)	735 (543–1122)	1122 (784–1344)	.04
- Peak urine ADV DNA load (log10 copies/mL)	6.0 (6.0–6.0)	6 (6.0–6.0)	>.999
- Peak plasma ADV DNA load (log10 copies/mL)	5.7 (5.1–6.0)	5.4 (5.1–6.0)	.70
Treatment, n (%)			
- Cidofovir	9 (75)	4 (33)	.04
- Intravenous immunoglobulin	4 (25)	2 (17)	.35
Outcome, n (%)			
- Time to virological resolution (median, IQR; days)	56 (35–60)	43 (28–52)	.24
- Time to clinical resolution (median, IQR; days)	10 (5–17)	6 (5–11)	.30
- Opportunistic infection other than ADV	9 (75)	1 (8)	<.001
- Cytomegalovirus coinfection	6 (50)	1 (8)	.03
- Normal allograft function	3 (25)	3 (25)	1.00
- Transient allograft dysfunction	6 (50)	6 (50)	1.00
- Allograft dysfunction	2 (17)	3 (25)	.62
- Allograft failure	1 (8)	0	.30
- Acute T-cell–mediated rejection	2 (17)	1 (8)	.54
- Antibody-mediated rejection	1 (8)	0	.30
- Hemodialysis required after transplantation	1 (8)	0	.30
- Mortality (non-ADV–related)	1 (8)	0	.30

Abbreviations: ADV, adenovirus; DNA, deoxyribonucleic acid; IQR, interquartile range; RBC, red blood cell.

DISCUSSION

Herein, we have reported the most recent and comprehensive data on the epidemiology, clinical characteristics, management, and outcomes of ADV infection in KT recipients from a retrospectively analyzed cohort at a single transplant center. The genitourinary tract was the most commonly involved system, followed by some unusual presentations rarely seen in clinical practice. Nucleic acid amplification testing with or without histopathological testing is the main diagnostic tool used to achieve a diagnosis. Patients who developed ADV infection early posttransplant seem to have more lymphopenia at diagnosis, opportunistic infection (other than ADV), and receive cidofovir therapy. Although reduction of the immunosuppression regimen combined with IV cidofovir evidently can achieve a favorable clinical and virological outcome, transient allograft dysfunction remains a substantial consideration.

Kidney transplant recipients have been considered to be at low to moderate risk of ADV infection compared with those who undergo liver or thoracic organ transplantation, likely due to less intense immunosuppression [9]. A large cohort study of KT performed previously at our center provided an opportunity to investigate this uncommon infection after KT. The

prevalence of ADV infection in KT recipients were decreased slightly during 2 periods of time approximately a decade apart, 4.9% from 2007 to 2010 [3], and 3.2% during the current study period of 2015 to 2019. Time to diagnosis varied similarly in the 2 studies, ranging widely from a few months to years after KT [3]. Although ADV infection can occur all year round without seasonal variability [10], the majority of ADV infection in our cohort occurred during the wet season. Kidney transplant recipients with ADV infection can present with symptoms ranging from absent or mild to severe disseminated disease [8]. The present cohort was concordant with previous studies with regard to similar initial presentations and organ involvement of ADV infection with hemorrhagic cystitis in the majority of patients. Nanmoku et al [11] recently reported a high incidence of ADV genitourinary tract infection (4.5%) in their cohort. In contrast, we also detected uncommon presentations of ADV infection that are somewhat unique and specific to immunocompromised patients, such as pneumonitis, epididymo-orchitis, and interstitial nephritis, due to the availability of NAAT and immunohistochemical testing at our institution, in which clinicians who are managing these patients should be aware of. In the present study, median initial and peak ADV loads were both >5 log copies/mL, which is greater than they were in a previous study [3].

Observations in the present study were concordant with our previous study in which patients with early infection (onset within 3 months after KT) that was more severe tended to have lower ALCs at weeks 1 and 3 than patients with late infections [3]. In the present cohort, half of the patients developed ADV infection within 3 months post-KT, and these patients exhibited variable ALCs. Nierenberg et al [12] reported that lymphopenia (<500 cells/mm^3) measured prior to transplantation is a potential tool for predicting opportunistic infection after liver transplantation. Absolute lymphocyte count indirectly represents impairment of nonspecific cell-mediated immunity (CMI) in these patients. Our team recently reported low nonspecific CMI as indicated by the total lymphocyte count and lymphocyte subset proportions ($CD4^+$ and $CD8^+$ T-cells), as well as ADV-specific CMI in patients diagnosed with ADV infection, wherein this immunity was later restored after resolution [7]. Because there is no commercial assay available for measuring ADV-specific immunity in clinical practice, we encourage the use of a practical and simple tool to at least stratify and predict those who may develop severe infection.

Although no ideal management strategy for ADV infection has been established, all patients underwent reduction of their immunosuppression regimen as recommended in a current guideline [8], including discontinuation of mycophenolate, maintenance of low calcineurin inhibitor trough level, and the lowest dose of prednisolone tolerated [2] in the present study. More than half of the patients received IV cidofovir (compared with a quarter in a previous study [13]) due to the recent increased availability of the medication at our institution. Cidofovir was considered to be cost-prohibitive in our resource-limited setting. Some patients were able to complete the induction phase but not the maintenance phase as recommended in the aforementioned guideline [8]. However, both early clinical and virological improvement in those patients would be less likely to require further treatment. The combination of an anti-ADV agent and optimized immunosuppression has been shown to improve clinical and virological outcomes, and the strategy reportedly facilitates more rapid clinical resolution although it takes approximately 2 months to achieve virological clearance. The present patients tolerated IV cidofovir well, without hematological or ocular toxicities. We found those who received IV cidofovir were more likely to develop allograft dysfunction. However, the majority of the patients developed transient increases in serum creatinine, which is known to be derived from multifactorial etiologies, including cidofovir exposure, but the incidence of permanent damage in this context is reportedly low [14]. Patients diagnosed with EOI were more likely to receive IV cidofovir therapy; this could be explained by the complexity of the infection during a period with more intense immunosuppression. We found less allograft dysfunction had occurred in those who received a once-weekly regimen compared with the thrice-weekly regimen (40% vs 25%) and a true explanation for this different outcome has been elucidating. However, we did not observe other significant complications apart from nephrotoxicity in our cohort.

Although a few patients did not receive oral probenecid (because a high urine drug concentration was achieved in order to treat ADV genitourinary tract infection), the allograft outcome was acceptable. This may have been due to aggressive IV saline hydration concomitantly with cidofovir therapy. However, it is important to monitor renal function closely (including proteinuria) both before and during treatment.

Anti-ADV agents were implemented in the majority of the current patients who were diagnosed with ADV disease, facilitating evaluation of the efficacy of these agents. Cidofovir with and without IVIG has been reported to be effective in some SOT, including KT recipients diagnosed with disseminated disease [15, 16]. The true efficacy of cidofovir and/or IVIG is difficult to assess based on outcome, because all patients underwent reduction of their immunosuppression regimen. Because there has been no randomized control trial of cidofovir and IVIG to support efficacy, a current guideline suggested considering those agents for severe or disseminated ADV disease and hypogammaglobulinemia, respectively [8].

Apart from antiviral agents and adjunctive therapies, it has been reported that ADV-specific immunity is related to ADV clearance in KT recipients [5, 7]. Allograft rejection may occur

as a consequence of reduction of an immunosuppressive regimen. Therefore, 1 goal is to balance immunosuppression during infection and maintain the allograft by resuming immunosuppression as soon as the infection is controlled. A future study measuring specific ADV-specific immunity in order to facilitate optimal management in this setting is encouraged. Although KT recipients with disseminated disease are at a high risk of mortality, there were no cases of disseminated disease-associated mortality in the present study. That was likely due to early diagnosis, prompt reduction of an immunosuppressive regimen, and vigilant management [6].

The current study had some limitations. There is an inherent possibility of bias due to the retrospective nature of the study. The true incidence of ADV infection likely was underestimated due to a lack of preemptive ADV load monitoring, which would have facilitated the diagnosis of asymptomatic ADV infection. Such preemptive ADV load monitoring currently is not advocated, and, in Humar et al [17], half of the patients developed transient and self-limiting reactivation without clinical significance. Accordingly, preemptive monitoring is not recommended in the aforementioned guidelines [8]. Additionally, approximately one-third of patients had CMV coinfection, a sole effect of each pathogen that contributes to the idea that the symptoms could be limited. An immunomodulatory effect of CMV infection is known to place patients at risk of infection from another opportunistic pathogen [18]. Last, because the rarity of the disease could limit a sample size, independent risk factors analyzed from multivariate analysis to investigate from this small cohort would not be allowed.

During recent years, ADV has remained a relatively uncommon pathogen that can cause genitourinary tract infection in adult KT recipients. Low ALC at the time of diagnosis may predict an increased risk of ADV infection in KT recipients early post KT. Effective management is facilitated by early diagnosis and is assisted by readily available NAAT, supportive care, and reduction of immunosuppression. This combination evidently can achieve favorable clinical and virological outcomes. Although transient worsening of allograft function may occur, it is not associated with high mortality.

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