Adenovirus Interstitial Nephritis After Kidney Transplant
Case Series and Literature Review

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Key Points
- Adenovirus Interstitial Nephritis has nonspecific clinical manifestation, and kidney biopsy played an essential role in establishing its condition.
- The most specific histopathological finding is interstitial nephritis with a granulomatous pattern.
- The evolution is favorable in most cases, and there was recovery of kidney function a few months after the diagnostic.

Abstract
Background Post-kidney transplant (KT) adenovirus (AdV) nephritis is a condition with potential for acute allograft dysfunction, and evidence on its management is scarce.

Methods This study is an original case series based on kidney biopsy (KB) of seven patients obtained at a health center specialized in kidney pathology from 2009 to 2023. We also performed a nonsystematic literature review on patients described in the literature.

Results KB was used to define the diagnosis of all patients. The average time to diagnosis after transplantation was 32.9 months. The most prevalent symptoms were fever, macroscopic hematuria, and dysuria. The GFR reduced on average four times in relation to the baseline GFR. The main findings of KB were acute tubular necrosis (100%), necrotizing granulomatous interstitial nephritis (100%), and viral inclusions (100%). The therapies used were human Igs, antivirals, and reduction of immunosuppression. The clinical course was favorable in six of the seven patients. Our literature review found 44 patients with AdV interstitial nephritis, and the outcome was favorable in most reported patients.

Conclusions AdV interstitial nephritis is a rare condition with important implications for KT recipients. KB plays a very important role in confirmation. This study fills gaps in the current literature on AdV interstitial nephritis and contributes to the understanding of this potential complication in the follow-up of KT recipients.

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Introduction
Modern immunosuppression regimens have provided kidney transplant (KT) recipients improved clinical outcomes —especially with a lower incidence of rejection[1] and increased allograft survival.[2] On the other hand, infections have become the main post-KT complication. In this context, viral infections have particular relevance because of their potential to cause acute and chronic allograft dysfunction.[2,3] Of particular note are polyomavirus (PyV),[3] the most common[4] (2%–6%)[2,5]; cytomegalovirus (CMV; 5.8%)[6]; and adenovirus (AdV; 4.1%).[7] The latter causes significant post-KT nephropathy, but

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current understanding of this nephropathy is limited in relation to the other viral infections.[5]

AdVs are nonenveloped double-stranded DNA viruses. They present 113 genotypes[8] divided into seven groups according to their molecular characters.[4] They are found globally, and their transmission is common up to 6 years of age.[4] Most patients do not have clinical repercussions.[4] However, AdV infection can be associated with more serious manifestations in immunocompromised patients, including disseminated disease and potentially fatal outcomes.[2,5] The most frequent histopathological findings in the kidney tissue are interstitial inflammation with granulomas, focal parenchymal necrosis, and nuclear ground-glass inclusions. Although characteristic, there is frequent overlap with other viral infections in kidney graft (CMV, PyV).[9]

Symptomatic AdV infection is a significant complication after KT,[10] and unlike what occurs with PyV, the Kidney Disease Improving Global Outcomes guidelines do not recommend screening for AdV in KT recipients.[5,11] AdV mainly causes hemorrhagic cystitis and tubulointerstitial nephritis.[2] Histopathological findings of AdV nephritis (AdVN) are often characterized by strong evidence of diffuse mononuclear interstitial inflammation on kidney biopsy (KB).[2]

The damage caused by AdV is caused by direct and indirect mechanisms. The cytopathic effects caused by the virus constitute direct aggression, and these are added to the inflammatory response triggered after the viral invasion of the tissue. Proinflammatory cytokines and their effects on cells trigger indirect injury to kidney tissue.[5] The association of this damage with the concomitant immune response provides consequences similar to transplant-related ischemia-reperfusion injury.[12]

AdVN diagnostic criteria are not standardized in the literature, and there is no single way to confirm the diagnosis.[13] Current studies confirm the diagnosis through the combination of histopathological evidence (light microscopy [LM] and/or electron microscopy [EM]), laboratory (detection of genetic material of AdV by immunohistochemistry [IH]), and clinical symptoms. The main differential diagnosis is PyV nephritis because CMV infection in allograft is exceptionally rare.[12]

The available knowledge about the clinical manifestations and histopathological characteristics of AdVN is incipient and primarily based on case reports.[5] Therefore, screening, diagnosis, and treatment proposals for this condition are limited in KT. Given these limitations, our study presents both a retrospective analysis of an original AdVN case series from a national reference center for kidney pathology and an independent nonsystematic review of cases reported in the literature.

Methods

Series of cases of post-KT AdVN nephropathy between January 2009 and December 2023 were obtained from KB reports from the Immunofluorescence and Electron Microscopy Laboratory of the University Hospital of the Federal University of Maranhão, Brazil, a tertiary care referral center and national reference center in nephropathology.

Patients receiving KT under investigation for allograft dysfunction were selected for this study on the basis of the result of KB suggestive of AdVN involvement. Sociodemographic (age, sex, and ethnicity), clinical (underlying kidney disease, time elapsed since KT, and reason for KB indication), and blood test (basal GFR, creatinine at the time of KB, and proteinuria) data were obtained from electronic medical records. GFR was calculated using the CKD Epidemiology Collaboration formula for all patients, except for one patient whose age was 16 years. In this case, the Schwartz formula was used. We described immunosuppressive therapy used, comorbidities and their respective therapies, serology for infectious agents, and clinical evolution of patients up to 6 months after AdVN diagnosis. The patients' blood test follow-ups were assessed using serum creatinine values after 3 and 6 months, as well as 24-hour proteinuria after 6 months.

All patients underwent allograft biopsy during the symptomatic period of viral nephropathy, which are mainly fever, hematuria, and dysuria. Kidney tissue samples were analyzed by LM, immunofluorescence, EM, and IH. For LM, hematoxylin-eosin staining, periodic acid–Schiff staining, Jones' methenamine silver staining, and Masson's trichrome staining were performed. The anti-C4d antibody test was performed with clone SP91 (Spring Bioscience). The diagnosis of AdV infection was established by observing characteristic findings of AdVN on KB confirmed by (*1*) urinary PCR for AdV[13] or (*2*) typical AdVN findings on EM as a crystalline arrangement of viral particles with a diameter between 70 and 80 nm.[13]

A nonsystematic literature review was conducted on reported cases of patients with post-KT AdVN. We searched the terms "kidney" and "adenoviridae infections," using the platforms PubMed (209 articles), Web of Science (133 articles), and Embase (89 articles), including articles in English until 2024. Three authors screened the articles to find case reports or case series. After excluding duplicate and out-of-scope articles, 30 studies were included in the final review, covering 44 patients.

Data were entered into Microsoft Excel tables and were subsequently analyzed using Stata 12.0 software. Categorical variables were described in terms of absolute and relative frequencies. Continuous variables were analyzed by calculating mean and SD. The study was approved by the Ethics Committee (Hospital Universitário da Universidade Federal do Maranhão/University Hospital/Federal University of Maranhao protocol 4.750.825).

Results

During the study period, 672 kidney biopsies were performed. Of these, seven patients (1.04%) were diagnosed with AdVN in the description of the allograft biopsy. The diagnostic criteria applied for each patient are summarized in Table 1. Six patients were male, and the average age was 38.7±16.4 years. Only one patient was of non-White ethnicity. Two patients underwent a qualitative urine RT-PCR test to detect AdV genetic material, with a positive result. The remaining patients had diagnostic confirmation through LM/EM findings (Table 1).

The underlying nephropathy was known in three of seven patients: one patient with membranous nephropathy, one patient with diabetic kidney disease, and one patient with FSGS. All patients had been on KRT for at least 1 year before KT. None of them had undergone repeat

Table 1. Demographic characterization and data relating to kidney transplantation and diagnostic methods used to confirm AdV infection in a case series of AdV interstitial nephritis

Case	Age	Sex	Ethnicity	Underlying Nephropathy	KT Time (mo)	Type of KT	Maintenance IS	GFR Baseline	DM/ AH	HBV/ HCV/ CMV	Induction	AdV Diagnosis
1	27	F	WH	DM-1	5	DD	FK+MMF+PD	104	+/+	−/−/+	Thymoglobulin	KB+PCRUr
2	38	M	WH	Unknown	17	LD	FK+MMF+PD	69	−/−	−/−/+	Basiliximab	KB+EM
3	45	M	WH	Unknown	76	LD	FK+MMF+PD	50	−/+	−/−/+	Methylprednisolone	KB+EM
4	66	M	WH	MN	80	DD	FK+MMF+PD	31	+/+	−/−/+	Basiliximab	KB+EM
5	30	M	WH	Unknown	42	DD	FK+MMF+PD	40	−/−	−/−/+	Basiliximab	KB+EM
6	49	M	WH	Unknown	1	LD	FK+MMF+PD	45	−/+	−/−/+	Basiliximab	KB+EM
7	16	M	B	FSGS	12	DD	FK+MMF+PD	56	−/−	−/−/+	Basiliximab	KB+PCRUr[a]

AdV, adenovirus; AH, arterial hypertension; B, Black; CMV, positive serology for cytomegalovirus (IgG); DD, deceased donor; DM, diabetes mellitus; EM, electron microscopy; F, female; FK, tacrolimus; GFR, GFR (ml/min per 1.73 m^2); HBV, positive serology for hepatitis B; HCV, positive serology for hepatitis C; IS, immunosuppressants; KB, kidney biopsy; KT, kidney transplant; LD, living donor; M, male; MMF, mycophenolate mofetil; MN, membranous nephropathy; PCRUr, PCR in urine for AdV; PD, prednisone; WH, white.
[a]More than 99,000 viral copies.

Table 2. Clinical presentation, kidney function at disease onset, and KB findings in a case series of adenovirus interstitial nephritis

Case	Signs and Symptoms			Supplementary Tests	
	Fever	Dysuria	Hematuria	Initial GFR (ml/min per 1.73 m^2)	KB Findings
1	+	+	+	20.7	TIN with suppuration, hemorrhage foci and viral cytopathic effects
2	+	+	+	7.7	Granulomatous TIN with ATN foci and viral inclusions
3	+	+	+	10.8	Granulomatous TIN with ATN and viral inclusions
4	+	+	+	15.3	Granulomatous TIN with ATN and viral inclusions
5	−	+	+	13.1	Granulomatous TIN and viral inclusions
6	−	+	+	23.7	Granulomatous TIN and viral inclusions
7	−	−	+	25	Granulomatous TIN with ATN and viral inclusions

ATN, acute tubular necrosis; KB, kidney biopsy; TIN, tubulointerstitial nephritis.

KT. Of the seven patients, four received allograft from a deceased donor. The average age when the KT was performed was 36.14±13.68 years (Table 1).

Three patients underwent quantitative serum RT-PCR for CMV, with negative results. Among the seven patients, five had immunosuppression for KT induced with basiliximab. One of the patients had induction with thymoglobulin and the other with methylprednisolone. The maintenance therapeutic regimen at the time of AdV infection is given in Table 1.

Two patients had previous allograft rejection; one of them was treated with plasmapheresis (after a recurrence

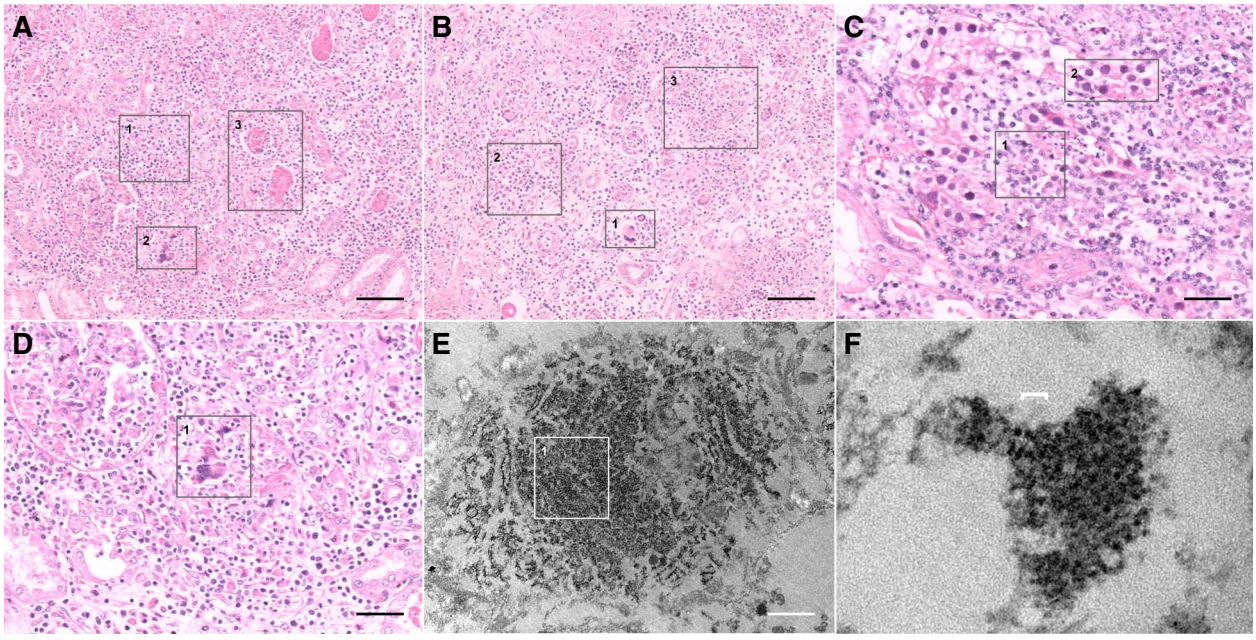

Figure 1. Kidney biopsies findings. LM with hematoxylin and eosin staining (A–D) and EM (E and F) reveal different patterns of inflammation in kidney allograft biopsies in patients with AdVN. (A) Severe interstitial inflammation findings represented by neutrophil infiltration (box 1) and giant cell (box 2); tubular necrosis with epithelial necrotic cellular debris (box 3; original magnification ×200. bar=100 mm). (B) Giant cell (box 1) surrounded by inflammatory infiltrate (box 2) and tubular necrosis (box 3; original magnification ×200. bar=100 mm). (C) Inflammatory infiltrate (box 1); viral inclusion (box 2) represented by smudged nuclei (original magnification ×400. bar=50 mm). (D) Severe involvement of the kidney parenchyma with giant cells present (box 1; HE stain, original magnification ×400. bar=50 mm). (E) Viral inclusion in infected epithelial tubular cells are arranged in a crystalline array with hexagonal outline and a diameter of 70–110 nm (original magnification ×15,000. bar=1 nm). (F) Detailed viral particles (original magnification ×80,000. bar=100 nm). AdVN, adenovirus nephritis; EM, electron microscopy; HE, hematoxylin-eosin; LM, light microscopy.

Table 3. Histopathological characterization of kidney histological compartments in a series of cases of adenovirus interstitial nephritis

Case	Glomerular Compartment	Interstitial and Tubular Compartment	IF/TA	Vascular Compartment	Necrotizing Granulomatous Pattern	Viral Inclusions	C4d
1	Unchanged	TIN	−	Unchanged	+	+	Not performed
2	Unchanged	TIN and ATN	−	Unchanged	+	+	Not performed
3	Unchanged	TIN	−	Unchanged	+	+	Negative
4	Unchanged	ATN	+	Intimal fibroelastic thickening	+	+	Negative
5	Unchanged	Marked fibrosis	+	Marked hyaline arteriolosclerosis	+	+	Not performed
6	Unchanged	TIN	−	Unchanged	+	+	Negative
7	Unchanged	TIN	−	Unchanged	+	+	Not performed

ATN, acute tubular necrosis; C4d, antibody-mediated rejection; IF/TA, interstitial fibrosis and tubular atrophy; TIN, tubulointerstitial nephritis.

of FSGS) and the other with methylprednisolone. All seven patients had negative serology for hepatitis B and C viruses, and all had reactive IgG and nonreactive IgM serology for CMV (Table 2). The baseline GFR before AdVN was 56.42±24 ml/min per 1.73 m^2, ranging from 40 to 104 ml/min per 1.73 m^2 (Table 1). All patients had normal 24-hour proteinuria at the time of symptom onset.

Patients had an average time of 32.9 months from KT to the onset of symptoms (minimum 20 days and maximum 80 months). Predominant symptoms included fever (5/7), macroscopic hematuria (6/7), and dysuria (6/7). Serum creatinine values at the beginning of the infection averaged 4.8 mg/dl (2.9–8.42 mg/dl), with an average increase of 4 times the baseline serum creatinine value. The average GFR at the beginning of the infection was 16.6 ml/min per 1.73 m^2 (7.7–25 ml/min per 1.73 m^2), with an average reduction of 4 times the baseline (Table 2). Two of the seven patients underwent cystoscopy to investigate hematuria. In both patients, direct invasive examination revealed a pattern with enanthematous mucosa. In one, a bladder biopsy was performed, which revealed nonspecific chronic cystitis.

The main indication for KB was acute allograft dysfunction. The main histopathological findings in the kidney tissue were present in all patients: acute tubular necrosis, necrotizing granulomatous interstitial nephritis, and viral inclusions. See Figure 1. The histopathological characterization of each kidney histological compartment is presented in Table 3. From the seven patients, five had their kidney tissue sample submitted to EM. EM revealed viral inclusions in infected tubular epithelial cells. Such inclusions were arranged in a crystalline arrangement with a hexagonal outline, with a diameter in the range of 70–110 nm, consistent with AdV (Figure 1). For more information about histopathological findings see Supplemental Material. EM is not routinely performed at our service; this method was used in these five patients as a way to establish the diagnosis of AdVN, given the unavailability of other methods at the time of managing these patients.

Five patients received intravenous Ig (Table 4). Three of the patients underwent discontinuation of mycophenolate in their immunosuppression regimen. One patient received reduced doses of immunosuppressants. Two patients had tacrolimus replaced by everolimus after the infection diagnosis. Most of the patients showed recovery of the basal GFR (measured 3 months after AKI), although there was no complete recovery of the previous creatinine level.

Table 4. Therapeutic regimens used and temporal evolution of kidney function markers in a series of adenovirus nephritis cases

Treatment				Laboratorial Outcomes			
				GFR (ml/min per /1.73 m^2)			
Case	GCV/ACV	IVIg	IS Discontinued	Baseline	Onset	3 mo	6 mo
1	−/−	−	No	104	20.7	−	−
2	+/+	+	MMF, PD	69	7.7	53	55
3	+/−	−	No	50	10.8	41	37
4	+/−	+	MMF	31	15.4	22	21
5	−/−	+	MMF	40	13.1	28	32
6	+/−	+	MMF	45	23.7	55	62
7	−/−	+	No	56	25	41	40

ACV, aciclovir; GCV, ganciclovir; IS, immunosuppressants; IVIg, intravenous Ig; MMF, mycophenolate mofetil; PD, prednisone.

Table 5. Cases of adenovirus nephritis after kidney transplantation described in the literature

Author (Year)	Age (yr)	Sex	Time after Transplant	Organs or Systems Involved	Diagnostic Test	Treatment	Outcome
Myerowitz *et al.*[25] (1975)	61	Female	55 d	Lungs, US	KB+histopathology+PCR	Not specified	Death
Ardehali *et al.*[26] (2001)	45	Male	6 yr	Lungs, heart, liver, US, GI tract	KB+histopathology+PCR	Not specified	Death
Emovon *et al.*[27] (2003)	46	Female	2 yr	US	KB+histopathology	Ribavirin+IVIg	Recovered
Saquib *et al.*[23] (2009)	68	Male	26 d	Lungs, US	KB+histopathology+PCR	Cidofovir+IVIg	Retransplantation
Barraclough *et al.*[28] (2009)	68	Male	2 wk	US	KB+histopathology+PCR	Cidofovir+IVIg	Recovered
Gaspert *et al.*[29] (2009)	64	Male	2 mo	US	KB+histopathology+PCR	Not specified	Kidney function not recovered
Kozlowski *et al.*[30] (2010)	44	Male	12 d	US	KB+histopathology+PCR	Valganciclovir	Recovered
Watcharanana *et al.*[10] (2011), case 1	32–67	Not specified	4 wk	US	PCR	Not specified	Recovered
Watcharanana *et al.*[10] (2011), case 5	32–67	Not specified	4 wk	US	PCR	Cidofovir+IVIg	Recovered
Watcharanana *et al.*[10] (2011), case 6	32–67	Not specified	4 wk	US	PCR	Not specified	Recovered
Watcharanana *et al.*[10] (2011), case 7	32–67	Not specified	4 wk	US	PCR	Not specified	Recovered
Varma *et al.*[31] (2011)	57	Male	11 d	US	KB+histopathology+PCR	IVIg	Recovered
Sujeet *et al.*[32] (2011)	65	Female	3 yr	US	KB+histopathology+PCR	Cidofovir	Recovered
Parasuraman *et al.*[13] (2013)	44	Male	22 d	US	KB+histopathology+PCR	Cidofovir+IVIg	Recovered
Dawood *et al.*[33] (2014), case 1	70	Male	27 mo	US	KB+histopathology+PCR	Cidofovir+IVIg	Recovered
Dawood *et al.*[33] (2014), case 2	60	Male	4 wk	US	KB+histopathology+PCR	Cidofovir+IVIg	Recovered
Lachiewicz *et al.*[34] (2014)	20	Female	6 mo	US	KB+histopathology+PCR	Cidofovir+IVIg	Recovered
Rady *et al.*[35] (2014)	63	Male	6 wk	US	KB+histopathology+PCR	GCV+IVIg	Recovered
Park *et al.*[36] (2015)	32	Female	10 mo	US	KB+histopathology+PCR	Ribavirin+IVIg	Recovered
Hatlen *et al.*[1] (2016)	45	Male	6 wk	Lungs, US	KB+histopathology+PCR	IVIg	Recovered
Veer *et al.*[21] (2017)	65	Female	1 yr	Lungs, US	KB+histopathology+PCR	IVIg	Recovered
Barros Silva *et al.*[14] (2017)	38	Male	18 mo	US, GI tract	KB+histopathology	GCV+IVIg	Recovered
Seralathan and Kurien[7] (2018)	37	Male	4 mo	US, lungs	KB+histopathology+PCR	Valganciclovir	Recovered
Pettengill *et al.*[37] (2019)	36	Male	1 mo	US	KB+histopathology+PCR	Cidofovir+probenecid	Recovered
L Moreira *et al.*[15] (2019)	40	Male	17 d	US+GI tract	KB+histopathology+PCR	Valganciclovir	Recovered
Al Qa'qa *et al.*[38] (2020)	66	Male	17 mo	US, skin	KB+histopathology+PCR	Reduction of IS	Recovered
Thorne *et al.*[20] (2020)	61	Male	7 mo	US	KB	Reduction of IS	Recovered
Watanabe *et al.*[39] (2021)	52	Female	21 mo	US	KB+histopathology+PCR	Valganciclovir	Recovered
Sanathkumar *et al.*[40] (2021)	45	Male	16 d	US	KB+histopathology+PCR	IVIg	Death
Ahmed *et al.*[41] (2021)	56	Male	2 wk	US	KB+histopathology+PCR	Cidofovir	Hemodialysis
Fujita *et al.*[42] (2023)	40	Male	4.5 yr	US, GI tract	KB+histopathology+PCR	IVIg	Recovered
Lum *et al.*[43] (2023)	30	Male	16 mo	US, lungs	KB+histopathology+PCR	Cidofovir+probenecid	Recovered
Lilley *et al.*[16] (2023)	51	Male	45 d	US	KB+histopathology	Cidofovir+GCV+IVIg	Recovered
Jagannathan *et al.*[5] (2023)	29	Male	72 d	US, GI tract	KB+histopathology+PCR	Reduction of IS+IVIg	Recovered
Jagannathan *et al.*[5] (2023)	44	Male	4 yr	US	KB+histopathology+PCR	Reduction of IS+IVIg+ cidofovir	Recovered
Jagannathan *et al.*[5] (2023)	76	Male	8.5 mo	Non specific	KB+histopathology+PCR	IVIg+cidofovir	Death
Jagannathan *et al.*[5] (2023)	18	Male	32 dias	Asymptomatic	KB+histopathology+PCR	IVIg+PD	Kidney function not recovered

Table 5. (Continued)

Author (Year)	Age (yr)	Sex	Time after Transplant	Organs or Systems Involved	Diagnostic Test	Treatment	Outcome
Jagannathan *et al.*[5] (2023)	60	Male	1.8 yr	US	KB+histopathology+PCR	Reduction of IS+IVIg	Kidney function not recovered
Jagannathan *et al.*[5] (2023)5	50	Male	3 yr	US	KB+histopathology+PCR	Reduction of IS	Kidney function not recovered
Jagannathan *et al.*[5] (2023)	39	Female	4 mo	US	KB+histopathology+PCR	Reduction of IS+IVIg	Recovered
Jagannathan *et al.*[5] (2023)	22	Male	2.5 yr	US, GI tract	KB+histopathology+PCR	Reduction of IS+cidofovir	Recovered
Jagannathan *et al.*[5] (2023)	50	Male	12.5 yr	Asymptomatic	KB+histopathology+PCR	Reduction of IS	Recovered
Jagannathan *et al.*[5] (2023)	34	Male	1.8 yr	US, GI tract	KB+histopathology+PCR	Reduction of IS+IVIg +valganciclovir	Recovered
Jagannathan *et al.*[5] (2023)	57	Male	8 mo	Non specific	KB+histopathology+PCR	IVIg	Recovered

GCV, ganciclovir; GI, gastrointestinal; IS, immunosuppressant; IVIg, intravenous Ig; KB, kidney biopsy; PD, prednisone; US, urinary system.

One patient (case 1) did not receive antivirals, Igs, or reduction of immunosuppression. This is justified by the fact that this was the first case of AdVN to occur in our research center, and therefore, there was no high suspicion for this diagnosis. The clinical course was unfavorable, requiring allograft nephrectomy during the course of the disease.

All patients underwent empiric broad-spectrum antibiotic therapy (the most frequent drugs used in antibiotic schemes were meropenem and teicoplanin) after the onset of urinary symptoms associated with graft dysfunction, given the initial suspicion of bacterial infection of the kidney graft. There was no improvement in clinical laboratory parameters with this therapy.

Our literature review included 44 patients of AdVN (Table 5). Among the 40 patients whose sex was specified in the original study, 32 were male. The average age at the onset of the disease was 47.8 years. The average time between KT and the onset of the condition was 17.2 months, ranging from 11 days to 12 years. In 26 patients, the symptoms occurred only in the urinary system, and the respiratory system was affected in seven patients. The other affected systems were the gastrointestinal tract and cutaneous system. One of the patients had diffuse involvement (respiratory, urinary, gastrointestinal system, liver, and heart), and only two patients were asymptomatic.

Discussion

AdVN is a rare condition whose diagnosis was suspected after acute allograft dysfunction that did not respond to antibacterial therapy and had a favorable prognosis in most of the patients. Our results can be summarized in four elements: (*1*) the clinical manifestation of this condition is nonspecific, and KB played an essential role in establishing its diagnosis; (*2*) the most specific histopathological finding was interstitial nephritis with a granulomatous pattern; (*3*) the therapy used was varied among observed cases and included reduction of immunosuppression and use of antivirals and intravenous human Igs; and (*4*) the evolution was favorable in most patients, and there was recovery of kidney function 3 months after the disease onset.

AdVN is an infrequent, but very relevant, complication in patients undergoing KT. It presents potential unfavorable outcomes in terms of kidney dysfunction and even survival for the patient.[10] The nonspecific nature of its clinical manifestations (often overlapping with other more common infections in transplant recipients) creates the need to improve timely diagnosis (such as its clinical behavior and histopathological characteristics).[10]

The pathogenesis of AdVN and the severity of the clinical presentation depend on the interaction of factors related to the allograft receptor, the virus in question (including its serotype), and the type of immunosuppression instituted.[12] Human infection by AdV most commonly occurs through subgroup B—normally serotypes 7, 11, 34, and 35. The last three are strongly associated with hemorrhagic forms of the infection (such as cystitis and necrotizing interstitial nephritis).[3] There is no established relationship between AdV infection and allograft rejection, but it is likely that these two elements are indirectly related.[4] It is possible that pathogenesis begins with immunosuppression, facilitating infection or reactivation of latent infection. Next, acute rejection may be the primary aggressive factor in allograft, and viral replication in tissue already subjected to injury is then facilitated.[4] Another possibility is the reduction of immunosuppressive therapy, an important factor in the treatment of AdVN, is the trigger for acute rejection of allograft.[4]

Reducing immunosuppression is a key element in the treatment of AdVN.[7] There are reports in the literature of significant recovery of kidney function by only reducing the intensity of immunosuppression.[7]

In our series of cases, the diagnosis was made by combining at least one direct finding (IH, EM, and PCR in urine) and one indirect finding (histopathology) of AdV infection in allograft. In our center, performing PCR for AdV in urine is not routine in patients with acute allograft dysfunction. There is intense heterogeneity regarding the diagnostic criteria for AdVN in the literature. Diagnostic tools include clinical elements (in general, urinary tract symptoms[11]), histological,[4] and, especially, methods that allow the detection of the genetic material of the virus (evidenced by positive immunohistochemical staining for AdV in a kidney fragment[14]), and positive viruria and/or viremia,[15] among others. Among these, RT-PCR in urine is the most sensitive, but its specificity is limited because there may be asymptomatic viremia in the first year after KT, but there are no recommendations in the current literature for monitoring or treating asymptomatic viremia.[7] The detection of genetic material from the virus in blood does not occur in all patients with AdVN and is not used in isolation for the diagnosis of this condition.[16] KB is fundamental in the diagnosis because it helps in the etiological diagnosis and exclusion of other differential diagnoses.[7,16]

On KB, the main EM finding in AdVN in transplant recipients is the presence of smudge-type inclusion bodies within the nuclei of tubular epithelial cells.[17] These inclusions are specific for AdV and appear as dark, basophilic material with blurred margins, and it may be associated with viral inclusion bodies, cellular damage, and immune complex deposition.[17]

The diagnosis is most commonly confirmed using viral PCR, identifying known AdV serotypes. Furthermore, quantitative PCR can also be used to monitor the therapy used.[4] However, the sensitivity of direct detection of antigens through rapid tests is not sufficient to diagnose immunocompromised patients, such as transplant recipients.[18]

The presence of AdV in KT recipients is relatively common, with positive viremia in approximately 6.5% and viruria in 11%[13] of patients in the first year after KT.[12] The reported incidence of infection in KT recipients is 4.1%, with the majority resulting from reactivation of latent infection.[13] Allograft involvement, on the other hand, is a rare condition, but potentially causes worse outcomes. It is also known that disseminated infection in immunocompromised patients is fatal in more than 60% of patients.[19] AdV graft infection should be considered when the patient presents with allograft dysfunction, hematuria, and sterile pyuria.[13] Among the biopsy findings, the tubulointerstitial

granulomatous pattern is the most characteristic finding of AdVN and is particularly rare in other viral infections of the graft.[19]

The average time of onset of AdVN after KT identified by Watanabe *et al.*[39] was 6 weeks, different from our study. On the other hand, the most prevalent symptoms described in this same study are similar in prevalence to those seen in our patients—hematuria (94.7%), fever (88.9%), dysuria (80%), and AKI (97.7%).

In our literature review, AdVN diagnoses were established by combining KB, histopathology, and AdV RT-PCR. Other diagnostic strategies used were performing allograft biopsy with histopathology, PCR for AdV, and allograft biopsy with IH, each of these alone. The therapeutic regimens reported were antivirals (especially cidofovir, ganciclovir, and valganciclovir), intravenous Igs, reduced immunosuppression, and combinations of these elements. There have also been reported patients in which specific therapy for the disease was not instituted. The clinical course was favorable in 34 of the reported patients (77.2%), a number similar to that seen in our study (85.7%). In all five cases (11.3%) in the literature in which there was no specific therapy, a favorable evolution was observed, which is not in line with the outcome observed in the only patient in our study in which there was no specific therapy (Table 5).

The primary goal of AdVN treatment is to reduce viral replication and preserve graft function. Immunosuppression reduction is often the cornerstone of treatment.[21] A careful reduction of immunosuppression is essential to control viral replication while minimizing the risk of rejection.[21] However, abrupt withdrawal can lead to graft rejection, so we recommend that this should be done gradually under close monitoring. In Brazilian centers' experience, discontinuation of mycophenolate or azathioprine has been shown to be useful in controlling viremia or viruria. In severe cases, maintenance of corticosteroid therapy alone may be necessary.

There is limited evidence supporting the use of antivirals for AdVN, usually based on case reports.[15] Cidofovir has been used in some patients, but its efficacy is uncertain, has significant side effects, and is not available for use in Brazil.[4] Other antivirals, such as ganciclovir, have been explored and the use of Igs or plasmapheresis in severe cases, all with uncertain efficacy.[22–24]

We recommend close monitoring for symptoms of AdVN in post-KT patients, such as fever and gross hematuria. Monitoring AdV DNA levels in blood or urine can help assess disease progression and response to treatment. There are no data to support evidence on the best method of monitoring therapeutic strategies. However, it is accepted that the combination of resolution of hematuria and fever, associated with a drop in urinary or blood viral load, is necessary as a monitoring strategy.

The main strength of this report is the detailed case series, enriched by the histopathological description, and a literature review on AdVN, contributing to the knowledge of this rare entity. The histopathological findings are summarized, highlighting the most frequent findings in AdVN-confirmed biopsies, which helps the kidney pathologists favor this differential diagnosis. The comprehensive review identifies patterns of clinical and laboratory presentation and progression, along with different therapeutic choices.

A limitation of our study was the absence of a single protocol for the diagnosis and treatment of patients with AdVN. Some diagnostic resources were not available at the time of suspicion of AdVN. This limitation may result in underdiagnosis.

It is noted that AdVN after KT is a rare condition that potentially causes morbidity and negative outcomes in patients. It is a disease whose diagnosis is challenging, and KB plays a key role in confirmation and in ruling out other differential diagnoses. There is still not a consensus for the treatment of AdVN in the current literature, and the main elements of the therapeutic arsenal are antivirals, human Igs, and reduced immunosuppression. The prognosis was favorable in most cases in our study and in the literature.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/A912.

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Data Sharing Statement

Anonymized data created for the study are or will be available in a persistent repository upon publication; Partial restrictions to

the data and/or materials apply. Observational Data. Figshare. The reference for the repository is: CAMPOS, MARCOS (2025). Supplemental Material: Kidney biopsy findings from a series of seven cases of adenovirus nephritis after kidney transplantation. https://doi.org/10.6084/m9.figshare.28665623. Deidentified data are available upon reasonable request to the corresponding author.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A913.

Supplemental Material. KB findings from a series of seven patients with AdVN after kidney transplantation.

References

1. Hatlen T, Mroch H, Tuttle K, et al. Disseminated adenovirus nephritis after kidney transplantation. *Kidney Int Rep.* 2018;3(1):19–23. doi:10.1016/j.ekir.2017.08.004
2. Masutani K. Viral infections directly involved in kidney allograft function. *Nephrology (Carlton).* 2018;23(suppl 2):31–37. doi:10.1111/nep.13285
3. Agrawal V, Gupta RK, Jain M, Prasad N, Sharma RK. Polyomavirus nephropathy and cytomegalovirus nephritis in renal allograft recipients. *Indian J Pathol Microbiol.* 2010;53(4):672–675. doi:10.4103/0377-4929.72025
4. Al-Heeti OM, Cathro HP, Ison MG. Adenovirus infection and transplantation. *Transplantation.* 2022;106(5):920–927. doi:10.1097/TP.0000000000003988
5. Jagannathan G, Weins A, Daniel E, et al. The pathologic spectrum of adenovirus nephritis in the kidney allograft. *Kidney Int.* 2023;103(2):378–390. doi:10.1016/j.kint.2022.10.025
6. Cordero E, Casasola C, Ecarma R, Danguilan R. Cytomegalovirus disease in kidney transplant recipients: incidence, clinical profile, and risk factors. *Transplant Proc.* 2012;44(3):694–700. doi:10.1016/j.transproceed.2011.11.053
7. Seralathan G, Kurien AA. Adenovirus interstitial nephritis: an unusual cause for early graft dysfunction. *Indian J Nephrol.* 2018;28(5):385–388. doi:10.4103/ijn.IJN_218_16
8. Seto D, Chodosh J, Brister JR, Jones MS. members of the adenovirus research community. using the whole-genome sequence to characterize and name human adenoviruses. *J Virol.* 2011;85(11):5701–5702. doi:10.1128/JVI.00354-11
9. Singh HK, Nickeleit V. Kidney disease caused by viral infections. *Curr Diagn Pathol.* 2004;10(1):11–21. doi:10.1016/j.cdip.2003.09.004
10. Watcharananan SP, Avery R, Ingsathit A, et al. Adenovirus disease after kidney transplantation: course of infection and outcome in relation to blood viral load and immune recovery. *Am J Transplant.* 2011;11(6):1308–1314. doi:10.1111/j.1600-6143.2011.03479.x
11. MacNeil KM, Dodge MJ, Evans AM, Tessier TM, Weinberg JB, Mymryk JS. Adenoviruses in medicine: innocuous pathogen, predator, or partner. *Trends Mol Med.* 2023;29(1):4–19. doi:10.1016/j.molmed.2022.10.001
12. Storsley L, Gibson IW. Adenovirus interstitial nephritis and rejection in an allograft. *J Am Soc Nephrol.* 2011;22(8):1423–1427. doi:10.1681/ASN.2010090941
13. Parasuraman R, Zhang PL, Samarapungavan D, Rocher L, Koffron A. Severe necrotizing adenovirus tubulointerstitial nephritis in a kidney transplant recipient. *Case Rep Transplant.* 2013;2013(1):969186. doi:10.1155/2013/969186
14. Barros Silva GE, Muglia VF, Filho NS, et al. Adenovirus pyelonephritis in the late posttransplant period. *Kidney Int.* 2017;92(2):520. doi:10.1016/j.kint.2017.03.016
15. L Moreira C, Rocha J, Silva M, et al. Adenovirus infection-A rare cause of interstitial nephritis in kidney transplant. *Nefrologia.* 2019;39(1):106–107. doi:10.1016/j.nefro.2018.06.001
16. Lilley CM, Borys E, Picken MM. Adenovirus-associated acute interstitial nephritis with graft survival and novel follow-up biopsy findings including karyomegaly: a case series. *Cureus.* 2023;15(5):e38452. doi:10.7759/cureus.38452
17. Mori K, Yoshihara T, Nishimura Y, et al. Acute renal failure due to adenovirus-associated obstructive uropathy and necrotizing tubulointerstitial nephritis in a bone marrow transplant recipient. *Bone Marrow Transplant.* 2003;31(12):1173–1176. doi:10.1038/sj.bmt.1704077
18. Medina I, Carpio C, Ruiz-Camps I, et al. Adenovirus-induced hemorrhagic cystitis after CD19-targeted chimeric antigen receptor T-cell therapy in a patient with large B-cell lymphoma. *Immunotherapy.* 2023;15(16):1369–1374. doi:10.2217/imt-2023-0111
19. Lusco MA, Fogo AB, Najafian B, Alpers CE. AJKD atlas of renal pathology: adenovirus infection. *Am J Kidney Dis.* 2018;71(1):e1–e2. doi:10.1053/j.ajkd.2017.11.001
20. Thorne P, Arroyo JP, Concepcion BP. Fever and gross hematuria in a kidney transplant recipient. *Kidney360.* 2020;1(7):712–713. doi:10.34067/KID.0000732020
21. Veer M, Abdulmassih R, Como J, Min Z, Bhanot N. Adenoviral nephritis in a renal transplant recipient: case report and literature review. *Transpl Infect Dis.* 2017;19(4):e12716. doi:10.1111/tid.12716
22. Monteilhet V, Saheb S, Boutin S, et al. A 10 patient case report on the impact of plasmapheresis upon neutralizing factors against adeno-associated virus (AAV) types 1, 2, 6, and 8. *Mol Ther.* 2011;19(11):2084–2091. doi:10.1038/mt.2011.108
23. Saquib R, Melton LB, Chandrakantan A, et al. Disseminated adenovirus infection in renal transplant recipients: the role of cidofovir and intravenous immunoglobulin. *Transpl Infect Dis.* 2010;12(1):77–83. doi:10.1111/j.1399-3062.2009.00452.x
24. Lion T. Adenovirus persistence, reactivation, and clinical management. *FEBS Lett.* 2019;593(24):3571–3582. doi:10.1002/1873-3468.13576
25. Myerowitz RL, Stalder H, Oxman MN, et al. Fatal disseminated adenovirus infection in a renal transplant recipient. *Am J Med.* 1975;59(4):591–598. doi:10.1016/0002-9343(75)90267-3
26. Ardehali H, Volmar K, Roberts C, Forman M, Becker LC. Fatal disseminated adenoviral infection in a renal transplant patient. *Transplantation.* 2001;71(7):998–999. doi:10.1097/00007890-200104150-00029
27. Emovon OE, Lin A, Howell DN, et al. Refractory adenovirus infection after simultaneous kidney-pancreas transplantation: successful treatment with intravenous ribavirin and pooled human intravenous immunoglobulin. *Nephrol Dial Transplant.* 2003;18(11):2436–2438. doi:10.1093/ndt/gfg365
28. Barraclough K, Oliver K, Playford EG, et al. Life-threatening adenovirus infection in a kidney transplant recipient. *NDT Plus.* 2009;2(3):250–253. doi:10.1093/ndtplus/sfp003
29. Gaspert A, Lüthi B, Mueller NJ, et al. Subacute allograft failure with dysuria and hematuria in a kidney transplant recipient. *Am J Kidney Dis.* 2009;54(1):154–158. doi:10.1053/j.ajkd.2008.11.008
30. Kozlowski T, Nickeleit V, Andreoni K. Donor-transmitted adenovirus infection causing kidney allograft nephritis and graft loss. *Transpl Infect Dis.* 2011;13(2):168–173. doi:10.1111/j.1399-3062.2010.00572.x
31. Varma MC, Kushner YB, Ko DS, et al. Early onset adenovirus infection after simultaneous kidney-pancreas transplant. *Am J Transplant.* 2011;11(3):623–627. doi:10.1111/j.1600-6143.2010.03408.x
32. Sujeet K, Vasudev B, Desai P, et al. Acute kidney injury requiring dialysis secondary to adenovirus nephritis in renal transplant recipient. *Transpl Infect Dis.* 2011;13(2):174–177. doi:10.1111/j.1399-3062.2010.00577.x
33. Dawood US, Nelson A, Wu D, Otto S, Russ GR. Disseminated adenovirus infection in kidney transplant recipient. *Nephrology (Carlton).* 2014;19(suppl 1):10–13. doi:10.1111/nep.12192
34. Lachiewicz AM, Cianciolo R, Miller MB, Derebail VK. Adenovirus causing fever, upper respiratory infection, and allograft nephritis complicated by persistent asymptomatic viremia. *Transpl Infect Dis.* 2014;16(4):648–652. doi:10.1111/tid.12248
35. Rady K, Walters G, Brown M, Talaulikar G. Allograft adenovirus nephritis. *Clin Kidney J.* 2014;7(3):289–292. doi:10.1093/ckj/sfu020
36. Park UJ, Hyun SK, Kim HT, Cho WH, Han SY. Successful treatment of disseminated adenovirus infection with ribavirin

and intravenous immunoglobulin in an adult renal transplant recipient: a case report. *Transplant Proc.* 2015;47(3):791–793. doi:10.1016/j.transproceed.2014.11.054
37. Pettengill MA, Babu TM, Prasad P, et al. Probable donor-derived human adenovirus type 34 infection in 2 kidney transplant recipients from the same donor. *Open Forum Infect Dis.* 2019; 6(3):ofy354. doi:10.1093/ofid/ofy354
38. Al Qa'Qa'S, Singhal P, Sainaresh Vellanki V, et al. SUN-326 adenovirus induced granulomatous tubulointerstitial nephritis in a renal allograft patient. *Kidney Int Rep.* 2020;5(3):S335. doi: 10.1016/j.ekir.2020.02.864
39. Watanabe M, Kaneko S, Usui J, et al. Literature review of allograft adenovirus nephritis and a case presenting as mass lesions in a transplanted kidney without symptoms of urinary tract infection or acute kidney injury. *Transpl Infect Dis.* 2021;23(2): e13468. doi:10.1111/tid.13468
40. Sanathkumar H, Kurien A, Raj Y, Fernando EM. Adenovirus-associated thrombotic microangiopathy and necrotizing interstitial nephritis in a renal transplant recipient: a case report and review. *Indian J Nephrol.* 2021;31(3):314–318. doi: 10.4103/ijn.IJN_344_19
41. Ahmed M, Karim MR, Choung HYG. A rare case of adenovirus interstitial nephritis and amr within two weeks of kidney transplant. *J Am Soc Nephrol.* 2021;32(10S):646–647. doi: 10.1681/ASN.20213210s1646c
42. Fujita Y, Fujishima R, Ueki K, et al. Allograft adenovirus nephritis accompanied by Crohn's disease in a kidney transplant recipient: a novel case report. *CEN Case Rep.* 2023;12(2): 215–220. doi:10.1007/s13730-022-00756-5
43. Lum EL, Zuckerman J, Gaynor P, Bunnapradist S. Adenovirus in a kidney transplant recipient. *Kidney Med.* 2023;5(4):100605. doi:10.1016/j.xkme.2023.100605