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Brief Communication

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Adenovirus Disease after Kidney Transplantation: Course of Infection and Outcome in Relation to Blood Viral Load and Immune Recovery

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Information on the clinical spectrum and management of adenovirus infection after kidney transplantation is limited. From April 2007 to April 2010, 17 kidney transplant recipients were diagnosed with adenovirus disease. The median time to infection was 5 (range, 2–300) weeks after transplantation. Of the 17 patients, 13 (76.5%) presented early, within 3 months posttransplant, and four (23.5%) presented late, more than 3 months after transplant. Besides urinary tract, involvement of other organs was common (63.6%) among patients with adenovirus viremia. Despite reduction of immunosuppression, six patients subsequently had a rise in the level of blood viral load, mostly within a week after diagnosis. However, only three (27.3%) patients with early infection developed disease progression. Compared to the late infection group, patients with early infection had significantly lower absolute lymphocyte counts at week 1 ($p = 0.01$) and 3 ($p = 0.002$) after diagnosis. Four patients received intravenous cidofovir. At 6-month follow-up, 10 (90.9%) patients had reversible graft dysfunction. Only one (5.7%) died from bacterial sepsis. Adenovirus disease is a significant complication following kidney transplantation. Early case recognition with reduction of immunosuppression is critical. Serial blood adenovirus viral loads and assessment of lymphocyte recovery are also useful in monitoring the course of infection.

Key words: Adenovirus, cidofovir, kidney transplantation, viral infection, viral load, viremia

Abbreviations: ADV, adenovirus; ALC, absolute lymphocyte count; PCR, polymerase chain reaction; ESRD, end-stage renal disease; CMV, cytomegalovirus; MMF, mycophenolate mofetil; HC, hemorrhagic cystitis; HSCT, hematopoietic stem cell transplantation.

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Introduction

Adenovirus (ADV) has increasingly been recognized as a cause of infection resulting in high morbidity and mortality among immunocompromised patients (1). In kidney transplant recipients, previous literature is primarily in the form of case reports (2–5). The present study reports the clinical and virologic characteristics and outcome of ADV disease following kidney transplantation, with attention to the significance of blood ADV viral load, the absolute lymphocyte count (ALC), the effect of reduction of immunosuppression and a subset of patients with early infection who received cidofovir.

Material and Methods

Kidney transplant recipients who were diagnosed with ADV disease from April 2007 to April 2010 were identified from Faculty of Medicine, Ramathibodi Hospital and Praram 9 Hospital, Bangkok, Thailand. Their medical records were retrospectively reviewed. Cases were identified based on a discharge diagnosis of ADV disease and laboratory database. During the study period, ADV polymerase chain reaction (PCR) tests were performed for kidney transplant recipients who presented with clinical symptoms compatible with viral syndromes or ADV disease; for example, fever, neutropenia plus thrombocytopenia, dysuria and hematuria, diarrhea, upper or lower respiratory symptoms. PCR analysis was performed on blood and other samples, such as urine, nasal swab, bronchoalveolar lavage fluid, bladder biopsy specimens, kidney biopsy specimens, pulmonary biopsy specimens, colon biopsy specimens, depending on the patients' symptoms. Most patients with positive ADV PCR in the urine alone had undergone cystoscopy showing hemorrhagic cystitis (HC). Patients with ADV in the urine or those with ADV in the blood were included. The length of follow-up was 6 months after diagnosis. During that period, 349 patients underwent kidney transplantation, 144 and 205 of which were deceased and living related, respectively. Induction therapy was given in 60% of cases, majority of which were interleukin-2 receptor antagonists. Antithymocyte globulin was used in 16 cases. This study was approved by the ethical committee for research involving human subjects of studied institutes.

Detection and quantitative analysis of ADV

Quantification of blood and urine ADV DNA was performed on a weekly basis. Urine ADV viral load was performed until the test became undetectable. Patients with ADV viremia and those with disease progression were prospectively monitored for change of blood viral load 1–2 times weekly until blood ADV DNA was undetectable on at least two consecutive occasions. The detection and quantitative analysis of ADV DNA was performed at the Division of Pathology, Ramathibodi Hospital. DNA extraction was done from 200 μL of plasma or urine or other body fluid using High Pure PCR Template Preparation kit (Roche Diagnostics, Germany), according to the manufacturer's directions. For the detection and quantitative analysis of ADV DNA, real-time PCR was done using the Lightcycler instrument. For primers and probes, LightMix Kit human ADV (TIB MOLBIOL GmbH, Berlin, Germany) was utilized. The kit was designed to detect all six major subgroups (subgenera or species A to F). A 129 bp fragment of the ADV in the hexon gene was amplified with specific primers and detected with probes labeled with LightCyclerRed 640 (Roche Diagnostics, Germany), according to the manufacturer's recommendations. The PCR products were verified by running a melting curve. A linear measurement range of the ADV viral load was 10^2 to 10^6 copies/mL. The sensitivity of the PCR assay permitted detection of ADV DNA at a level of 10 copies/mL. The turn around time of the PCR test was 48–72 h.

Case definition

ADV disease was defined as either (1) the detection of ADV DNA in patients' urine, and the presence of clinical symptoms that were not explained by other causes; for example, fever, dysuria/urgency or hematuria or (2) the detection of ADV DNA in patients' blood and the presence of above and/or other clinical symptoms; for example, diarrhea, cough and shortness of breath. Disseminated ADV disease was defined as clinical symptoms referable to more than one organ system, together with detection of ADV DNA in blood and one other body fluid. ADV disease early posttransplantation was defined as ADV disease that occurred within 3 months after kidney transplantation. ADV disease late posttransplantation was defined as ADV disease that occurred more than 3 months posttransplantation. Disease progression was defined as a clinical syndrome characterized by an increasing number of organ systems involved over time.

Statistical analysis

Descriptive statistics and tabulation were used to demonstrate the results. The median and range were used to describe continuous data. Frequency count and percentage were used for categorical data. Chi-square test was used for categorical data analysis. Friedman test was used to compare number of ALC between patients infected early and late posttransplantation, those with and without ADV viremia and those who had and did not have disease progression. A p-value <0.05 by a two-tailed test was considered statistically significant. All analysis was performed by using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

From April 2007 to April 2010, 17 kidney transplant recipients were diagnosed with ADV disease. Patients' median age (range) was 47 (32–67) years. Nine (69.2%) were male. The most common pretransplant diagnosis was end-stage renal disease (ESRD) of unknown cause. All patients and donors were seropositive for cytomegalovirus (CMV) prior to transplantation. Ten (58.3%) patients had received a kidney transplant from a living-related donor. The median time to diagnosis was 5 (2–300) weeks after transplantation. Thirteen (76.5%) developed disease early postkidney transplantation (early infection group), with median time to diagnosis of 4 (range, 2–10) weeks. Four (23.5%) developed disease late posttransplantation (late infection group) with median time to diagnosis of 193 (range, 174–300) weeks. Eight (47%) patients received induction therapy. Seven (53.8%) patients were in the early infection group and were more recently exposed to induction agents, including basiliximab (4, 30.7%), daclizumab (2, 15.4%) and antithymocyte globulin (1, 7.7%). Six (35.3%) patients, all of whom were in early infection group had posttransplant complications in the month prior to the diagnosis, including delayed graft function (n = 1), acute rejection (n = 2), urinary tract infection (n = 2) and CMV reactivation (n = 1). Two patients with early infection received antirejection therapy that included pulse-methyl prednisolone (1, 7.7%) and antithymocyte globulin (1, 7.7%). One patient in the late infection group had received basiliximab. The most common maintenance immunosuppressive regimen was prednisolone, mycophenolate mofetil (MMF) and cyclosporine (10, 58.8%), followed by prednisolone, MMF and tacrolimus (6, 35.3%). There was no statistically significant difference with regard to the demographic characteristics between patients in the early and late infection groups. Patients' characteristics are shown in Table 1.

Clinical, virological and basic laboratory findings associated with adenoviral disease are shown in Table 2. The major clinical presentations were dysuria/urinary urgency (15, 88.2%) and fever (14, 82.4%). Eleven (64.7%) patients had an acute rise in serum creatinine. The median rise in serum creatinine was 0.2 (range, 0–3.1) mg/dL. At diagnosis, blood ADV DNA was detected in nine (52.9%) patients, five (38.5%) of whom were from the early infection group. The median first detected urine and blood ADV viral loads were over 6 (range, 3.7–>6) and 2.9 (range, 2.1–5.8) log copies/mL, respectively. At diagnosis, there was no difference in the clinical presentation, the level of viral load or the ALC between the early and late infection groups.

After diagnosis, all patients underwent reduction of immunosuppression. The median time from the first PCR test to the reduction of immunosuppression was 0 (range, −9 to 7) days. Six (35.3%) and 11 (64.7%) patients were on tacrolimus-based and cyclosporine-based regimens, respectively. All patients who received tacrolimus-based regimen had reduction of MMF dosage. MMF was withheld in four patients, and two others had 30% reduction of the dosage. Four patients had reduction of either tacrolimus or prednisolone dose. The median percentage of tacrolimus dose reduction was 5 (0–62.5). The median percentage of prednisolone dose reduction was 33 (0–100). The median whole blood concentrations of tacrolimus were 7.6 (range, 5.7–13) and 5.05 (range, 4.1–6.1) ng/mL before and after the reduction, respectively. For patients on cyclosporine-based regimens, the median percentage of cyclosporine dose reduction was 20 (12.5–60), resulting in a decrease

Table 1: Demographic characteristics of 17 adenovirus-infected kidney transplant recipients

Characteristics	Early infection(n = 13)	Late infection (n = 4)	Total—n (%)
Age, years, median age (range)	47 (32–67)	40 (32–51)	47 (32–67)
Sex, male/female	7/6	2/2	9/8 (52.9/47.1)
Cause of end-stage renal disease			
Unknown	4	3	7 (41.2)
Hypertension	3	0	4 (23.5)
Chronic glomerulonephritis	1	1	3 (17.6)
Diabetes mellitus	2	0	2 (11.8)
Other*	3	0	3 (17.6)
Second kidney transplantation	2	2	4 (23.5)
Type of donor			
Deceased	4	3	7 (41.2)
Living	9	1	10 (58.3)
CMV D+/R+	10	7	17 (100)
Induction therapy			
Antithymocyte globulin	1	0	1 (5.9)
Daclizumab	2	0	2 (16.7)
Basiliximab	4	1	5 (29.4)
Maintenance therapy			
Pred/MMF/cyclosporine	8	2	10 (58.8)
Pred/MMF/tacrolimus	4	2	6 (35.3)
Pred/cyclosporine/everolimus	1	0	1 (5.9)
Complication within a month prior to diagnosis			
Delayed graft function	1	0	1 (5.9)
Acute rejection	2	0	2 (11.8)
Urinary tract infection	2	0	2 (11.8)
CMV reactivation	1	0	1 (5.9)
Antirejection therapy			
Antithymocyte globulin	1	0	1 (5.9)
Pulse-methylprednisolone	1	0	1 (5.9)

*Other included renal stone (n = 1), polycystic kidney disease (n = 1), IgA nephropathy (n = 1).
Abbreviations: MMF = mycophenolate mofetil; CMV = cytomegalovirus.

Table 2: Clinical and virological characteristics of patients infected with adenovirus (n = 17)

Characteristics	Early infection (n = 13)	Late infection (n = 4)	Total, n (%)
Time to diagnosis, weeks after transplantation, median (range)	4(2–10)	193(174–300)	5(2–300)
Clinical presentations			
Dysuria or urgency	11	4	15 (88.2)
Fever	10	4	14 (82.4)
Bilateral testicular pain	4	0	4 (44.4)*
Acute diarrhea	1	3	4 (23.5)
Lower abdominal pain	0	2	2 (11.8)
Rhinorrhea or sore throat	1	0	1 (5.9)
Cough and shortness of breath	1	0	1 (5.9)
Hematuria and pyuria	12	4	16 (94.1)
Acute rise in serum creatinine	8	3	11 (64.7)
Basic laboratory characteristics			
Hematuria and pyuria	12	4	16 (94.1)
Serum creatinine, median(range) (mg/dL)	1.7 (1.1–6.2)	2.1 (1.6–2.5)	1.7 (1.1–6.2)
Median rise in serum creatinine (range) (mg/dL)	0.2 (0–3.1)	0.3 (0–1.3)	0.2 (0–3.1)
Absolute lymphocyte count at first positive PCR (range) ($\times 10^6/mm^3$)	974(152–3175)	1, 108(882–1378)	1, 030(152–3175)
Virological characteristics			
Positive urine adenovirus DNA at diagnosis	13	4	17 (100)
Median (range) level of urine adenovirus viral load, (log copies/mL)	> 6 (3.7– > 6)	5.5 (4.1– > 6)	> 6 (3.7– > 6)
Positive blood adenovirus DNA at diagnosis	5	4	9 (52.9)
Median (range) level of blood adenovirus viral load, (log copies/mL)	3.3 (2.1–5.8)	2.9 (2.7–3.4)	2.9 (2.1–5.8)

*The percentage was calculated from a total number of male patients.

in cyclosporine concentration from 271 (range, 189–391) to 169 (range, 114–200) ng/mL. Eight patients had a reduction in the dosage of prednisolone of 50% (25–100). Five patients received unchanged dosage of MMF and six others had at least a 30% reduction in dose. One patient received an unchanged dose of everolimus (15 mg/day).

Following reduction of immunosupression, six patients had a rise in blood ADV viral load. Of the six patients, two in early infection group developed ADV viremia after an initial negative blood test. The median increase in blood viral load was 0.3 (range, 0.1–3.8) log copies/mL. The rise in blood viral load generally occurred within 1 week after the first positive PCR. The median time to peak blood ADV viral load was 6 (range, 2–16) days. For patients without ADV viremia (n = 6), all had HC and none had disease progression. However, four (66.7%) had prolonged duration of dysuria and hematuria. The median duration (range) of the urinary symptoms was 3.6 (range, 1.4–9.6) weeks. All recovered with reversible graft dysfunction.

For patients with ADV viremia (n = 11), as shown in Table 3, seven (63.6%) had HC plus other clinical syndromes; for example: enteritis, pneumonitis, or bilateral orchitis.

Patient E2 and E3 with disease progression and patient E4 and E5 with virological progression received intermittent low-dose intravenous cidofovir treatment (low-dose because of concerns regarding drug-related renal toxicity) (6). Oral probenecid (1 g) was given 3 h before and 1 and 8 h after cidofovir administration. Patient E3, on hemodialysis received cidofovir 5 mg/kg per week, divided into two doses. The larger dose was used because approximately 50% of the drug is removed during dialysis (7). As shown in Figure 1, patients E2, E4 and E5 cleared ADV in blood within 2 weeks. Patient E3 cleared the virus in 3 weeks but had irreversible graft dysfunction, and subsequently died from bacterial sepsis. Figure 1 demonstrates the kinetics of blood ADV viral load in the four patients during treatment with intravenous cidofovir. No patient with late infection received antiviral therapy. However, all of the four remained on reduced dose of immunosuppression. None had disease progression. All had clinical recovery at a median of 1.7 (range, 1.1–2.4) weeks.

Outcome

All patients cleared ADV from their blood and urine. The median time to clearance of ADV from blood and urine was 2 (range, 1–3) and 4.5 (range, 2–7) weeks. The median duration of urinary symptoms was 2 (range, 0.5–9.6) weeks. Ten (90.9%) of the 11 patients with an initial rise in serum creatinine had reversible graft dysfunction within a median time of 3 (range, 1–12) weeks. At 6-month follow-up, the median serum creatinine level (range) was 1.55 (0.7–2.5) mg/dL and the mortality rate was 5.9%. Patients in the early infection group had a statistically lower median ALC compared to the late infection group at week 1 (981 (114–1692) vs. 2022 (1311–2226) $\times$ 10^6/mm^3, p = 0.01) and week 3 (1308 (423–2448) vs. 2742 (2310–3700) $\times$ 10^6/mm^3, p = 0.002) following the first positive PCR.

However, there was no difference in the ALC, either between patients who had and did not have viremia, or those with and without disease progression (Figure 2).

Discussion

In this study, we highlight the importance of ADV infection among kidney transplant recipients, which appears to be a common cause of morbidity among kidney transplant recipients in Thailand. The current series constitutes the largest series to date, and offers an opportunity to characterize the clinical course of posttransplant ADV infection, response to therapy and graft outcomes in more detail. In addition, this study incorporated close monitoring of quantitative ADV blood and urine viral loads, and included an analysis of ALCs in relation to severity of disease.

Of note, three-fourths of these infections occurred early posttransplantation and only 10% of the patients received intensified immunosuppression for acute rejection.

All patients in this series were diagnosed with ADV disease in the presence of clinical symptoms and positive ADV DNA in urine. Approximately half had ADV viremia initially. The majority of the patients had a classic clinical syndrome of HC, consisting of fever and dysuria/hematuria (3, 4) and almost two-thirds had acute allograft dysfunction. This finding underlines the possibility that the major organ involved by ADV is the allograft, consistent with studies in small bowel transplant recipients (8–11). In addition, this case series demonstrates that involvement of other organ systems is common, including gastrointestinal tract, testis and only noted among patients with ADV viremia. In contrast to a recent surveillance study that found that presence of ADV DNA in patients' blood was largely asymptomatic (12), the current study found that presence of blood viral load was associated with severe ADV disease. However, these two studies were different with regard to study design and study populations. The fact that the reference study performed a surveillance test among asymptomatic recipients of various types of solid organs, including heart, liver, kidney and kidney–pancreas, has to be taken into account.

Among hematopoietic stem cell transplant (HSCT) recipients, the level of ADV DNA in blood is a surrogate marker of disseminated disease, response to antiviral treatment and high mortality (13,14). From our data, an increase in the level of blood viral load was common during infection. Although most of these rises were small, disease progression could occur and correlated with an initial high viral load or a change in the level of blood viral

Table 3: Initial presentation, course of infection, treatment and outcome of patients with adenovirus viremia

	Initial presentation		Course of infection 3 weeks after diagnosis				
Patient*	Clinical diagnosis	First blood ADV viral load (log copies/mL)	Clinical findings/ pathological diagnosis of kidney tissue	Peak blood ADV viral load (log copies/mL)	Time to test (weeks) after diagnosis	Specific treatment after diagnosis	Outcome
E1	HC	Undetectable	Acute allograft dysfunction/ viral associated nephritis	2.7	2	No	Alive, improved graft function
E2	HC and bilateral orchitis	Undetectable	Persistent symptoms, diarrhea, progression to disseminated infection	3.8	0.5	IVIG and IV cidofovir 3 mg/kg per week at week 0, 1 and 3	Alive, improved graft function
E3	Pneumonitis, HC and bilateral orchitis with delayed graft function	5.8	Disseminated disease, hemodialysis dependent/ acute tubular necrosis	5.8	0	IV cidofovir 5 mg/kg per week (divided as two times a week) at week 0, 1 and 3	Sepsis, death on hospital day 63
E4	HC, upper respiratory tract infection and bilateral orchitis	3.3	Persistent fever and dysuria	3.6	0.5	IV cidofovir 3 mg/kg per week (divided as three times a week) at week 0, 1 and 3	Alive, excellent graft function
E5	HC and bilateral orchitis	3.4	Acute allograft dysfunction/ acute rejection**	3.5	0.5	IVIG, IV cidofovir 1 mg/kg two doses at week 0 and another dose at week 2	Alive, improved graft function
E6	HC	2.8	Improved	2.8	0	No	Alive, excellent graft function
E7	HC	2.1	Persistent dysuria	2.1	0	No	Alive, excellent graft function
L1	HC, acute allograft dysfunction and enteritis	3.4	Persistent gross hematuria and dysuria	3.0	1	No	Alive, excellent graft function
L2	HC, acute allograft dysfunction and enteritis	2.8	Persistent gross hematuria and dysuria/ no rejection, no tubulitis, no viral inclusion	3.1	1.5	No	Alive, improved graft function
L3	HC and acute allograft dysfunction	2.9	Improved	2.9	0	No	Alive, excellent graft function
L4	Leukopenia, HC, and enteritis	2.7	Urinary tract infection	3.0	1	No	Alive, excellent graft function

ADV = adenovirus; HC = hemorrhagic cystitis; ND = not done; IV = intravenous.
*Patients E1–E7 (n = 7) and L1–L4 (n = 4) were infected early and late posttransplantation, respectively.
** A 3-day treatment with intravenous pulse methyl prednisolone was given at week 1.

load. These findings demonstrate the significance of blood ADV viral load and support the use of quantitative analysis of blood ADV DNA for early detection and monitoring of ADV viremia in order to identify patients at risk for severe disease.

According to our data, patients with early infection were more frequently exposed to induction therapy and the complication rate was higher within this group. Although there were no significant differences with regard to the initial clinical spectrum or degree of viremia between the early

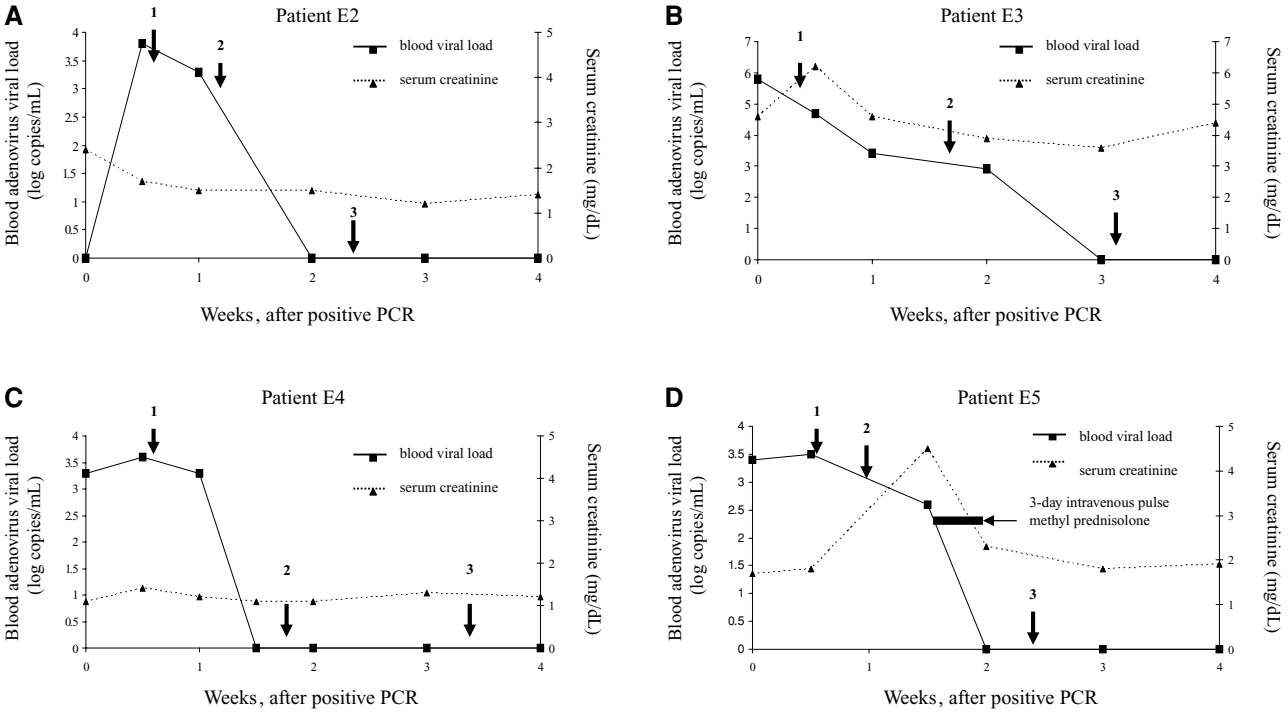

Figure 1: Time course of blood ADV viral load and serum creatinine among the four patients who received intravenous cidofovir treatment. For patients E2 (A) and E3 (B), treatment was started due to disseminated viral disease. Patients E4 (C) and E5 (D) had a rising level of ADV viremia within the first week. During the infection, patient E5 had acute rejection and received 3-day treatment with intravenous pulse methyl prednisolone in a week after the initiation of intravenous cidofovir. Arrows indicate treatment with intravenous cidofovir.

and late infection groups, disease progression occurred exclusively in patients with early infection. Induction therapy is most likely to have a significant impact on the immune system in the first 3–6 months after administration. From our analysis, patients with early infection appeared to have significantly lower ALC at several time points compared to those with late infection. This finding underscores the influence of immune recovery during the course of infection (15,16) and deserves further investigation with regard to the effect of newer immunosuppressive agents, including IL-2 antagonists and lymphocyte-depleting agents for induction therapy. Currently, there is no consensus on the recommended timing and dosage of antiviral treatment. Although intravenous cidofovir might be an alternative in

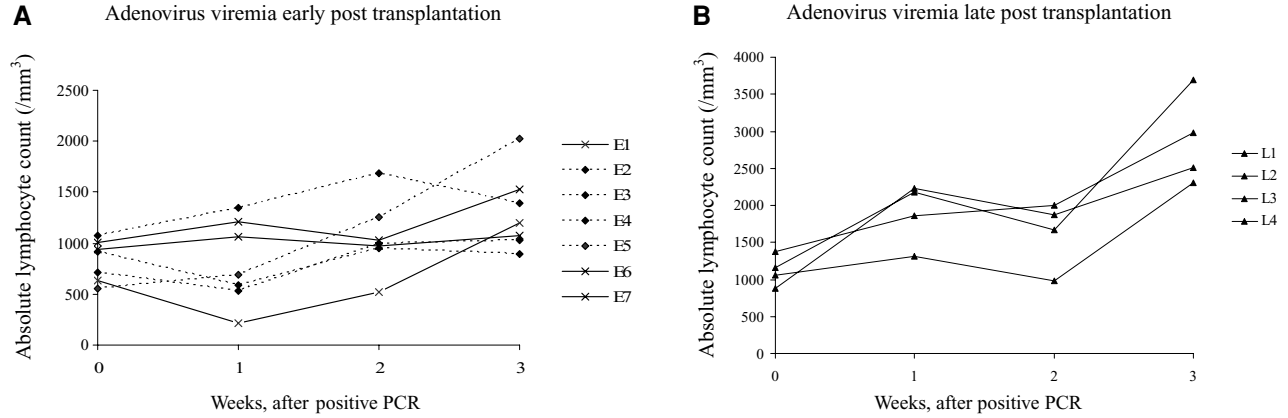

Figure 2: Lymphocyte recovery in patients with ADV viremia early (n = 7) (A) and late posttransplantation (n = 4) (B). During week 0 to week 3, patients with early infection (E1–E7) had significantly lower median values of the absolute lymphocyte count (ALC) at week 1 ($p = 0.01$) and 3 ($p = 0.002$) than did those with late infection (L1–L4).

a subset of patients who had more severe disease, the present study showed that antiviral agents are not always indicated for treatment of ADV disease following kidney transplantation. On the other hand, early case recognition and reduction of immunosuppression can be an effective approach to control the infection.

Limitations of the current study included the fact that asymptomatic renal transplant recipients were not routinely monitored for ADV DNA in urine or blood, so the true incidence of asymptomatic infections in this patient population is not known. In addition, serologic and strain-specific information was not available to determine whether these infections were donor-derived, as opposed to reactivation of prior infection in the recipient, or acquired through community or nosocomial exposures. The scattering of infections over time rather than clustering in one time period suggests against an infection control issue in the transplant ward. Further molecular epidemiologic studies would be of interest, but are beyond the scope of this article, which seeks primarily to expand on available information on the clinical course and management of patients with symptomatic posttransplant ADV infection.

In summary, the present study demonstrates that ADV disease is a major infectious complication after kidney transplantation. This clinical experience underscores the importance of clinical recognition and early detection of the infection. Reduction of immunosuppression, together with serial assessment of lymphocyte recovery and change of blood viral load is useful to identify patients who remain at risk for disease progression, particularly among those who had infection early posttransplantation.

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