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Clinical Course of Polyoma Virus Nephropathy in 67 Renal Transplant Patients

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Abstract. Polyoma virus (PV) can cause interstitial nephritis and lead to graft failure in renal transplant recipients. The clinical course of patients with polyoma virus nephritis (PVN) is not well understood, partially due to its relatively low incidence. This study is a retrospective analysis of our experience over 4 yr. The specific purpose is to outline the clinical course and outcome of patients with PVN and to study the relationship between immunosuppression and the disease process. Between June 1997 and March 2001, 67 patients with graft dysfunction were found to have biopsy-proven PVN. The diagnosis was made at a mean of 12.8 ± 9.9 mo posttransplantation. The majority of patients were men (79%) with a mean age of 54 ± 14 yr (range, 28 to 75). All patients received immunosuppression with a calcineurin inhibitor (tacrolimus in 89% of patients). All patients except two received mycophenolate mofetil and prednisone. After the diagnosis of PVN, maintenance immunosuppression was reduced in 52 patients and remained unchanged in 15 patients. After reduction of immunosuppression, eight patients (15.3%) developed acute rejection and six (11.5%) became negative for PV in biopsy and urine. After a mean observation period of 12.6 mo (mean of 26 mo posttransplantation), 16.4% of patients had lost their grafts (8 of 52 in the reduction group and 3 of 15 in the no change group). In comparison to a case-matched polyoma virus–negative control group, the PVN patients were older ($P = .0004$) and there was a predominance of men ($P = 0.02$). Kaplan-Meier analysis demonstrated that patients with PVN had reduced graft survival compared with negative controls ($P = .0004$). It is concluded that PVN is a serious hazard for renal transplant recipients and contributes directly to graft loss. Antiviral drugs are needed, as the reduction of immunosuppression alone may not significantly improve graft function in patients with already established PVN. Although multiple factors probably play a role in the development of PVN, judicious use of immunosuppressive agents is indicated to minimize the occurrence of this infection.

Polyoma virus nephropathy (PVN) has been associated with premature loss of kidney function in renal transplant patients and should therefore be considered in the differential diagnosis of renal allograft dysfunction (1–18). A complete understanding of the pathobiology of PVN has been hindered in part by its low incidence (usually considered to be between 2 to 5% of the renal transplant population) (7). There are currently no described epidemiologic factors for this disease process, and it is unknown whether this is an acquired infection with the graft or whether it represents recipient reactivation with immunosuppression. At the present time, there are no standard means of diagnosis short of a kidney biopsy demonstrating interstitial nephritis with the characteristic inclusion bodies (7). Detection and quantification of BK virus DNA in plasma by PCR is potentially useful for the identification of patients with clinically significant PV reactivation (19), but these methods have yet to be standardized.

The first cases of PVN in renal transplant patients were reported in the 1970s (1,20). However, a significant incidence of PV infection in the renal transplant population has only been seen in recent years. A reemergence (19) of this pathogen became evident after 1995 with the initial report by Pappo *et al.* (10) and was confirmed by several subsequent reports from different centers (5,8,13,16). Although awareness of the clinical and pathologic features of PVN undoubtedly resulted in an increase in the diagnosis of this infection in the past few years, the absolute increase in the number of cases of PVN indicates new risk factors. A clear temporal association between the increase in PVN and the use of newer more potent immunosuppressive drugs (6,7,8,13,21) has suggested that these agents have not only dramatically reduced the acute rejection rates but have also likely created an environment more permissive for viral reactivation.

The clinical management of patients with PVN has proved to be challenging. On the basis of the theory that active viral

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infection is the result of overimmunosuppression, the immunosuppression is often decreased after the diagnosis of PVN. As reported in few clinical studies, this approach has had varying results; a significant proportion of patients have progressed to graft loss due to PVN or acute rejection (6,7,12,14,18). Due to the lack of better therapeutic strategies, the antipolyoma virus agent cidofovir (22) has been used in low doses (0.25 to 1 mg/kg every 2 to 3 wk) in a small number of patients followed by clearance of BK viruria (23). Follow-up studies are not available to determine if treatment with cidofovir, an agent with known nephrotoxic effects, would result in long-term improvement of graft survival in patients with PVN.

In the current report, we describe the clinical course of our first 67 patients with PVN. We particularly outline the posttransplant clinical course before and after the diagnosis of PVN and the relationship with the immunosuppressive treatment. For the purpose of further understanding this disease, we compared the group of patients with PVN with a group of control patients with graft dysfunction without PVN.

Materials and Methods

Study Design

A retrospective analysis of our kidney transplant patients resulted in the identification of 67 patients with PVN diagnosed between June 1997 and March 2001. These patients were identified from 1512 patients who underwent 1 to 8 renal biopsies ($n = 2995$) for allograft dysfunction during that period. During the study period, 1315 renal transplants were performed in our center.

The patients with PVN ($n = 67$) had their clinical course compared with a case-matched control group that consisted of 162 patients biopsied for allograft dysfunction during the same time period who were negative for PVN by histology and urine cytology. The two groups were matched for transplant date and immunosuppressive regimen. Data collected from both groups included demographics, HLA match, type of transplant, type of induction and maintenance immunosuppression, history of delayed graft function, previous acute rejection episodes, pretransplant diabetes, and ureteral obstruction. The baseline creatinine, creatinine at the time of diagnosis of PVN, modifications of immunosuppression after the diagnosis of PVN, and the status of graft function at the conclusion of the study were also evaluated. In the study population and the control group, biopsies were performed for graft dysfunction defined as an increase in the serum creatinine by 20% over the baseline.

Histologic Diagnosis

The histologic diagnosis of PVN proceeded according to standard methods (6–8). These included the observation of PV cytopathic changes in tubular epithelium and confirmation with immunohistochemical stain (SV40 antibody; Access Biomedical, Campo CA), electron microscopy, and PCR for BK virus. The severity of PVN in the first biopsy was histologically graded as described previously (18). In brief, mild PVN consisted of focal viral cytopathic/cytolytic changes with absent or minimal inflammation; moderate and severe PVN consisted of cytopathic/cytolytic changes associated with tubulointerstitial inflammation and patchy or diffuse atrophy, respectively. Urine samples were evaluated for viruria (decoy cells) within 24 h of the renal biopsies according to methodology previously described (18).

Immunosuppression

A variety of induction protocols were used: basiliximab (Simulect, 20 mg on days 0 and 4), Muromonab-CD3 (OKT3, 2.5 to 5 mg for 7 to 14 d), equine lymphocyte Ig (Atgam, 10 to 20 mg/kg for 7 to 14 d), rabbit lymphocyte Ig (Thymoglobulin, 1 to 1.5 mg/kg for 7 d), and daclizumab (Zenapax, 1 mg/kg on day 0 and every 2 wk for a total of five doses).

All patients received three intravenous doses (250 to 500 mg) of methylprednisolone followed by an oral prednisone taper to 0.3 mg/kg by postoperative day 15. Prednisone was further tapered in the outpatient setting to maintenance dosages of 5 to 10 mg/d by 3 mo posttransplant. For cadaveric renal transplant recipients, tacrolimus (FK506, 0.1 mg/kg in two divided doses) or cyclosporine (CSA, 10mg/kg in two divided doses) was started when the serum creatinine fell below 3 mg/dl or on postoperative day 10 if delayed graft function persisted. Living donor transplant recipients received 3 d of FK506 or CSA before transplantation to achieve therapeutic trough levels of 12 to 15 ng/ml (FK506) or 300 to 350 ng/ml for CSA at the time of transplantation. Target trough levels of tacrolimus were lowered to 10 to 12 ng/dl after the first year posttransplantation. Likewise, CSA goal trough levels were decreased to 200 ng/ml after the first year. Mycophenolate mofetil (MMF) was started perioperatively at a dosage of 1 g twice daily (1.5 g twice daily for African American cadaveric recipients). Azathioprine was used before mycophenolate mofetil became available at a dose of 3 mg/kg intravenously in the operating room then 2 mg/kg per d orally thereafter. For the control patients, all CSA, FK506 levels, prednisone, and MMF doses documented throughout the clinical course were tabulated and mean values calculated. Similar calculations were performed for the study group patients before the diagnosis of PVN.

The immunosuppression protocols in the patients with PVN were compared with the immunosuppression protocols of the general transplant population for the study period. The proportion of patients on FK506 and on CSA was determined in both groups.

Statistical Analyses

A comparison was also performed between patients with PVN and control patients with allograft dysfunction but no PVN. A third comparison was done among patients with PVN, contrasting those who had a reduction in immunosuppression with those with no such change. The primary outcome was allograft failure, and Kaplan-Meier curves were used to compare each group with regard to incidence of allograft failure. Cox proportional hazard models were used to adjust for multiple covariates. All means were expressed with SEM and compared using the t test. All categorical variables were expressed with proportions and compared using the χ^2 statistic. SPSS (Chicago, IL) statistical software was used for this study.

Results

Incidence of PVN

The 67 patients with PVN represented 4.4% of all patients biopsied during the period of the study ($n = 1512$). The incidence of PVN in relationship to the total number of transplants performed during the study period ($n = 1315$) was 5.1%.

Characteristics of Patients with PVN (See Table 1)

A total of 174 biopsies were performed in the 67 patients with PVN, representing 5.8% of all biopsies performed during same period. Each patient with PVN had one to seven biopsies ($n = 144$; mean, 2.1 per patient).

The group of patients with PVN included 53 men (79%) and 14 women (21%). Within this group, the male predominance was statistically significant ($P < .001$). The mean age was 54 yr (range, 28 to 75). Thirty-two transplants were from living donors (25 related; 7 unrelated), and 35 were from cadaveric donors. A history of pretransplant diabetes mellitus was found in 21 patients.

No induction was used in 27 patients. Induction with basiliximab was given to 22 patients. Of the remaining patients, ten were induced with Muromonab-CD3, five with equine lymphocyte Ig, two with rabbit lymphocyte Ig, and one with daclizumab. After transplantation, 23 patients had delayed graft function (required dialysis in the first week posttransplant). Maintenance immunosuppression consisted of FK506, MMF, and prednisone in 60 patients and CSA (Neoral), MMF, and prednisone in five patients. Azathioprine (Imuran) and prednisone were used with tacrolimus or CSA in two patients.

Clinical Course in Patients with PVN

Before the diagnosis of PVN, eight patients presented with one episode each of biopsy-proven acute allograft rejection. The rejection episodes were type Ia in four patients, type Ib in three patients, and type IIa in one patient, as classified by the Banff 97 grading scheme (24). The other 59 patients had no documented acute rejection before the diagnosis of PVN.

The diagnosis of PVN was made at an average of 12.8 mo posttransplantation (range, 2 to 52 mo). In the first biopsy showing PVN, mild disease was found in 30 patients, moderate disease in 24, and severe PVN in 13 patients. In all patients, at least one concurrent urine sample showed "decoy" cells.

After the diagnosis of PVN, maintenance immunosuppression remained unchanged in 15 patients and was arbitrarily reduced in 52 patients. Reduction in immunosuppression consisted of a decrease in target level of FK506 from 10 to 15 ng/ml to 6 to 8 ng/ml in 30 patients and CSA from 150 to 200 mg/ml to 75 to 100 mg/ml in 4 patients. FK506 was changed to low-dose CSA in eight patients. Sirolimus was used instead of a calcineurin inhibitor in three patients (FK506 in two; CSA in one). MMF was discontinued in 36 patients, and the dose was decreased to 50% in 14 patients. All patients continued to receive prednisone; the dose being decreased in only 2 patients.

After reduction of immunosuppression, eight patients (15.3%) developed biopsy-proven acute allograft rejection (type IA in three patients, type IB in four patients, and type IIA in one patient). Repeated episodes of acute rejection were seen in three patients. The clinical course of the eight patients who suffered episodes of acute rejection after reduction of immunosuppression varied. Three patients lost their grafts due to cycles of PVN and acute rejection, and three patients had progressive but slow deterioration of graft function, having a mean last creatinine of 6 mg/dl (range, 5.3 to 6.5) at the end of the observation period. The remaining two patients had stable graft function (creatinine of 2.2 and 2.6 mg/dl, respectively) and became negative for PV in subsequent biopsies and urine cytologies.

Three additional patients who did not have acute rejection after immunosuppression was decreased also became negative for PV (biopsies and urine) within 2 to 6 mo. Their last creatinines were 2.1, 3.3, and 4.2 mg/dl, respectively.

Patients were followed for a mean of 12.6 mo after the diagnosis of PVN (range, 3 to 45) and a mean of 26 mo posttransplantation (range, 19 to 71). The mean last creatinine for all patients was 3.97 mg/dl (range, 1.2 to 12). For patients who lost graft function, the last creatinine before the need for dialysis was computed.

During the observation period, 11 patients (16.4%) lost their grafts secondary to persistent PVN ($n = 9$) or a combination of PVN and rejection ($n = 2$). Graft loss occurred at a mean of 11 mo (range, 3 to 26) after the diagnosis of PVN. Six patients, aged 51 to 76 yr (mean, 65), died with functioning grafts at a mean time of 13 mo (range, 4 to 33). The cause of death was due to cardiovascular disease in five patients and sepsis in one patient.

Graft function at the end of the observation period was not different in patients in whom immunosuppression was reduced after the diagnosis of PVN as compared with patients who continued with unchanged immunosuppression. Kaplan-Meier analysis demonstrated a similar rate of graft loss ($P = 0.7$; Figure 1). There was no difference in graft survival when reduction *versus* discontinuation of MMF or tacrolimus was specifically considered. Similarly, at the end of the study there was no difference in graft function in relation to histologic severity of PVN at the time of diagnosis, type of transplant, HLA match, age, gender, history of diabetes, posttransplantation time at diagnosis, delayed graft function, and previous acute rejection.

Ureteral obstruction was observed in 6 (8.9%) of the 67 patients within 4 mo of the histologic diagnosis of PVN. Histologic material from the ureter was not available in these patients to determine the etiology of the obstruction.

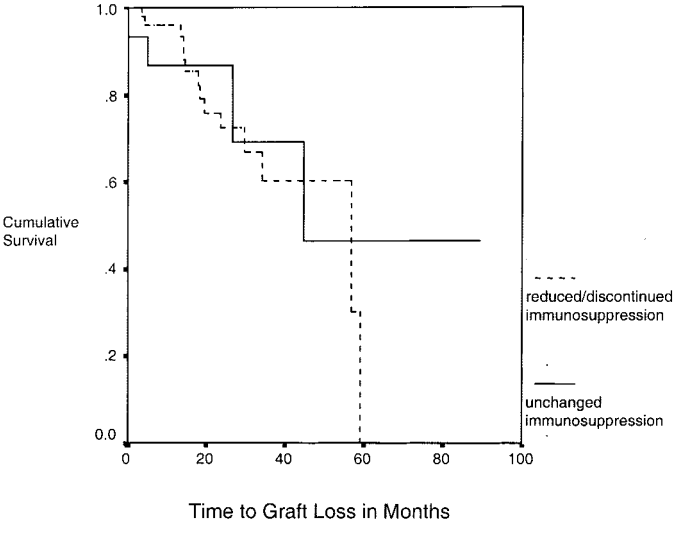

Figure 1. Graft survival analysis. Comparison between patients with decreased immunosuppression ($n = 52$) and unchanged immunosuppression ($n = 15$) after the diagnosis of polyoma virus nephropathy ($P = 0.07$).

Comparison between Patients with PVN and Negative Control Group

The characteristics of the PVN group and the control group are compared in Table 1. Kaplan-Meier analysis demonstrates that at any given time patients with PVN had a reduced graft survival ($P = 0.0004$; Figure 2). There was no evidence that a particular immunosuppressive agent was responsible for PVN, as there was no difference in dose of prednisone, MMF, FK506, or CSA levels between the PVN group and the control group.

Patients with PVN were older ($P = 0.0004$), and there was a predominance of men ($P = 0.02$). Mean age and proportion of men was similar in the control group and the general transplant population. No other significant differences were found between the two groups.

Comparison of Immunosuppression Regimens between the PVN Group and the General Transplant Population

Of the1315 renal transplants performed during the study period, 1063 patients with ≥3 mo of follow-up were treated with a calcineurin inhibitor + MMF + prednisone (962 FK506 and 101 CSA). The remaining patients were either treated with other protocols or had markedly reduced immunosuppression or had lost their grafts in the early posttransplantation period.

In the PVN group, the ratio of patients receiving FK506 compared with those receiving CSA was not statistically different from that of the entire cohort receiving calcineurin inhibitors (FK506, $n = 62$; CSA, $n = 5$ [12:1]) and (FK506, $n = 962$; CSA, $n = 101$ [9.5:1]), respectively ($P = .38$).

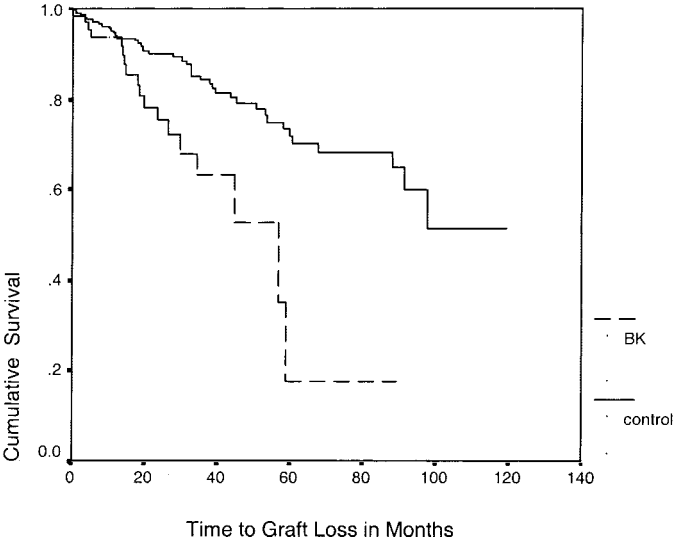

Figure 2. Graft survival analysis. Comparison between patients with polyoma virus nephropathy and controls ($P = 0.004$). BK: 67 patients with graft dysfunction and PV in biopsy and urine; mean follow-up, 26 mo. Control: 162 patients with graft dysfunction and no evidence of PV in biopsy and urine; mean follow-up, 25.3 mo.

Discussion

Three decades after the discovery of the BK virus (1), little is known about the natural history of this organism (25). As in other transplant centers, our center has observed an increased frequency of PVN in renal transplant recipients since our first case was diagnosed in 1997. The true incidence of PVN is difficult to estimate, particularly because a cumulative increase over time is likely to occur. We have seen PVN appearing as late as 5 yr posttransplantation. Of patients biopsied for graft dysfunction in our program, 4 to 5% were found to have PVN. Whereas patients with active PVN have persistently abundant

Table 1. Characteristics of patients with polyoma virus nephropathy (PVN) and negative control group[a]

	PVN	Control[b]	*P*
Patients	67	162	
Mean age (yr)	53.1	46.3	0.001
Men	79%	65%	0.02
Living donor	44.8%	36.4%	NS
Mean HLA mismatch	2.08	2.9	NS
DGF (need for dialysis first wk post Tx)	34.3%	30.6%	NS
Acute rejection	11.9%	19.8%	NS
History of diabetes	32.8%	34%	NS
Ureteral obstruction	8.9%	8.6%	NS
Mean number of biopsies	2.1	1.9	NS
Mean post-transplantation follow-up (mo)	26	25.3	NS
Prednisone (mean dose)	17.2 ± 5.9[c]	16.2 ± 5.3	NS
MMF (mean dose)	1622 ± 514[c]	1816 ± 800	NS
Tacrolimus (mean dose)	11.4 ± 195[c]	10.7 ± 353	NS
Cyclosporine (mean dose)	294.7 ± 110.2[c]	260.3 ± 73.8	NS
Mean graft survival (mo)	47.8	88.7	0.0004

[a] MMF, mycophenolate mofetil.
[b] Patients matched for transplant date and immunosuppression type who were evaluated for graft dysfunction and had biopsies and urines negative for PV.
[c] Mean dose before the diagnosis of PVN.

excretion of decoy cells in urine, a larger proportion of patients (16 to 19%) experience episodic excretion of decoy cells at some point in the posttransplantation course. These patients may or may not develop PVN later (8,18).

All patients diagnosed with PVN presented with variable deterioration of graft function manifested by an increased serum creatinine. Due to the lack of specificity in the clinical presentation, an accurate diagnosis and differentiation from other causes of graft dysfunction could be achieved only by the evaluation of renal biopsies. Concurrent evaluation of urine cytology for exfoliation of PV-infected cells was extremely helpful. In our experience, proper diagnosis can be better achieved with the combined use of these two diagnostic modalities. We have consistently observed that patients with negative urine cytology for PV are unlikely to have clinically significant PV renal disease; the opposite being true in patients that excrete abundant infected cells (18). Other investigators (6,9,16) have also reported the usefulness of urine cytology. Persistence of decoy cells in urine cytology is used by some as an indication to perform BK virus DNA studies in plasma (19).

Although histologically proven PVN was observed as early as 2 mo after transplantation, the mean time to diagnosis was 12 mo posttransplantation. The latter is slightly longer than the previously reported mean time of 9 mo posttransplantation (5,6,16,26). In our experience, male gender and increased age of the transplant recipient represented risk factors for developing PVN. The significance of these findings is unclear at this time because they are not consistent with reports from other centers that showed no gender predilection (5,6,16). Also, the mean ages reported in the other largest series (22 and 7 patients) have been 46.4 and 49.2 yr, which are closer to that of our control group.

As described in this report, renal transplant recipients with graft dysfunction due to biopsy- proven PVN have a much worse graft outcome compared with patients with graft dysfunction due to other causes (Figure 2 and Table 1). The final outcome of graft appeared to be independent of the histologic degree of severity of PVN at diagnosis, although patients presenting with more advanced disease had higher creatinine levels at all time points.

With the reemergence of PV as a pathogen (19), there has been a search for specific immunosuppressive agents or regimens that could be linked to the infection. FK506 and MMF have been regarded as possible causative factors in the increased incidence of PVN because most cases of PVN have been associated with the use of these drugs (5,7,9,16,13,18). Fewer cases have also been reported to occur in renal transplant patients not treated with FK506 and MMF but treated with other immunosuppressive agents such as sirolimus and cyclosporine (16,27,28). In fact, two of our patients with PVN received azathioprine instead of MMF. In the current study, we could find no difference in the levels or doses of immunosuppressive drugs between patients who developed PVN and those who did not. Particularly, we could not demonstrate that the use of FK506 was associated with higher risk for developing PVN in patients receiving MMF compared with CSA. Despite the lack of conclusive evidence linking PVN to a specific regimen or drug, it is still likely that the increased incidence of PVN in our program since 1997 reflects a more global effect of intensive immunosuppression. Our program instituted FK506 in 1994 as part of our transplant protocol and MMF in 1995. Due to the frequent use of organs from marginal donors and a large proportion of African American recipients, the overall immunosuppression used in our program may be more substantial compared with what other programs use. Hirsch (19) recently proposed that multiple factors could lead to the development and progression of PVN in the context of sustained immunosuppression. These factors could include injury of tubular epithelium (9), more aggressive viral genotypes, and transplantation from a seropositive donor into a seronegative recipient. The unexplained increased risk for PVN in men and older recipients in our study group can also be explained in light of the possible multifactorial pathogenesis of PVN. Older patients may be in a sense more immunosuppressed when treated with the same amount of immunosuppression compared with younger patients. All of the above factors may be part of a combination of possible interchangeable risk factors that could promote the development of PVN.

The incidence of PVN in our center is similar to that reported in one other center for patients receiving FK506- or MMF-based immunosuppression (19), but it slightly higher than that reported by most centers (7). This difference may reflect our more intensive effort to use urine cytology and biopsies to identify this pathogen. The increasing incidence of PVN in our center has prompted us to use more customized immunosuppression to minimize the risks for developing this disease.

Although we could not identify an immediate improvement in renal function after empiric reduction of immunosuppression once PVN was diagnosed, a minority of patients (11%) became negative for PV in subsequent biopsies and urine samples. Disappearance of PV was not seen in any patient in whom immunosuppression was not reduced. The immunosuppression reduction in our patients was random and variable in approach, the time of diagnosis varied significantly from patient to patient, and there was a relatively short duration of follow-up; a definite answer regarding the relationship between PVN and reduction in immunosuppression cannot therefore be provided by this study. The similar persistent loss of renal function in patients with and without decreased immunosuppression may be due to relatively late intervention, inadequate decrease in immunosuppression, or the inability to eradicate the viral pathogen once the nephritis appeared. The majority of our patients already had some degree of irreversible tissue damage (tubulointerstitial atrophy) in the first biopsy showing PVN. These findings emphasize the need for early diagnosis and prompt therapeutic intervention. Application of molecular techniques, *e.g.*, quantitative viral DNA in blood, may prove to be beneficial in the future if the diagnosis of PV reactivation can be done before tissue damage is established. During the observation period, the overall percentage of graft loss in our group of patients was low (16.4%) in comparison with 80%, 67%, and 42% reported previously (5,6,16). It is likely, how-

ever, that the graft loss in our patients will become more substantial with longer follow-up.

Although an association between PV ureteritis and obstruction has been clearly presented in previous reports (29), we did not see an increase in the incidence of clinically significant ureteral stenosis in comparison with the control group. The incidence of ureteral stenosis was similar in both groups and similar to the incidence seen in the renal transplant program overall.

History of diabetes mellitus has been implicated in association with PV disease in renal transplants (3). We did not see evidence of this association in our study. Similarly, there was no association between PVN and delayed graft function or previous episodes of acute allograft rejection. Our results are consistent with the study of Priftakis *et al.* (30), which demonstrated no direct association between PV viruria with ischemia time or previous rejection episodes.

In summary, this large experience provides an early glimpse at the severity of this infectious disease process with the largest cohort to date. It also highlights the need for developing information to identify those patients at risk with a screening test for both donor and recipients and a treatment strategy for those unfortunate patients who manifest PVN. In this era of more effective immunosuppressive agents, tailoring of the regimens may be necessary to prevent PVN from becoming a more significant pathogen.

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