High Incidence of Malignancy in Polyomavirus-Associated Nephropathy in Renal Transplant Recipients

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ABSTRACT

Human polyomaviruses (PV), including JC and BK virus, have been reported to cause polyomavirus-associated nephropathy (PVAN), in renal transplant patients. PV infection has been demonstrated to be associated with malignancies in animals; however, the association between malignancy and viral infections in humans is not clear. We retrospectively reviewed our 864 (M:F = 502:362) kidney transplant patients over the past 25 years. We identified PVAN in 6 patients (0.69%), including BK nephropathy ($n = 5$) and JC nephropathy ($n = 1$). Three patients (50%) improved after reducing the immunosuppression, but 3 (50%) progressed to graft loss despite this reduction. Malignancy occurred in 5 out of the 6 patients (83%; $P < .0001$ compared with patients without PVAN), including transitional cell carcinoma ($n = 2$), renal cell carcinoma ($n = 1$), squamous cell carcinoma of skin ($n = 1$) and Kaposi sarcoma ($n = 1$). We concluded that kidney transplant patients with PVAN are at a significantly greater risk to develop malignancy. Whether this is due to a direct effect of PV infection or the result of overimmunosuppression remains to be determined in a future study.

Human polyomaviruses (PVs), including JC (JCV) and BK (BKV), are known to cause polyomavirus-associated nephropathy (PVAN) in 2% to 5% of renal transplant recipients in the past decade.[1] BKV was first isolated in 1971 from the urine of a recipient with a ureteral stricture [2], but the incidence of PVAN did not increase until the introduction of tacrolimus and mycophenolate as immunosuppressive agents. In organ transplant patients BKV mainly invades the urinary tract and may cause hemorrhagic cystitis and PVAN. However, the prevalence of JC viruria is high in Taiwan.[3] We also previously also demonstrated that JCV was able to cause PVAN.[4] As a result of excessive immunosuppressive therapy, reactivation of both viruses is the main etiology of PVAN. The oncogenicity of PVs has already been documented in both animal and *in vitro* studies. The impact of PV (BKV and JCV) infections on neoplasms has not been established in human beings.[5–7] In the present case series, we examined the correlation of clinical courses and malignancy among patients with PVAN.

MATERIALS AND METHODS

Study Design and Population

We retrospectively reviewed patients transplanted from May 1983 to December 2007. Prospectively maintained medical records were used for this analysis, with permission from the Institutional Review Board (IRB TCVGH no. C08037). Diagnosis of PVAN was based on biopsy findings of focal interstitial mononuclear cell infiltrates, necrotic tubular epithelium, and homogeneous intranuclear inclusion bodies, and further confirmed by immunohistochemical staining with specific antibody for BKV or JCV. The diagnosis of malignancy was confirmed pathologically in each case.

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Table 1. Demography of Patients with PVAN in Renal Transplantation

		Creatinine (mg/dL)			ACR		
Pt	Original Disease	Initial	Onset of PVAN	Final	Times	Treatment	Concomitant Infection
1	CTIN	2.1	2.7	4.7	3	MTP × 2	Herpes zoster; condyloma
2	CGN	1.2	2	1.2	1	MTP × 1	Recurrent UTI
3	CTIN	0.9	1.8	1.4	3	MTP × 3	UTI, pneumonia, cryptococcus, norcardia
4	CGN	2.1	2.6	3	5	MTP × 3	HZV, CMV pneumonia, UTI,
						ALG × 2	Deep fungal infection
5	CGN	1.3	1.8	1.4	1	Recycle	Urosepsis, HZV, CMV, Pneumonia, carbuncle, candidiasis
6	IgAN	1.7	2.1	1.8	1	Recycle	UTI

Abbreviations: PVAN, polyomavirus-associated nephropathy; CTIN, chronic tubulointerstitial nephritis; CGN, chronic glomerulonephritis; IgAN, IgA nephropathy; ACR, acute cellular rejection; MTP, methylprednisolone 500 mg for 3 days; ALG, antilymphocyte globulin; HZV, herpes zoster; UTI, urinary tract infection; Recycle, large-dose prednisolone therapy.

RESULTS

Diagnosis of PVAN

Among 990 (M:F = 575:415) patients over the past 25 years, PVAN was confirmed pathologically in 6 patients (0.69%), including BK nephropathy ($n = 5$) and JC nephropathy ($n = 1$). Their clinical data are summarized in Table 1. The posttransplant period to onset of PVAN was 1.3 ± 0.6 years (range 0.8–2.4 years). Graft function improved after reducing the immunosuppressive agents in 3 cases (50%), whereas 3 patients (50%) progressed to graft loss despite similar management.

High Prevalence of Malignancy in PVAN Patients

The overall prevalence of malignancy was 114 (11.5%) of our recipients during the same period. The most common malignancy was transitional cell carcinoma (TCC; $n = 53$: 46.5%), followed by hepatic cell carcinoma (HCC; $n = 29$; 25.4%), renal cell carcinoma (RCC; $n = 6$; 5.3%), and skin cancer ($n = 6$; 5.3%). Malignancies occurred in 5 of the 6 PVAN patients (83%), which was significantly different from the incidence among patients without PVAN ($P < .0001$). The period to malignancy after transplantation was 4.0 ± 2.5 years (range 1.6–6.9 years). The malignancies were 2 TCC in the urinary bladder and native kidneys 1 RCC in the native kidneys, 1 squamous cell carcinoma in the abdominal skin, and 1 Kaposi sarcoma on the left leg.

DISCUSSION

In earlier reports, the incidence of cancer in renal transplant recipients ranges from 2.3% to 31%. The cumulative incidence of malignancy increases with the duration of follow-up and patient age. In our previous report, the risk of cancer in posttransplant patients after 10 years was 13.8-fold higher than the general population.[8] The extraordinarily high incidence of genitourinary tract malignancy observed in our transplant patients, was again discovered among our PVAN recipients. We postulate that PV infections may induce chronic inflammation, predisposing to malignant transformation of cells by exogenous carcinogens, or alternatively, that the infectious agents themselves may be involved in the initiation or promotion of cancer.

In conclusion, renal transplant patients complicated with PVAN are significantly increased risk to develop a malignancy. Whether this is due to a direct effect of PV infection or the result of over immunosuppression remains to be determined in a future study.

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