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Polyomaviruria in Renal Transplant Patients Is Not Correlated to the Cold Ischemia Period or to Rejection Episodes

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Polyomaviruria was observed in one-third of all renal transplant patients, irrespective of whether their renal grafts came from a living or cadaver donor, and was not correlated to graft rejection episodes. This suggests that the renal graft ischemia period is not the major cause of polyomavirus reactivation and that reactivation of polyomavirus is not a dominant cause of graft rejection.

BK virus (BKV) and JC virus (JCV) are widely spread human polyomaviruses that remain latent in the kidney and, possibly, also in the blood and the brain (5, 9, 11, 19). Reactivation can be manifested as symptom-free viral excretion in the urine and is more frequently observed in immunosuppressed patients (10). In such patients BKV can also be associated with hemorrhagic cystitis or ureteral stenosis, while JCV can cause progressive multifocal leukoencephalopathy (PML) (1, 6, 8, 17).

In renal transplant recipients the incidence of BK and JC viruria has been reported to be in the range of 14 to 65%, and reactivation has been speculated to be of donor or recipient origin (7, 13, 15, 16, 18, 19). In half the patients viruria occurs within the first 3 months after transplantation and can be transient or last for weeks or years (13). Ureteral stenosis, graft rejection, rise in serum creatinine level, impaired renal function, and PML have been described in renal transplant patients with polyomaviruria (2, 6, 8, 19). Nevertheless, it has been difficult to assess the clinical significance of viral infection for disease development. It has been suggested that damage of the ureter by ischemia or by inflammation may reactivate latent polyomavirus infection in the ureteric epithelium and cause ureteral stenosis (6, 8). In line with this hypothesis are recent findings in a murine experimental system in which reactivation of polyomavirus is observed in adult mice after occlusion of the renal artery (3). However, so far none of the previous reports have focused on the fact that the renal graft ischemic period (i.e., the period after removal of the renal graft from the donor and until transplantation, when the renal graft is kept at about 4°C in an icebox) may influence polyomaviruria. Hence, polyomaviruria may vary between living donor (LD) and cadaver donor (CD) graft recipients. This could partly explain the marked difference in graft survival rates between LD grafts (1-year graft survival rate, 90 to 95%) and CD grafts (1-year graft survival rate, 75 to 80%) (12). Furthermore, the difference in survival rates are independent of HLA matching since the same rates are observed among both related and spouse donors (12).

To study if polyomaviruria is correlated to renal graft ischemia, we investigated if the presence of polyomaviruria varied in two groups of patients with different renal graft ischemia times. Thus, one group of patients received renal grafts from LDs and the ischemia period was only about 30 min, whereas the second group of patients received renal grafts from CDs and the average cold ischemia time was 17 h in our department.

Three hundred eighty-three urine samples were collected during the period from 1995 to 1998 from 170 patients (of northern European origin and of 2 to 73 years of age) from 1 week to 2 years after transplantation and were analyzed for the presence of polyomaviruses. The majority of all urine samples were analyzed shortly after collection. If possible, the samples were analyzed within 24 to 48 h; otherwise, they were stored at −20°C and were analyzed within a week by a nested PCR for simultaneous detection of BKV and JCV DNA (4). The 176-bp fragment of BKV DNA and the 173-bp fragment of JCV DNA obtained after amplification with the inner primer pair could easily be distinguished after restriction enzyme digestion with *Bam*HI or *Hin*fI (4, 14). One hundred four patients received a kidney from a CD, while 66 received a kidney from an LD. Data concerning ureteral stenosis or graft rejection were collected from the patients' records. As a control group for comparison, urine samples from 14 laboratory staff were included (4).

Of 170 patients, 55 (33%) were found to be positive for human polyomavirus in their urine samples at some time point after transplantation. A detailed description of the data is presented in Table 1. After restriction enzyme cleavage, BKV DNA was found in the urine samples of 12 (7%) patients, JCV DNA was found in the urine samples of 37 (22%) patients, and both BKV and JCV DNAs were found in the urine samples of 6 (3.5%) patients (Table 1). There was no significant difference between excretion of human polyomaviruses in recipients of

TABLE 1. Presence of BKV and JCV DNA in urine samples within 24 months after transplantation from patients with LD or CD grafts

Source of donor	No. (%) of urine samples				
	Total	BKV positive	JCV positive	BKV and JCV positive	BKV and JCV negative
LD	66	5 (7.5)	15 (23)	4 (6)	42 (63.5)
CD	104	7 (7)	22 (21)	2 (2)	73 (70)
Total	170	12 (7)	37 (22)	6 (3.5)	115 (67.5)

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TABLE 2. Presence of polyomavirus and rejection episodes in patients receiving LD or CD renal grafts

Source of polyomaviruria	No. of patients with the following rejection characteristics/total no. of patients in graft group (%):					
	LD grafts		CD grafts		Total	
	With rejection	Without rejection	With rejection	Without rejection	With rejection	Without rejection
BKV	1/5 (20)	4/5 (80)	3/7 (43)	4/7 (57)	4/12 (33)	8/12 (67)
JCV	3/15 (20)	12/15 (80)	10/22 (45)	12/22 (55)	13/37 (35)	24/37 (65)
BKV and JCV	1/4 (25)	3/4 (75)	1/2 (50)	1/2 (50)	2/6 (33)	4/6 (67)
Neither BKV nor JCV	25/42 (60)	17/42 (40)	27/73 (37)	46/73 (63)	52/115 (45)	63/115 (55)
Total	30/66 (45)	36/66 (55)	41/104 (40)	62/104 (60)	71/170 (42)	99/170 (58)

kidneys from living related individuals (36.5%) versus recipients of kidneys from cadavers (30%). Furthermore, no difference with regard to the excretion of BKV, JCV, or both BKV and JCV was observed between the same two groups of patients (Table 1). There was no significant difference in the excretion of human polyomaviruses in the urine between men (30%) and women (36%) (data not shown). Furthermore, no difference with regard to the excretion of BKV (6% of men and 8% of women), JCV (21% of men and 23% of women), or both BKV and JCV (3% of men and 5% of women) was observed between the sexes (data not shown).

The majority of renal transplant patients were between 30 and 60 years of age, and the rate of excretion of polyomaviruses in the urine varied between 20 and 50% in these age groups (data not shown). This incidence is similar to that observed in our control group, where JC viruria was observed in half the subjects but in whom, however, BK viruria was absent (4). Nevertheless, it maybe of interest to mention that three of the four (75%) transplant patients ages 2 to 10 excreted polyomavirus (data not shown).

In 71 (42%) of 170 patients, one or more graft rejection episodes were detected according to the data from the patients' records (Table 2). Of the 71 patients with rejection episodes, 19 (27%) patients excreted polyomaviruses, while in a group without rejection 36 (36%) of 99 patients had polyomaviruria. This information is shown separately in Table 2 for BKV and JCV and for patients with LD or CD grafts. There was no difference in the onset of polyomaviruria between the patients with and without rejection episodes. None of the patients exhibited ureteral stenosis during the 2-year follow-up period.

In summary, as in previous reports the incidence of polyomaviruria in our group of transplant recipients was about 30%, irrespective of the source of the renal graft. Furthermore, in our study we found that excretion of JCV dominates over excretion of BKV. However, although the observed JC viruria in our transplant group is within the range observed and previously published by us and others for healthy adults, which is about 10 to 50%, BKV was also excreted, and this is not observed in immunocompetent individuals (4, 13, 15, 20). Also, similar to previous findings, an early onset of viruria is observed in the majority of the patients in our study (13). Nevertheless, the presence of polyomaviruria was not correlated to graft rejection episodes. This suggests that the renal graft ischemia period is not the major cause of polyomavirus reactivation and that reactivation of polyomavirus is not a dominant cause of or result of graft rejection.

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REFERENCES

1. **Arthur, R. R., K. V. Shah, S. J. Baust, G. W. Santos, and R. Saral.** 1986. Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. N. Engl. J. Med. **315:**230–234.
2. **Arthur, R. R., and S. J. Shah.** 1989. Occurrence and significance of papovaviruses BK and JC in the urine, Prog. Med. Virol. **36:**42–61.
3. **Atencio, I. A., F. F. Shadan, X. J. Zhou, N. D. Vaziri, and L. P. Villarreal.** 1993. Adult mouse kidneys become permissive to acute polyomavirus infection and reactivate infections in response to cellular damage and regeneration. J. Virol. **67:**1424–1432.
4. **Bogdanovic, G., M. Brytting, P. Cinque, M. Grandien, E. Fridell, P. Ljungman, B. Lönnqvist, and A.-L. Hammarin.** 1994. Nested PCR for detection of BK and JC virus DNA Clin. Diagn. Virol. **2:**211–220.
5. **Chesters, P. M., J. Heritage, and D. J. McCance.** 1983. Persistence of DNA sequences of BK and JC viruses in normal human tissues and in diseased tissues. J. Infect. Dis. **147:**676–684.
6. **Coleman, D. V., A. M. Field, S. D. Gardner, K. A. Porter, and T. E. Starzl.** 1973. Virus-induced obstruction of the ureteric and cystic duct in allograft recipients. Transplant. Proc. **5:**95–98.
7. **Coleman, D. V., S. D. Gardner, and A. M. Field.** 1973. Human polyomavirus infection in renal allograft recipients. Br. Med. J. **3:**371–375.
8. **Coleman, D. V., S. MacKenzie, S. D. Gardner, S. D. J. Foulding, B. Amer, and W. Russell.** 1978. Human polyomavirus (BK) infection and ureteral stenosis in renal allograft recipients. J. Clin. Pathol. **31:**338–347.
9. **Dörries, K., E. Vogel, S. Gunther, and S. Czub.** 1994. Infection of human polyomaviruses JC and BK in peripheral blood leukocytes from immunocompetent individuals. Virology **198:**59–70.
10. **Dörries, K.** 1996. Virus-host interactions and diagnosis of human polyomavirus-associated disease. Intervirology **39:**165–175.
11. **Elsner, C., and K. Dörries.** 1992. Evidence of human polyomavirus BK and JC infection in normal brain tissue. Virology **191:**72–80.
12. **Fehrman-Ekholm, I., H. E. Wilczek, C. Brattström, G. Tyden, F. Duraj, and C. G. Groth.** Kidney transplantation using living unrelated donors gave the same excellent results as living related donors. Transplant. Int., in press.
13. **Gardner, S. D., E. F. MacKenzie, C. Smith, and A. A. Porter.** 1984. Prospective study of the huan polyomaviruses BK and JC and cytomegalovirus in renal transplant recipients. J. Clin. Pathol. **37:**578–586.
14. **Hammarin, A.-L., G. Bogdanovic, V. Svedhem, R. Pirskanen, L. Morfeldt, and M. Grandin.** 1996. Analysis of PCR as a tool for detection of JC virus DNA in cerebrospinal fluid for diagnosis of progressive multifocal leukoencephalopathy. J. Clin. Microbiol. **34:**2929–2932.
15. **Hogan, T. F., B. L. Padgett, D. L. Walker, E. C. Borden, and J. A. McBain.** 1980. Rapid detection and identification of JC virus and BK virus in human urine by using immunofluorescence microscopy. J. Clin. Microbiol. **11:**178–183.
16. **Lecatsas, G., O. W. Prozesky, J. V. Wyk, and H. J. Els.** 1973. Papova virus in urine after renal transplantation. Nature **241:**421–425.
17. **Major, E. O., K. Ameniya, C. S. Tornatore, S. A. Houff, and J. R. Berger.** 1992. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease in the human brain. Clin. Microbiol. Rev. **5:**49–73.
18. **Marshal, W. F., A. Telenti, J. Proper, A. J. Aksamit, and T. F. Smith.** 1991. Survey of urine from transplant recipients for polyomaviruses JC and BK using the polymerase chain reaction. Mol. Cell. Probes **5:**125–128.
19. **Shah, K. V.** 1996. Polyomaviruses, p. 2027–2043. *In* B. N. Fields, D. M. Knipe, P. M. Howley, et al. (ed.), Virology, 3rd ed. Lippincott-Raven Publishers, Philadelphia, Pa.
20. **Sundsfjord, A., T. Flaegstad, R. Flo, A. R. Spein, M. Pedersen, H. Permin, J. Julsrud, and T. Traavik.** 1994. BK and JC viruses in human immunodeficiency virus type 1-infected persons. Prevalence, excretion, viremia and viral regulatory regions. J. Infect. Dis. **169:**484–490.