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Correlation of BK Polyomavirus (BKPyV)-specific Immunity and BKPyV Viruria within 6 months after Kidney Transplantation: A Prospective Cohort Study

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Background

- BK polyomavirus (BKPyV)-associated nephropathy (BKPyVAN) is an attributable cause of allograft dysfunction among kidney transplant (KT) recipients
- Since viral-specific immunity has been shown to be correlated with viral containment in solid organ transplant (SOT) recipients, we investigated an association of BKPyV-specific immunity and BKPyV viruria in KT recipients.

Methods

- A prospective cohort study of all adult KT recipients between January and August 2019 was conducted
- High-level BKPyV viruria: BKPyV VL in urine > 7log10 copies/mL, measured by polymerase chain reaction
- BKPyV-specific immunity was measured by an intracellular cytokine assay measuring the percentage of IFN-γ-producing $CD4^+$, $CD8^+$, NK, and NKT cells, after stimulation with large-T antigen (LT) and viral capsid protein 1 (VP1)
- The incidence of high-level BKPyV viruria within 6 months after KT was estimated by the Kaplan-Meier method.
- Clinical and immunological factors were analyzed using Cox proportional hazard model.
- BKPyV-specific immune responses prior to and at 1 month after KT were compared using a mixed-linear regression test.

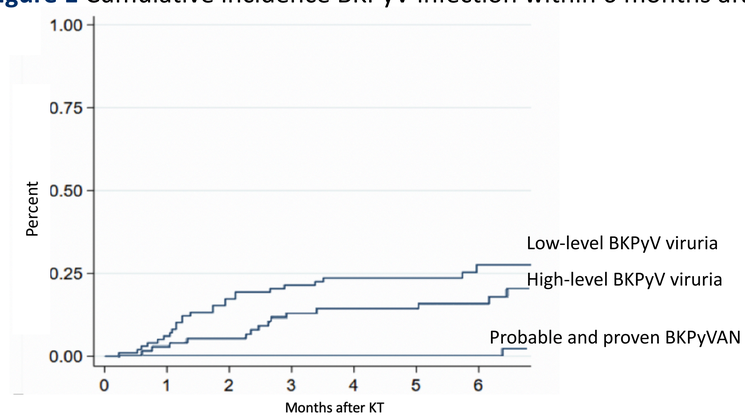
Results

- Among 90 evaluable patients, 37% were female with a mean age (± SD) of 42 ± 12 years
- Sixty-four and 68 % received deceased-donor KT and induction immunosuppressive therapy, respectively.
- The cumulative incidence of high-level BKPyV viruria within 6 months was 20%.
- In multivariate analysis, panel-reactive antibody of 11-50% (HR 13.35; 95%CI, 1.93-92.59; P = 0.009), %NK cells (HR 1.26; 95%CI, 1.08-1.47; P = 0.004), and %VP1-specific NK cells (HR 1.25; 95%CI, 1.09-1.43; P = 0.002) were independently associated with high-level BKPyV viruria
- Among those with high-level BKPyV viruria, the mean %NK, %VP1-specific NK cells and %NKT cells at 1-month post-KT were significantly increased over time as compared to pre-KT (coefficient: 1.20; 95%CI, 0.03-2.37; P = 0.04), (2.60; 95%CI, 1.08-4.12; P = 0.001), and (0.20; 95%CI, 0.05-0.35; P = 0.008), respectively.

Table 1 Clinical Characteristics of 90 KT recipients

Characteristics	N (%)	Characteristics	N (%)
Female	33 (36.7)	Terminal creatinine (median, IQR)	0.86 (0.69-1.17)
Age (mean ± SD)	42 ± 12	Maintenance therapy	
ESRD etiologies (%)		Tacrolimus	74 (82.2)
Diabetic nephropathy	6 (6.7)	Cyclosporin	17 (18.9)
Hypertension	5 (5.6)	Mycophenolate	40 (44.4)
Glomerulonephritis	15 (16.7)	sodium	56 (62.2)
Unknown	61 (67.8)	Mycophenolate	90 (100)
Type of transplant		mofetil	
DDKT	58 (64.4)	Prednisolone	
LRKT	32 (35.6)	PRA (%)	
HLA mismatch (%)		1-10	82 (91.1)
0	10 (11.1)	11-50	4 (4.4)
1-3	66 (73.3)	>50	4 (4.4)
4-6	14 (15.6)		
Induction therapy		CMV serostatus (%)	
Basiliximab	59 (65.6)	D+/R+	86 (95.6)
Anti-thymocyte	3 (3.3)	D-/R+	1 (1.1)
globulin	28 (31.1)	D+/R-	2 (2.2)
None		D-/R-	1 (1.1)

Figure 1 Cumulative incidence BKPyV infection within 6 months after KT



Conclusions

- ❖ A presence and increasing proportion of NK, VP1-specific NK and NKT cells were observed among KT recipients with early and clinically significant BKPyV viruria
- ❖ BKPyV-specific NK and NKT cell immune monitoring could potentially stratify those at risk of BKPyV viruria

Table 2 Univariate and multivariate analysis of clinical and immunological factors associated with high-level BKPyV viruria

Factors	Univariate			Multivariate		
	HR	95%CI	P-value	HR	95%CI	P-value
Female sex	1.04	0.39-2.82	0.933			
Age	1.01	0.97-1.05	0.695			
Diabetic nephropathy	8.10	2.39-27.42	0.001			
DDKT	0.95	0.35-2.58	0.895			
Terminal creatinine	0.45	0.13-1.54	0.202			
HLA mismatch	1.16	0.44-3.05	0.767			
PRA %, 11-50 vs. 1-10	4.76	1.06-21.41	0.042	13.35	1.93-92.59	0.009
ATG induction therapy	4.70	0.49-45.27	0.180			
ALC ≤ 500 cells/mm^3	0.67	0.22-2.09	0.495			
$\%CD4^+$	0.96	0.89-1.03	0.237			
$\%CD8^+$	1.05	0.97-1.14	0.207			
%NK	1.17	1.03-1.34	0.020	1.26	1.08-1.47	0.004
%LT-specific NK	0.89	0.58-1.38	0.625			
%VP1-specific NK	1.20	1.06-1.36	0.004	1.25	1.09-1.43	0.002
%NKT	7.31	0.07-753.80	0.401			
%LT-specific NKT	0.90	0.57-1.44	0.670			
%VP1-specific NKT	1.15	1.01-1.31	0.782			

Table 3 Mixed linear effect between immunological factors and time (pre-KT vs. 1-month post-KT) among all KT recipients with high-level BKPyV viruria

Factors Mean	High-level BKPyV viruria (n= 18)		
	Coefficient	95%CI	P-value
$\%CD4^+$	-1.253	-7.650-5.145	0.701
%LT-specific $CD4^+$	-0.001	-0.009-0.006	0.755
%VP1-specific $CD4^+$	0.003	-0.005-0.012	0.372
$\%CD8^+$	4.277	-0.484-9.039	0.078
%LT-specific $CD8^+$	-0.001	-0.017-0.014	0.876
%VP1-specific $CD8^+$	0.025	-0.004-0.055	0.094
%NK	1.202	0.033-2.371	0.044
%LT-specific NK	-0.307	-1.503-0.911	0.621
%VP1-specific NK	2.602	1.083-4.121	0.001
%NKT	0.199	0.051-0.348	0.008
%LT-specific NKT	-1.671	-5.331-1.990	0.371
%VP1-specific NKT	-0.319	-3.041-2.403	0.819