There are no relevant conflicts of interest to disclose.

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Immune Monitoring in BK Virus Nephropathy: How to Identify Recipients at the Highest Risk?

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INTRODUCTION

Infection has become one of the main hurdles of disease-free survival after renal transplantation. Due to intensified induction and maintenance immunosuppression the morbidity of viral infections including CMV, BKV, and EBV has increased in kidney transplant recipients (KTRs) over the last decades. Therefore, virus-specific immune control is of paramount importance to restrict reactivation of latent viruses.

Reactivation of latent BKV-infection in KTRs can cause so-called BKV-associated nephropathy (BKVN) with graft failure in up to 30% of cases. BKV monitoring strategies have been implemented to improve the management of BKV-replication in the immunocompromised host. Quantification of BKV load in urine and serum have been evaluated to allow identification of a subgroup of KTRs at high risk for progression to BKVN. In addition monitoring of BKV-specific immunity has been considered to guide preemptive therapeutic interventions and to assess the response to antiviral therapy in KTRs with BK viremia.

PATIENTS AND METHODS

We attempted to identify risk factors associated with BKV reacitvation by analyzing all KTRs transplanted in our single transplant center from 2004 to 2012 with a clear differentiation of BK viremia vs. BKVN. Further we prospectively monitored overall and BKV-specific immunity prior to transplantation and for the first 3 months posttransplantation. Frequencies of alloreactive, BKV-, and CMV-specific interferon-γ-(IFNg)-secreting lymphocytes were analyzed using an Elispot assay after stimulation of peripheral blood mononuclear cells (PBMC) with donor lymphocytes, BKV-, and CMV-proteins. We attempted to quantify the extent of immunosuppression by enumeration of lymphocyte subpopulations and cytokines.

	BKV Group (n=103)	Control Group (n=235)	P value	BK nephropathy (n=24)	BK viremia (n=79)	P value
Age, yr	54 (18-76)	54 (19-77)	*0.742*	55 (24-70)	54 (18-76)	*0.815*
Male sex, n (%)	71 (69)	162 (69)	*0.802*	17 (71)	54 (68)	*0.578*
Cadaveric donation, n (%)	76 (74)	177 (75)	*0.786*	20 (83)	56 (71)	*0.294*
First kidney allograft, n (%)	85 (83)	209 (89)	*0.116*	20 (83)	65 (82)	*1*
Cold ischemia time, hr:min	11:09 (4:00-29:10)	10:25 (2:43-24:08)	*0.469*	09:15 (4:23-29:10)	11:18 (4:00-22:43)	*0.205*
CMV seropositivity, n (%)	68 (66)	159 (68)	*0.802*	15 (63)	53 (67)	*0.806*
CMV viremia, n (%)	57 (55)	93 (40)	***0.006****	13 (54)	44 (56)	*1*
Concomitant CMV viremia, n (%)	31 (30)	-	-	6 (25)	25 (32)	*0.618*
CMV D+R-, n (%)	15 (15)	34 (14)	*1*	1 (4)	14 (18)	*0.183*
BK nephropathy, n (%)	24 (23)	0 (0)	-	24 (100)	0 (0)	-
EBV viremia, n (%)	18 (17)	26 (11)	*0.116*	5 (21)	13 (17)	*1*
Malignancies in follow-up, n (%)	14 (14)	25 (11)	*0.461*	4 (17)	10 (13)	*0.734*
Delayed Graf Function, n (%)	28 (27)	69 (29)	*0.794*	6 (25)	22 (28)	*0.759*
Immunosuppression, n (%)						
Cyclosporine	21 (20)	50 (24)	*0.886*	2 (8)	19 (24)	*0.147*
Tacrolimus	82 (80)	185 (76)	*0.886*	22 (92)	60 (76)	*0.147*
Mycophenolate mofetil	95 (92)	226 (96)	*0.174*	24 (100)	71 (90)	*0.193*
Sirolimus/Everolimus	1 (1)	2 (1)	*1*	0 (0)	1 (1)	-
Steroids	98 (95)	223 (95)	*1*	24 (100)	74 (94)	*0.588*
Induction, n (%)						
IL-2R antagonist	83 (81)	212 (90)	***0.020****	19 (79)	64 (81)	*1*
Lymphocyte-depletion	20 (19)	23 (10)	***0.020****	5 (21)	15 (19)	*1*
ABO-incompatible	7 (7)	14 (6)	*1*	3 (13)	4 (5)	*0.349*
Acute rejection, n (%)						
Total	59 (57)	62 (26)	***<0.001***	15 (63)	44 (57)	*0.641*
Borderline/IA/IB	46 (45)	47 (20)	***<0.001***	12 (50)	34 (43)	*0.641*
IIA/IIB/III	13 (13)	15 (6)	*0.084*	3 (13)	10 (14)	*1*
Concomitant acute rejection, n (%)	36 (35)	-	-	7 (29)	29 (37)	*0.627*
Lymphocyte depletion	6 (6)	12 (5)	*0.794*	1 (4)	5 (6)	*1*
Total HLA mismatch, n (%)						
4-6 HLA mismatch	42 (41)	84 (36)	*0.394*	9 (38)	33 (42)	*0.814*
Donor age, yr	53 (13-85)	53 (3-85)	*0.323*	54 (17-74)	53 (13-85)	*0.785*

RESULTS

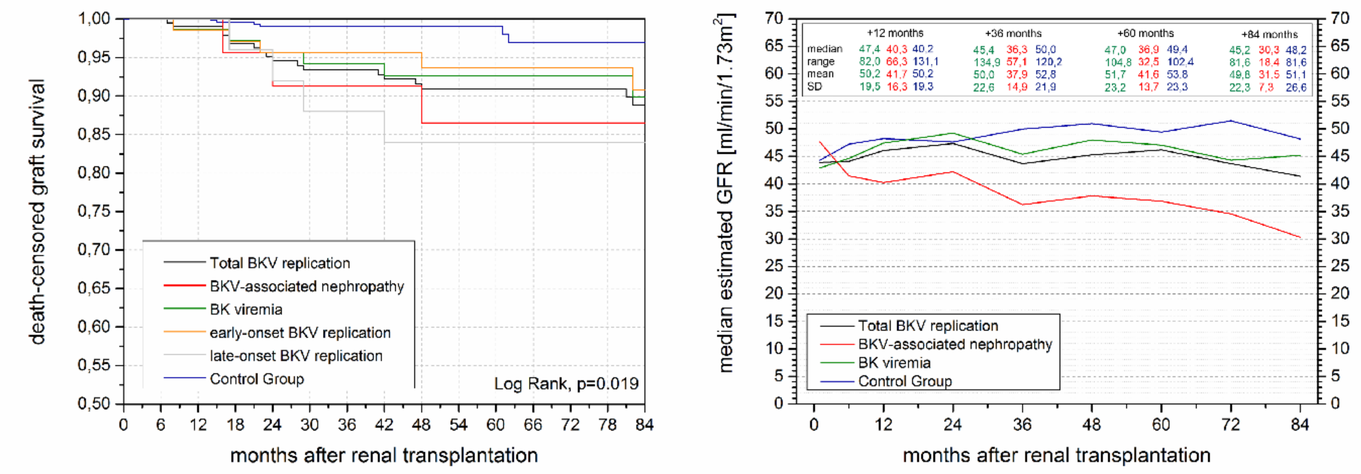

Figure 1AB: 1A Kaplan-Meier plot of death-censored graft survival by BKV-replication after renal transplantation. Reduced death-censored graft survival in the BKV group compared to the control group (Log Rank, p=0.005). **1B** Significantly decreased median eGFR was observed in KTRs with BKVN compared to the control group and KTRs with BK viremia only (p<0.05).

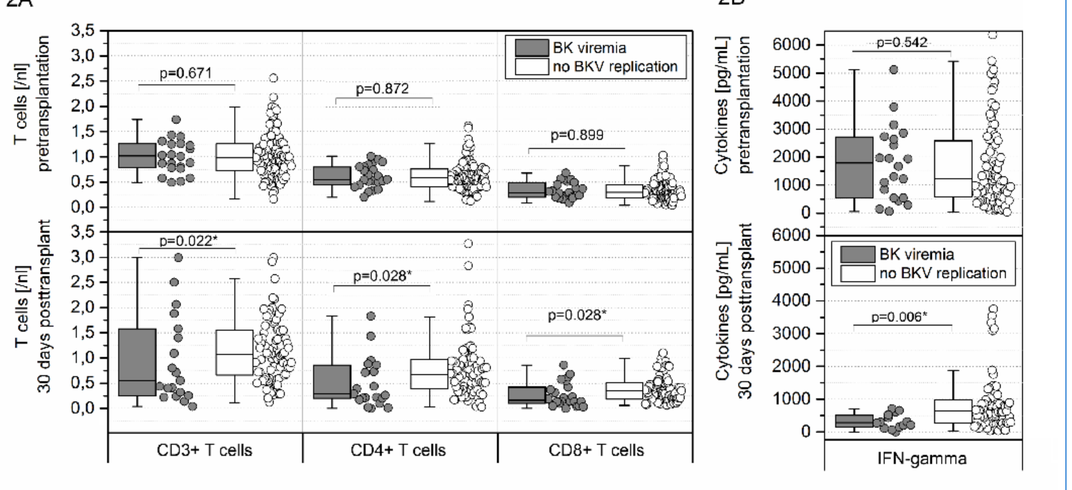

Figure 2AB. Significantly decreased CD3+, CD4+, and CD8+ T cell counts characterize patients with an increased risk for BK viremia after renal transplantation. **2B** Significantly decreased IFNg serum levels were observed in KTRs developing BKV-replication (p<0.05).

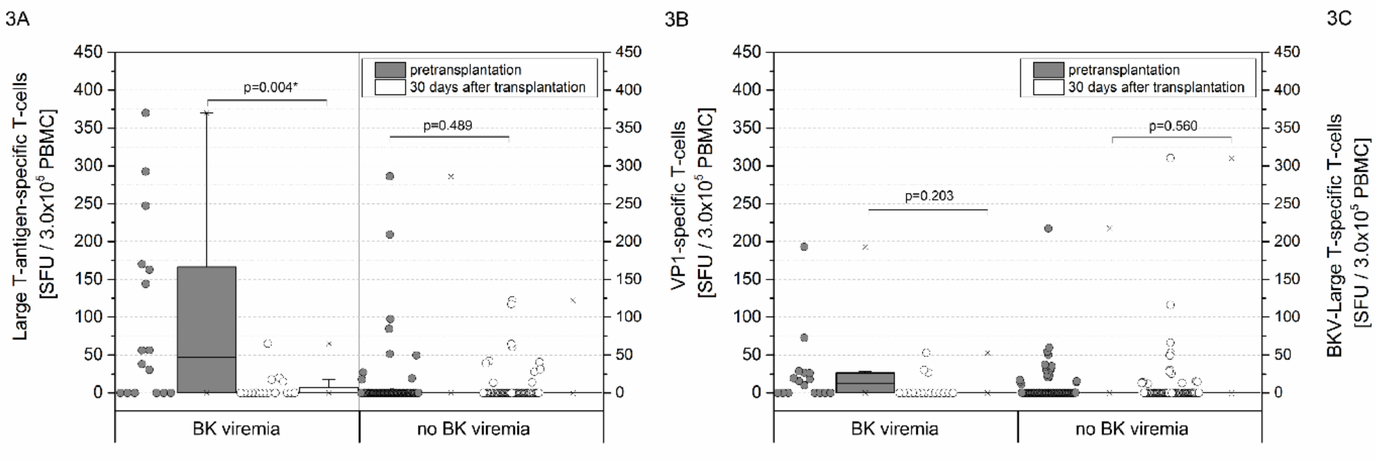

Figure 3A-C. 3AB Detectable BKV-specific cellular immunity prior to transplantation directed to BKV-Large T-antigen (A) and BKV-VP1 (B) characterizes KTRs at increased risk for developing early-onset BKV-replication. **3C** KTRs with early-onset BKV-replication show a significant decrease in BKV-Large T-antigen-specific T-cells from pre- to posttransplant.

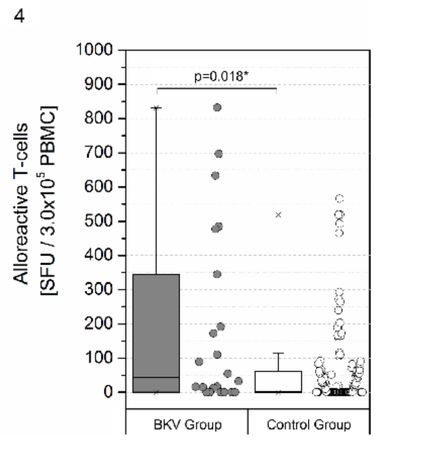

Figure 4. Significantly increased frequencies of alloreactive T-cells in KTRs developing early-onset BKV-replication.

CONCLUSIONS

1. **Overimmunosuppression as the most important risk factor for early-onset BKV-replication:** The incidence of BK viremia is disproportionately increased in KTRs with lymphocyte depletion induction, concomitant CMV-reactivation, and acute rejection episodes, most likely due to a largely intensified immunosuppressive treatment. CD4+ and CD8+ lymphopenia plus decreased serum IFNg levels in the early posttransplant period indicate overall impaired immune responses with an increased risk of viral replication due to a state of over-immunosuppression.
2. **No protection from BKV-reactivation in KTRs with pretransplant BKV-specific cellular immunity:** Our results suggest that BKV-specific cellular immunity is triggered by subclinical activation of BKV-infection in the recipient prior to transplantation. In KTRs developing BK viremia overimmunosuppression result in a decline of BKV-specific T-cells insufficient to further regulate BKV-replication or to control new BKV-infection from the donor. Pretransplant BKV-specific immunity was predominantly directed to BKV-Large T-antigen, which is in line with previous observations suggesting that anti-Large T-antigen responses are associated with control and protection from BKV-replication.
3. **Effects of BKV-replication on augmentation of alloreactive T-cells and vice versa:** Cross-reactivity of alloreactive T-cells with viral antigens may contribute to allograft injury and observed decreased graft survival in follow-up. Cellular alloimmunity, even late after transplantation may contribute to progressive immune-mediated graft injury and the increased risk of late-onset BK viremia in retransplant patients.

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