Annals of Diagnostic Pathology 42 (2019) 1–6

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

BK virus histopathologic disease severity does not predict allograft outcome in renal transplant recipients

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ARTICLE INFO

Keywords:
BK polyomavirus nephropathy
BKPyVN
Kidney transplantation
Kidney allograft loss

ABSTRACT

Aims: BK polyomavirus nephropathy (BKPyVN) is an important cause of allograft failure after renal transplantation. Despite early screening for the virus, allograft loss from BKPyVN is still experienced in up to 14% of all renal transplant recipients. The aim of this study was to investigate the association between BKPyVN histopathologic disease severity and allograft outcome at our center.

Methods: Kidney transplant recipients who had undergone transplantation between 2002 and 2014 with biopsy proven BKPyVN were eligible for this retrospective study. Each biopsy was re-evaluated by a single pathologist blinded to the clinical data and scored according to the Banff criteria for rejection and BKPyVN. Serum creatinine and BK viral load at the time of biopsy diagnosis as well as allograft outcomes to include allograft survival and serum BK viremia resolution were collected for each recipient to determine if BK virus histopathologic disease severity could predict allograft outcome.

Results: Twenty cases of BKPyVN were identified from 1031 total renal transplants performed. There was no statistical association between allograft loss and BKPyVN histopathology ($p = 0.49$). There was also no statistical association between BKPyVN histopathology and BK viral load at the time of biopsy diagnosis ($p = 0.38$) or serum BK viremia resolution ($p = 0.16$).

Conclusions: BKPyVN histopathology does not appear to be useful in predicting renal allograft outcome in those recipients diagnosed with BKPyVN which is in contrast to some previously published data.

1. Introduction

BK polyomavirus belongs to the polyomavirus family of double stranded, nonencapsulated DNA viruses that has the potential to infect humans. Primary infection is thought to occur in childhood with symptoms resembling an upper airway infection [1]. The virus enters cells by caveola-mediated endocytosis aided by the presence of an intact microtubule network during early infection [2]. The virus is present in the urogenital system of up to 90% of the general population in the latent phase through its interaction with GD1b and GT1b gangliosides found in renal tubular and transitional epithelium. There are no symptoms experienced by immunocompetent individuals [3]. The virus can reactivate however in immunocompromised individuals leading to high levels of viremia and potential renal pathology known as BK polyomavirus nephropathy.

BK polyomavirus nephropathy (BKPyVN) is a well-recognized cause of allograft dysfunction and loss after kidney transplantation. Transplant centers have developed program specific BK viremia screening protocols to recognize early viremia and implement interventions to prevent potential harm to the allograft. Both pre- and post-transplant factors may be responsible for BK polyomavirus reactivation and subsequent nephropathy including immunosuppression [4,5]. Interventions for nephropathy prevention range from reduction of immunosuppression to the initiation of therapeutics such as leflunomide, cidofovir and/or intravenous immunoglobulin which have demonstrated anti-BK virus benefit in small studies [6]. Despite this screening and early intervention approach, allograft loss from BKPyVN is still experienced in up to 14% of all renal transplant recipients [7].

It has been proposed that inflammation and fibrosis stage on allograft biopsy are important prognostic parameters for BKPyVN allograft outcome [8,9]. The aim of this study was to investigate the association between histopathologic features of BKPyVN and allograft outcomes at

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https://doi.org/10.1016/j.anndiagpath.2019.06.012

our center. Finding a clinicopathological correlation would assist in the clinical management of transplant recipients who develop BKPyVN and help potentially circumvent allograft loss.

2. Methods

2.1. Kidney transplant recipients

This retrospective study was approved by the Institutional Review Board (#201605773). Kidney transplant recipients who had undergone transplantation at our institution between 2002 and 2014 with biopsy proven BKPyVN were eligible for the study. No recipient with biopsy proven BKPyVN was excluded from the analysis. The following clinical characteristics were abstracted by a transplant physician from the medical record: age at transplant, gender, race, cause of kidney disease, second transplant (yes/no), serum creatinine (mg/dL) at the time of BKPyVN diagnosis, BK viral load (copies/mL) at the time of diagnosis, BK viremia resolution at the time of analysis (yes/no), functioning allograft (yes/no) at the time of analysis and cause of allograft failure.

2.2. Posttransplant BK screening/management protocol

Screening blood PCR assays for BK polyomavirus are obtained at 6, 12, 26, 39 and 52 weeks posttransplantation followed by screening PCRs at 16, 20 and 24 months posttransplantation. If PCRs remain persistently negative by 24 months, no further testing is done unless clinically indicated. Recipients with worsening allograft function at any time can undergo renal biopsy to clarify the cause of the acute kidney injury regardless of the BK viremia level.

If BK virus was detected on screening, mycophenolate was reduced if viral copy was < 10K and BK viral load monitored monthly. For a viral copy > 10K, mycophenolate was discontinued; tacrolimus dose reduced to achieve a lower level, and leflunomide initiated at a loading dose of 100 mg daily for 3 days followed by 20 mg daily provided there were no predisposing conditions for liver injury. The leflunomide dose was titrated to achieve effective BK viremia reduction or until a therapeutic drug level was achieved. A leflunomide (metabolite teriflunomide) level > 40 μg/ml is considered adequate.

2.3. Viral quantitation

Plasma samples were tested for BK viral DNA load at ARUP laboratories. Data were expressed as copies of viral DNA per milliliter (copies/mL). The quantitative range of this assay is 2.6–8.6 log copies/mL (390–390,000,000 copies/mL).

2.4. Kidney biopsies

Paraffin embedded renal biopsy tissue sections that had been stained with hematoxylin and eosin, Jones methenamine silver, trichrome and periodic acid Schiff stain were individually re-evaluated by a single pathologist blinded to the clinical data. The biopsies were scored according to the Banff criteria for rejection and BKPyVN [8,9]. Immunohistochemical polyoma stain for SV40 was also confirmed in each individual biopsy.

2.5. Statistical analysis

Results were reported as counts (n) and percentages (%) for categorical variables, mean (± SD) for normally distributed continuous variables, and median (range) for non-normally distributed continuous variables. Statistical analyses were performed using SAS v9.4. Pearson's chi-square (X^2) and Fisher's exact tests were used to determine significance of observed frequency differences. The generalized linear modeling (GLM) framework was used to determine significance of observed mean differences. An overall type I error of $\alpha = 0.05$ was used.

Table 1
BKPyVN recipient characteristics.

Recipient number	Age at transplant	Gender	Race	Cause of CKD/ESRD	Second transplant
1	66	Male	White	PKD	No
2	57	Male	Black	HTN	Yes
3	19	Male	White	Other	No
4	57	Male	White	PKD	Yes
5	59	Female	Hispanic	DN	No
6	7	Male	Other	Other	No
7	47	Male	Black	Other	No
8	68	Male	Other	GN	No
9	56	Male	White	PKD	No
10	40	Male	White	GN	Yes
11	17	Male	White	GN	Yes
12	65	Male	White	Other	No
13	55	Male	White	GN	No
14	36	Female	White	GN	No
15	63	Female	White	HTN	No
16	63	Male	Hispanic	DN	No
17	69	Male	White	DN	No
18	53	Female	White	Other	Yes
19	40	Male	White	DN	No
20	32	Male	White	GN	No

BKPyVN: BK polyomavirus nephropathy; CKD: chronic kidney disease; DN: diabetic nephropathy; ESRD: end stage renal disease; GN: immune complex glomerulonephritis; HTN: hypertensive nephropathy; PKD: polycystic kidney disease.

Due to our multiple pairwise group comparisons, we used the Bonferroni correction, where a p value < 0.0167 was considered statistically significant.

3. Results

3.1. Institutional BKPyVN prevalence and recipient characteristics

We identified 20 cases of biopsy proven BKPyVN out of 1031 renal allograft recipients (1.9% prevalence) from 2002 to 2014 at our institution. Key recipient demographics and the cause for renal disease are listed in Table 1. The mean age at the time of transplant was 48.4 years (± 18.3) and 16 (80%) of the recipients were male. Racial distribution was as follows: 14 (70%) white, 2 (10%) black, 2 Hispanic and 2 identified as other. Cause of native kidney disease included 6 (30%) immune complex glomerulonephritis, 4 (20%) diabetic nephropathy, 2 (10%) hypertensive nephrosclerosis, 3 (15%) polycystic kidney disease and 5 (25%) listed as other cause. This was a second renal transplant for 5 (25%) of these recipients. None of these 5 re-transplants had lost their previous allograft to BKPyVN.

3.2. Histopathologic features, BK viral load and serum creatinine at the time of biopsy BKPyVN diagnosis

Allograft biopsies were classified into grades A (early), B (florid), and C (late sclerosing) using the criteria set by the Banff Working Group on Polyomavirus nephropathy [8-10]. The biopsy stages with correlating viral load and serum creatinine at the time of biopsy diagnosis are listed in Table 2.

Five of the 20 BKPyVN cases (25%) showed early changes with very limited morphologic features (Fig. 1). There were few viral cytopathic effects or inclusions in the tubular epithelial cells as noted on special stains. Immunohistochemical staining was used to identify positive staining for SV40 in the renal tubular epithelial cell nuclei. There was minimal interstitial inflammation with < 10% tubular atrophy and interstitial fibrosis. The tubular epithelial cells did not exhibit basement membrane denudation or epithelial cell necrolysis. The median BK viral load for those recipients with early changes was 7795 copies/mL (range 1900–34,500) while the median serum creatinine was 1.9 mg/dL (range

Table 2
Histopathologic stage, BK viral load and serum creatinine at the time of BKPyVN diagnosis.

Recipient number	Biopsy stage	BK viral load (copies/ml)	Serum creatinine (mg/dL)	Time from transplant to biopsy diagnosis (months)
1	Early	34,500	2.4	15.3
2	Florid	80,900	4.3	21.1
3	Early	1900	1.5	2.0
4	Florid	9,757,615	3.8	7.4
5	Florid	92,200	1.8	23.6
6	Advanced	38,500	4.2	10.9
7	Early	29,400	3.8	2.5
8	Florid	88,200	1.5	10.3
9	Advanced	16,700	4.2	3.5
10	Florid	71,500	2.3	5.4
11	Florid	19,300	1.3	11.7
12	Florid	2,753,000	1.5	18.3
13	Advanced	5,000,001	4.3	11.3
14	Early	7795	1.9	5.6
15	Early	4999	1.6	15.7
16	Florid	43,100	2.9	19.2
17	Florid	12,200	3.2	19.3
18	Advanced	200,000	2.2	64.2
19	Florid	9200	7.5	119.4
20	Advanced	4,701,024	2.3	38.3

1.5–3.8) at the time of biopsy. Median time to biopsy diagnosis from transplant was 5.6 months (range 2.0–15.7).

Florid changes were noted in 10 (50%) of the BKPyVN cases. Changes were more conspicuous with intranuclear viral inclusions in tubular epithelial cells. The background showed moderate (< 50%) interstitial fibrosis, tubular atrophy and inflammation with increased viral staining noted (Fig. 2). These changes were also accompanied by virally induced tubular basement membrane denudation and individual cell necrolysis. There was prominent lymphoplasmacytic interstitial inflammation with admixed polymorphonuclear leukocytes. Lymphocytic tubulitis also often accompanied these changes. The median BK viral load for those recipients with florid changes was 76,200 copies/mL (range 9200–9,757,615) while the median serum creatinine was 2.6 mg/dL (range 1.3–7.5) at the time of biopsy. Median time to biopsy diagnosis from transplant was 18.8 months (range 5.4–119.4).

The late sclerosing (advanced) stage was marked by tubular atrophy and interstitial fibrosis exceeding 50% of the biopsy core with accompanying inflammation and viral staining (Fig. 3). Five BKPyVN cases (25%) showed features characteristic of advanced stage. There were prominent signs of viral replication and associated acute tubular injury. Interstitial inflammation was marked as was interstitial fibrosis and tubular atrophy. The median BK viral load for those recipients with advanced changes was 200,000 copies/mL (range 16,700–5,000,001) while the median serum creatinine was 4.2 mg/dL (range 2.2–4.3) at the time of biopsy. Median time to biopsy diagnosis from transplant was 11.3 months (range 3.5–64.2).

3.3. Clinical outcomes

Graft failure had occurred in 10 (50%) of the recipients diagnosed with BKPyVN at the time of the analysis (Table 3). Median follow-up

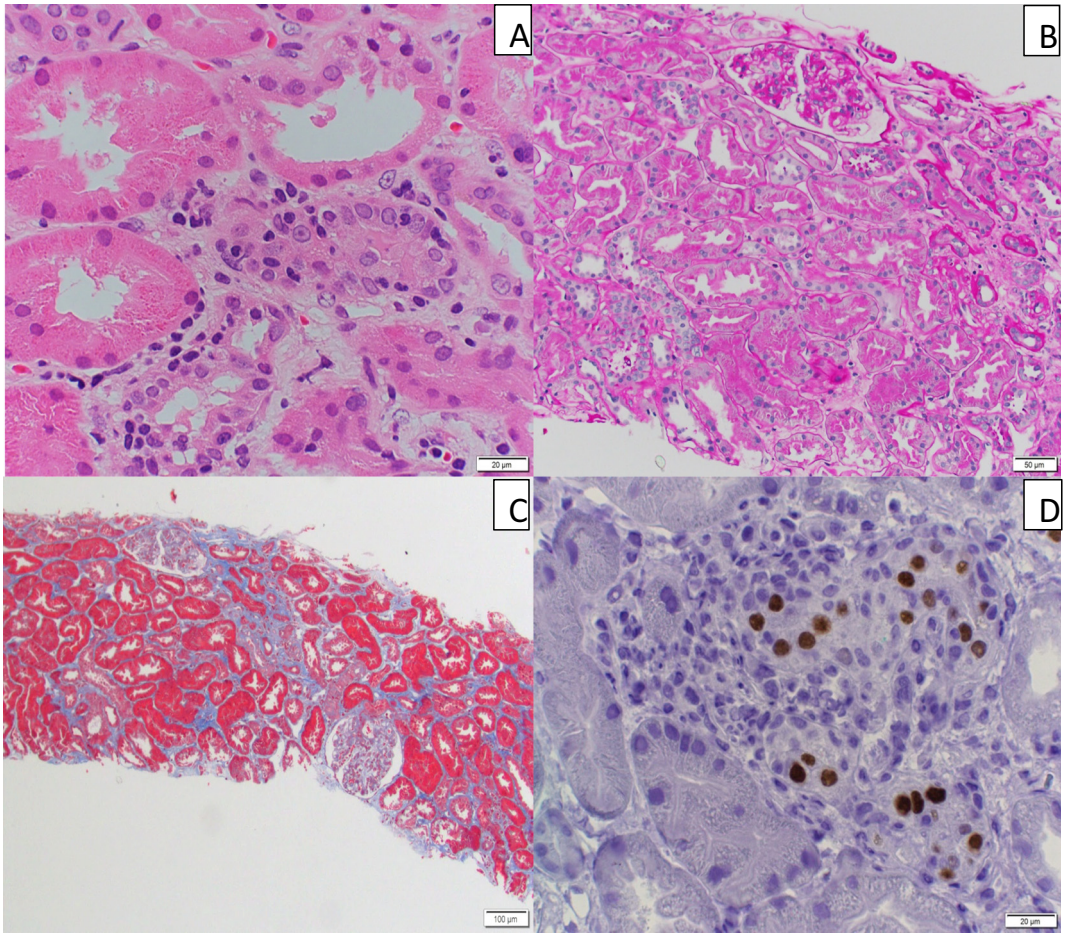

Fig. 1. Early stage (grade A) appearance. A: H + E stain of tubular epithelium showing few viral inclusions. B: PAS stain showing mild tubular atrophy. C: Trichrome stain showing mild interstitial fibrosis. D: SV40 polyomavirus IHC stain highlighting viral particles in tubular epithelial cell nuclei.

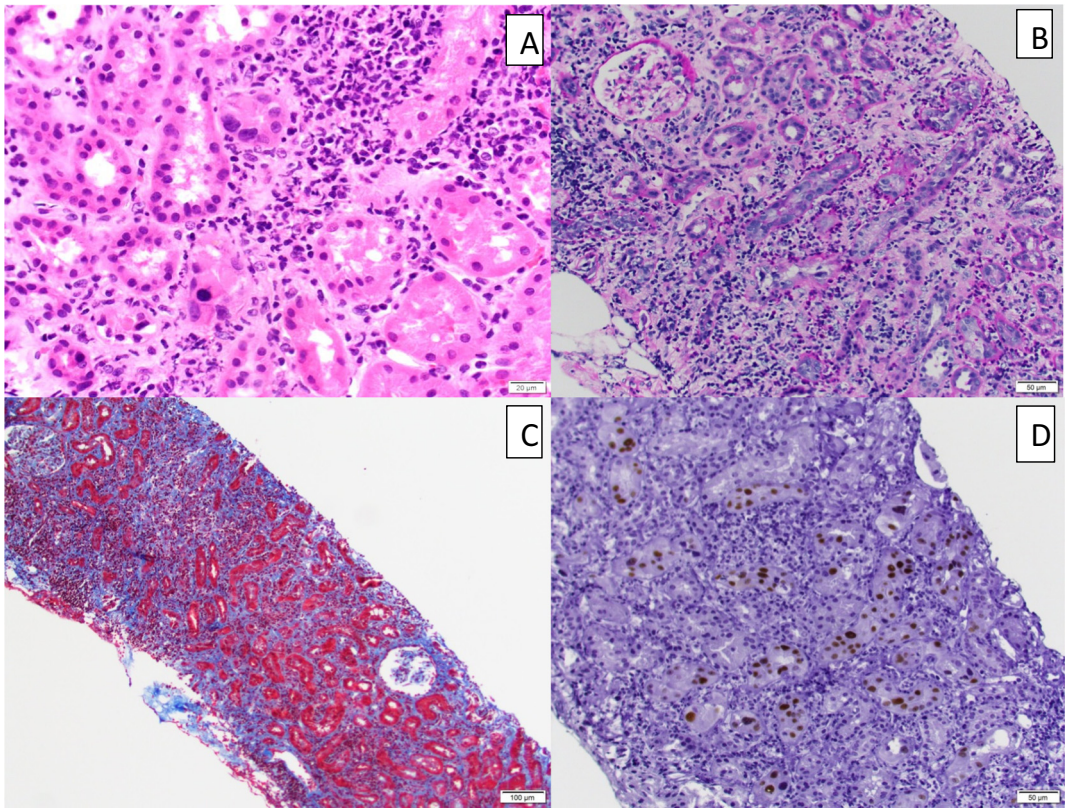

Fig. 2. Florid stage (grade B) appearance. A: H + E stain of tubular epithelium showing tubulo-interstitial inflammation and few tubular epithelial cells with smudged nuclei (viral inclusions). B: PAS stain showing interstitial inflammation and moderate tubular atrophy with thickened and wrinkled basement membrane. C: Trichrome stain highlighting extensive tubulointerstitial inflammation and moderate interstitial fibrosis. D: SV40 polyomavirus IHC stain highlighting viral particles in tubular epithelial cell nuclei.

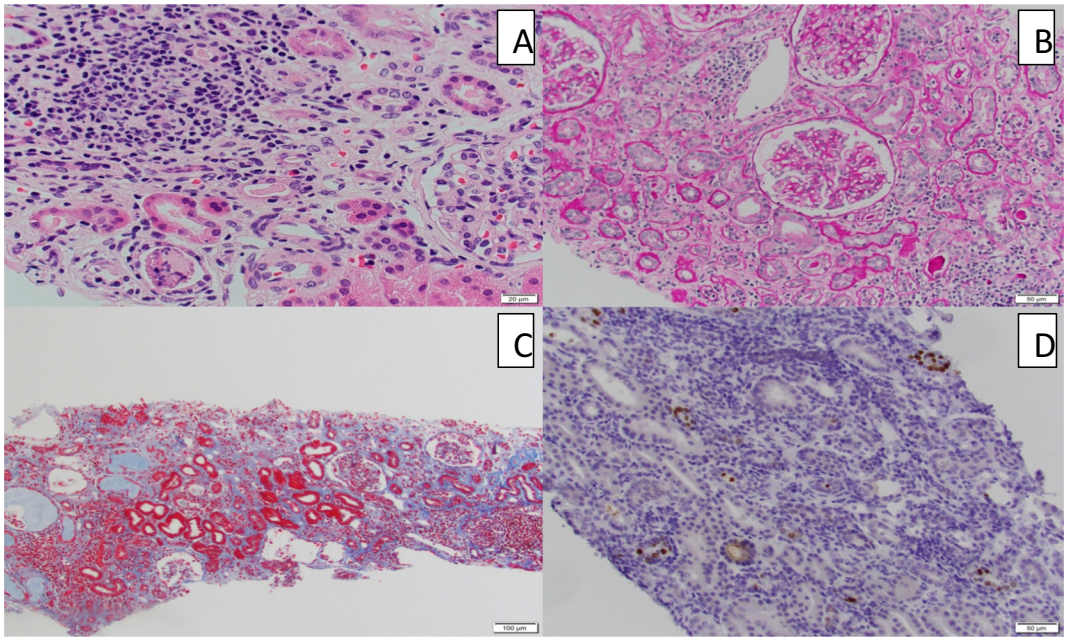

Fig. 3. Late sclerosing/advanced stage (grade C) appearance. A: H + E stain of tubular epithelium showing tubulo-interstitial inflammation, injury and tubular necrosis. B: PAS stain showing tubulointerstitial inflammation and marked tubular atrophy. C: Trichrome stain highlighting tubulointerstitial inflammation and extensive interstitial fibrosis. D: SV40 polyomavirus IHC stain highlighting viral particles in tubular epithelial cell nuclei.

Table 3
BKPyVN histopathologic stage and clinical outcomes.

Recipient number	Biopsy stage	BK viremia resolution	Allograft failure	Cause of allograft failure	Time from biopsy diagnosis to outcome (months)	Total follow-up time (months)
1	Early	No	No	n/a	12.4	27.7
2	Florid	No	Yes	BKPyVN	0.8	21.9
3	Early	No	No	n/a	23.6	25.6
4	Florid	Yes	No	n/a	53.1	60.5
5	Florid	No	Yes	Death (HF)	3.0	26.7
6	Advanced	No	Yes	BKPyVN	2.7	13.6
7	Early	No	Yes	Chronic rejection	9.8	12.3
8	Florid	No	No	n/a	51.9	62.2
9	Advanced	Yes	No	n/a	35.4	38.9
10	Florid	No	Yes	Death (sepsis)	84.0	89.4
11	Florid	Yes	No	n/a	12.8	24.5
12	Florid	No	Yes	Death (stroke)	73.0	91.3
13	Advanced	No	Yes	BKPyVN	11.9	23.3
14	Early	No	Yes	BKPyVN	11.7	17.3
15	Early	Yes	No	n/a	24.2	40.0
16	Florid	No	Yes	BKPyVN	47.1	66.3
17	Florid	Yes	No	n/a	21.0	40.3
18	Advanced	Yes	No	n/a	27.5	91.7
19	Florid	No	Yes	Death (unknown)	41.8	161.2
20	Advanced	Yes	No	n/a	29.4	67.7

time for the 20 BKPyVN cases was 43.3 months (range 12.2–157.6). All patients had undergone immunosuppression reduction to include mycophenolate discontinuation and were therapeutic on leflunomide. The most prominent histopathologic stage at diagnosis for those with allograft loss was florid (6 patients) followed by both early and advanced stage with 2 patients each. Of the 10 recipients with allograft loss, five lost the allograft from BKPyVN, four recipients died with a functioning allograft and one recipient lost the allograft from chronic rejection. Only 5 of the 10 recipients with a functioning allograft at the time of analysis had BK viremia resolution (undetectable viremia). Overall, there was no statistical association between allograft loss and BKPyVN histopathology ($p = 0.49$). There was also no statistical association between BKPyVN histopathology and BK viral load at the time of biopsy diagnosis ($p = 0.38$) or BKPyVN histopathology and serum BK viremia resolution ($p = 0.16$).

4. Discussion

Our retrospective study identified 20 cases of biopsy proven BKPyVN out of 1031 renal allograft recipients over a 13 year period at our institution. Histologically, these 20 BKPyVN cases were classified using the criteria set by the Banff Working Group on polyomavirus nephropathy which showed 5 grade A (early) stages, 10 grade B (florid) stages, and 5 grade C (late sclerosing) stages. Despite treatment with immunosuppression reduction and leflunomide, five (25%) recipients still experienced allograft loss due to BKPyVN. Histopathology was not statistically associated with BK viral load at the time of biopsy diagnosis, serum BK viremia resolution or allograft loss.

One potential explanation for a lack of statistical association in our study is that morphologic features of BKPyVN in renal allografts may be variable and focal. Pathologic changes are sometimes challenging to quantify for several reasons including sample variability, patchy nature of the viral cytopathic effects, pre-existing donor lesions with interstitial fibrosis, and calcineurin induced changes that cannot be differentiated from changes due to BK. Viral cytopathic changes can be more prominent in the medulla making an ascending route of viral infection plausible [9-11]. Viral cytopathic changes are by no means pathognomonic for BK virus however, as similar histology may also be identified with herpes simplex virus, adenovirus and cytomegalovirus so appropriate clinical context must be taken into account [12]. Highly sensitive and specific immunohistochemical stains are now easily available in most labs and should be employed where appropriate. Each of the allograft biopsies in this study consisted of two adequate core samples and each allograft biopsy was confirmed positive for SV40 immunohistochemical stain in the setting of BK viremia.

Another potential explanation for a lack of a statistical association between BKPyVN histopathology and clinical outcomes in our study is the limitation of our single center small sample size. The overall prevalence of BKPyVN at our center was 1.9% from 2002 to 2014 with an average of approximately 80 kidney transplants performed per year. While our findings did not reach statistical significance, there was a definitive trend in increasing median BK viral load as well as median serum creatinine at the time of biopsy with worsening histopathologic stage. Larger database analysis has demonstrated some usefulness of staging histopathologic features of BKPyVN [10]. Our assessment is that it is biologically plausible that a higher BK viral load could contribute to a worse histopathologic stage resulting in a higher serum creatinine at the time of biopsy. Whether histopathologic stage can be used to predict allograft loss is debatable as previously reported associations in larger studies may not be applicable to single center use.

It is important to try and identify BKPyVN early as allograft loss from BKPyVN is still experienced in up to 14% of all renal transplant recipients. Viruria and viremia have been suggested as potential screening modalities. Viruria is highly sensitive as active viral replication may show shedding of virally infected decoy cells; however viruria is less specific for BKPyVN compared to viremia as urine cytology interpretation requires a trained pathologist and may be confounded by reactive atypia and urothelial dysplasia [13-15]. BK viruria can also exist in both renal and non-renal solid organ transplants without accompanying viremia. It is also important to note that BKPyVN does not only occur in renal allografts but native kidney BKPyVN has been reported in lung [16,17], heart [18] and pancreas [19] transplant recipients. The decision to perform a renal biopsy in the setting of BK viremia is often based on the clinical scenario but immunosuppression reduction is the standard of practice for treatment. All of our BKPyVN cases had undergone immunosuppression reduction in addition to maintaining therapeutic leflunomide levels per protocol.

In conclusion, our single center retrospective analysis did not show a statistical association between histopathologic disease severity and allograft outcome. While worse histopathologic grade did appear to be associated with a higher BK viral load and a higher serum creatinine at the time of biopsy, the severity of the BKPyVN seen on biopsy did not appear to be associated with allograft loss nor eventual BK viremia resolution. These findings raise the possibility of yet unknown factors in

the genetic background of the donor and/or recipient that may contribute to BKPyVN allograft outcomes. The overall low prevalence of BKPyVN in the current transplant setting makes this entity somewhat difficult to study. Additional studies are needed to allow for better allograft outcome predictive models in order to better inform the clinical decisions of both clinicians and recipients.

Disclosures

For all authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of Competing Interest

None.

References

[1] Goudsmit J, Wertheim-van Dillen P, van Strien A, van der Noordaa J. The role of BK virus in acute respiratory tract disease and the presence of BKV DNA in tonsils. J Med Virol 1982;10:91–9.
[2] Eash S, Atwood WJ. Involvement of cytoskeletal components in BK virus infectious entry. J Virol 2005;79:11734–41.
[3] Low JA, Magnuson B, Tsai B, Imperiale MJ. Identification of gangliosides GD1b and GT1b as receptors for BK virus. J Virol 2006;80:1361–6.
[4] Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, et al. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. Am J Transplant 2013;13:136–45.
[5] Gard L, van Doesum W, Niesters HGM, van Son WJ, Diepstra A, Stegeman CA, et al. A delicate balance between rejection and BK polyomavirus associated nephropathy; a retrospective cohort study in renal transplant recipients. PLoS One 2017;12(6). Jun 13.
[6] Schaub S, Hirsch HH, Dickenmann M, Steiger J, Mihatsch MJ, Hopfer H, et al. Reducing immunosuppression preserves allograft function in presumptive and definitive polyomavirus-associated nephropathy. Am J Transplant 2010;10:2615–23.
[7] Hardinger KL, Koch MJ, Bohl DJ, Storch GA, Brennan DC. BK-virus and the impact of pre-emptive immunosuppression reduction: 5-year results. Am J Transplant 2010;10:407–15.
[8] Nickeleit V, Singh HK, Randhawa P, Drachenberg CB, Bhatngar R, Bracamonte E, et al. The Banff working group classification of definitive polyomavirus nephropathy: morphologic definitions and clinical correlations. J Am Soc Nephrol 2018;29:680–93.
[9] Drachenberg CB, Papadimitriou JC, Hirsch HH, Wali R, Crowder C, Noqueira J, et al. Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. Am J Transplant 2004;4:2082–92.
[10] Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation 2005;79:1277–86.
[11] Costa JS, Ferreira E, Leal R, Bota N, Romaozinho C, Sousa V, et al. Polyomavirus nephropathy: ten-year experience. Transplant Proc 2017;49:803–8.
[12] Kuppachi S, Kaur D, Holanda DG, Thomas CP. BK polyoma virus infection and renal disease in non-renal solid organ transplantation. Clin Kidney J 2016;9:310–8.
[13] Yalci A, Celebi ZK, Ozbas B, Sengezer OL, Unal H, Memikoglu KO, et al. Evaluation of infectious complications in the first year after kidney transplantation. Transplant Proc 2015;47:1429–32.
[14] Randhawa P, Vats A, Shapiro R. Monitoring for polyomavirus BK and JC in urine: comparison of quantitative polymerase chain reaction with urine cytology. Transplantation 2005;79:984–6.
[15] Boldorini R, Brustia M, Veggiani C, Barco D, Andorno S, Monga G. Periodic assessment of urine and serum by cytology and molecular biology as a diagnostic tool for BK virus nephropathy in renal transplant patients. Acta Cytol 2005;49:235–43.
[16] Schwarz A, Mengel M, Haller H, Niedermeyer J. Polyoma virus nephropathy in native kidneys after lung transplantation. Am J Transplant 2005;5:2582–5.
[17] Schmid H, Burg M, Kretzler M, Banas B, Grone HJ, Kliem V. BK virus associated nephropathy in native kidneys of a heart allograft recipient. Am J Transplant 2005;5:1562–8.
[18] Haririan A, Ramos ER, Drachenberg CB, Weir MR, Klassen DK. Polyomavirus nephropathy in native kidneys of a solitary pancreas transplant recipient. Transplantation 2002;73:1350–3.
[19] Bae SH, Chung BH, Park YK, Jo K, Yang CW, Kim YS, et al. Cytomegalovirus induced interstitial nephritis and ureteral stenosis in renal transplant recipient. Korean J Intern Med 2012;27:470–3.