KIR immunogenetics in BKV infection

Subjects: Immunology
Contributor: Ivana Kovacevic Vojtusek

BK virus (BKV) is a polyomavirus with high seroprevalence in the general population with an unremarkable clinical presentation in healthy people, but a potential for causing serious complications in immunosuppressed transplanted patients. Reactivation or primary infection in kidney allograft recipients may lead to allograft dysfunction and subsequent loss. Currently, there is no widely accepted specific treatment for BKV infection and reduction of immunosuppressive therapy is the mainstay therapy. Given this and the sequential appearance of viruria-viremia-nephropathy, screening and early detection are of utmost importance.

Keywords: BK Virus Infection, HLA, KIR receptors

1. Introduction

BK virus (BKV) is a small double-stranded DNA virus belonging to the *Polyomaviridae* family. Its genotype consists of a non-coding region, an early coding region (transcribing T antigen), a late coding region (transcribing three viral capsid proteins), and a fourth region which encodes the agnoprotein. The capsid consists of three proteins, VP-1 (the major structural protein), VP-2 and VP-3. BKV was first detected in a renal allograft recipient in 1971[1][2]. The virus consists of four serotypes marked I, II, III and IV, with serotype I being most prevalent[3]. It is estimated that seroprevalence of BKV is around 80% to 90%[4]. Primary infection (primoinfection) most probably occurs in early childhood via the fecal-oral or respiratory routes and afterwards the virus forms a persistent latent infection of the urothelial (transitional epithelium) and renal tubular cells [2][5][6]. Not much is known on the clinical manifestations of primary BKV infection in non-immunocompromised persons, but it has been shown that seroprevalence in children is around 91% and is reached at 5 to 9 years of age and that it is most likely asymptomatic or presents as an influenza-like illness[7][8]. In the general population, the latent infection normally does not produce any symptoms and reactivation does not occur. However, in the immunocompromised patient BKV infection has a very different course. It has been reported that in the vast majority of renal transplant patients BKV infection follows a clear sequential course of viruria-viremia-nephropathy-allograft loss with viruria present in 30% to 40% and viremia in 10% to 20% of such patients[9]. A study examining donor–recipient BKV genotypes showed a donor origin in viremic kidney allograft recipients[10]. BKV is closely related to two other polyomaviruses, Simian virus 40 (SV40) and JC virus (JCV). In fact, BKV shares 72% of the entire DNA sequence with JCV and 69% with SV40 of JCV is around 50–70% and its primoinfection is asymptomatic, but it can cause serious and frequently fatal infections in immunodeficient and immunosuppressed individuals. In patients with (mostly severe) immunodeficiency, it leads to progressive multifocal leukoencephalopathy (PML), a disease with a frequently dire prognosis characterized by motor deficits, altered consciousness, gait ataxia, and visual disturbances. In renal allograft recipients it can sometimes cause JCV-associated nephropathy (JCVAN), a rare disease which can sometimes lead to allograft loss. SV40 has a seroprevalence of 90% in children and 60% in adults and there is controversial evidence that it might lead to carcinogenesis in humans. However, this link remains to be confirmed. Antibodies to this virus are mostly used as surrogate markers for BKV-associated nephropathy (BKVAN) and JCVAN[4][7].

2. An Overview of BKV Infection and BKVAN in Kidney Transplantation

2.1. Risk Factors, Screening and Treatment of BKV Infection and BKVAN

While a great number of studies examined risk factors for BKV infection, the only meta-analysis published which systematically studied risk factors identified 8 risk factors associated with increased risk for BK viremia (maintenance therapy regimen including tacrolimus, allograft from a deceased donor, recipient of male sex, history of previous transplant, age at transplantation, ureteral stent use, delayed graft function and acute rejection episodes) and two associated with increased risk for BKVAN (maintenance therapy regimen including tacrolimus and acute rejection episodes)[11]. Another meta-analysis specifically examined the risk of therapeutic regimens including mammalian target of rapamycin (mTOR) inhibitors vs. calcineurin inhibitors (CNI) did not find any association of drug regimen with risk of BKV

infection[12]. When examining data from individual studies, risk factors for BKVAN can be divided into recipient-, donor- and allograft specific and include: male sex, older age of donor and recipient, cold ischemia time, delayed graft function, episodes of rejection, ureteral stent, use of anti-thymocyte globulin in induction, use of tacrolimus in maintenance therapy, ABO blood group system incompatibility, ischemia/reperfusion injury and recipient or donor seropositivity. Conversely, mTOR inhibitor use has been shown to be a protective factor[9][13][14][15][16].

The current BKVAN therapy protocol consists mainly of immunosuppressive therapy reduction[13] [21]. Moreover, an important point is distinguishing BKVAN from allograft rejection, since the two may present similarly, but are treated in completely opposite ways, i.e., treatment of misdiagnosed rejection in the presence of BKVAN might lead to allograft loss[17][18]. Furthermore, histological surveillance of BKVAN is also problematic from a clinical point of view, which has been thoroughly studied. Menter et al. explored the histopathology of resolving BKVAN which found that this stage is morphologically indistinguishable from interstitial rejection[19]. For an accurate diagnosis it is imperative to obtain adequate and deep samples as BKV has a tropism for renal medulla[20]. Aside from reduction of immunosuppression, which is the only viable treatment strategy, other therapies have been tested and occasionally used. Intravenous immunoglobulins have been shown to be useful in patients who do not respond to the initial reduction of immunosuppression[21] and might lead to additional BKV clearance[22]. A recent study possibly partially elucidated the mechanism behind this, demonstrating that intravenous immunoglobulin administration increases the titer of neutralizing antibodies specific for BKV[22]. On this basis, a very recent proof-of-concept study has stated that intravenous immunoglobulins might be useful in clinical practice and potentially reduce the risk of allograft loss[22]. Some studies showed good results using leflunomide, a prodrug to an antimetabolite A77 1726, usually by replacing mycophenolate mofetil, however, other studies demonstrated conflicting results and their use is controversial [23][24][25]. Cidofovir is an antiviral agent, used also for BKV infection,[26], but its usage is limited due to low efficacy and potential nephrotoxicity[27]. While initial studies showed an effect of quinolone antibiotics[28][29], this was disproven in further, better-designed randomized controlled studies[30][31]. Immunosuppression with everolimus after switching from CNIs were shown to be promising in one retrospective study[32]. Given the limited options of therapy and the established viruria-viremia-nephropathy sequential course, screening aimed at early detection of BK viruria and viremia is of paramount importance. It has been shown that screening for BKV DNAemia enables identification of at least 90% of patients at risk before significant repercussions for the allograft. However, quantitative nucleic acid testing (NAT) is still underutilized[33][34]. It has been demonstrated that most cases of BKVAN occur in the first 6 months or 1-year post-transplant and recent research showed that only around 20% to 30% of BKV DNAemia events occur later than 6 months post-transplant, which strongly points to the need for strict early surveillance[35][36][37]. Several screening and intervention strategies have been developed, based on testing frequency and detection method. Kidney Disease Improving Global Outcomes (KDIGO) guidelines for kidney transplant recipients suggest screening all recipients of BKV using quantitative plasma NAT at least monthly for the first 3 to 6 months after transplantation, then every 3 months until the end of the first post-transplant year, and subsequently whenever there is an unexplained rise in serum creatinine and after treatment for acute rejection[38]. American Society of Transplantation (AST) guidelines recommend quantitative NAT as the main testing method to be performed monthly up to month 9 post-transplant followed by testing every 3 months up to 2 years post-transplant or at the time of surveillance and indication of an allograft biopsy. Stepwise reduction of immunosuppressive medications is recommended when BKV plasma NAT is persistently (for 3 weeks and longer) greater than 1000 copies per milliliter (mL) [39]. Complementary to quantitative polymerase chain reaction (qPCR) DNA testing, several institutions also use other methods, such as urine cytology (decoy cells) and virus RNA[38]. Nankivell et al. found that, although decoy cells detection have a high specificity and negative predictive value for BKVAN, quantitative viremia determination by qPCR was superior having high sensitivity, specificity and negative predictive value[40]. However, urine cytology, especially quantification of decoy cells, might be a useful additional tool in experienced centers especially in situations when kidney biopsy cannot be performed. Given a recent study on the need for deep sampling during kidney biopsy for obtaining an adequate tissue sample, urine cytology might be useful in cases where no or scarce medulla was obtained . Looking for an integrated method of surveillance, a review by Comoli et al. summarized the current knowledge on BKV-specific cellular immunity, found that it is associated with viral clearance and that prospective monitoring for viremia coupled with specific immunity and B-cell alloimmune surveillance might lead to prevention and better outcomes in BKVAN[41].

2.2. Prognosis of BKV Infection and BKVAN

One of the first important studies focused on outcomes in patients with BKVAN found that in a cohort of 1001 renal and renal/pancreas allograft recipients, 41 patients developed BKVAN with median of 318 days to diagnosis and that allograft survival at 6 months, 1, 3, and 5 years was 97%, 90%, 58%, and 47%, respectively, compared to a contemporaneous cohort of patients without BKVAN which had significantly better 6 months, 1, 3 and 5 year allograft survival (94%, 92%, 83%, and 76%, respectively). Allograft loss occurred in 46% of subjects and BKVAN diagnosis was preceded with a steep fall in estimated glomerular filtration rate (eGFR)[42]. A small Chinese prospective study found that 5.6% of patients

developed BKVAN in the first year post-transplant and that a reduction in immunosuppression led to resolution in all patients[43]. In a study of 213 kidney transplant recipients, high BK viremia (defined as (≥10^4 copies/mL) occurred in 17.4% and low viremia occurred in 49.3% of patients, while BKVAN occurred in 4.2% of patients[44] . In another retrospective long-term study (mean follow up of over 7.7 years), the incidence of BKVAN was 4.0% and 60.0% of patients with BKVAN and acute rejection progressed to allograft loss[45]. In patients sequentially monitored for BK viruria and viremia in which the CNI dose was reduced first when sustained BK viremia occurred (>1000 copies/mL) at median follow up of 5 years, 11% of patients developed rejection[35]. A report that included 609 patients of which 130 developed BK viremia during the first post-transplant year and who were then classified as transient low viremia, transient high viremia, persistent low viremia, and persistent high viremia (based on BK viral load cut-off of 10,000 copies/mL and infection duration cut-off of 3 months) demonstrated that low viremia (either transient or persistent) did not affect long-term outcomes. Contrary to this, persistent high viremia was associated with higher risk for BKVAN and subsequent allograft dysfunction and transient high viremia was associated with worse long-term allograft function[46]. An analysis of outcomes of Chinese renal allograft recipients treated for BKVAN showed that after a mean follow up of 14.4 months, BK viruria disappeared in 19.5% and BK viremia in 90.2%. One-year graft survival was excellent, while 5-year graft survival was 85.7%[47]. In a study of 1904 renal allograft recipients of which 17.3% had BK viremia and 3.6% had BKVAN, high serum creatinine, early BKVAN (defined as occurring within 6 months post-transplant) and microvascular inflammation were independently associated with higher risk of allograft loss[48].

Re-transplantation after allograft loss due to BKVAN is considered safe after complete resolution of viremia and is frequently performed, especially considering that most BKV infection is donor-derived. A very recent study showed that there were no differences in death-censored graft survival, acute rejection episodes and patient survival between patients who underwent re-transplantation after first allograft loss due to BKVAN versus other causes[49].

References

1. Gardner, S.; Field, A.; Coleman, D.; Hulme, B. New Human Papovavirus (b.k.) Isolated from Urine after Renal Transplantation. Lancet 1971, 297, 1253–1257, doi:10.1016/s0140-6736(71)91776-4.
2. Helle, F.; Brochot, E.; Handala, L.; Martin, E.; Castelain, S.; François, C.; Duverlie, G. Biology of the BKPyV: An Update. Viruses 2017, 9, 327, doi:10.3390/v9110327.
3. Thongprayoon, C.; Khoury, N.J.; Bathini, T.; Aeddula, N.R.; Boonpheng, B.; Leeaphorn, N.; Ungprasert, P.; Bruminhent, J.; Lertjitbanjong, P.; Watthanasuntorn, K.; et al. BK polyomavirus genotypes in renal transplant recipients in the United States: A meta-analysis. J. Evid. Based Med. 2019, 12, 291–299, doi:10.1111/jebm.12366.
4. Egli, A.; Infanti, L.; Dumoulin, A.; Buser, A.; Samaridis, J.; Stebler, C.; Gosert, R.; Hirsch, H.H. Prevalence of Polyomavirus BK and JC Infection and Replication in 400 Healthy Blood Donors. J. Infect. Dis. 2009, 199, 837–846, doi:10.1086/597126.
5. Vanchiere, J.A.; Abudayyeh, S.; Copeland, C.M.; Lu, L.B.; Graham, D.Y.; Butel, J.S. Polyomavirus Shedding in the Stool of Healthy Adults. J. Clin. Microbiol. 2009, 47, 2388–2391, doi:10.1128/jcm.02472-08.
6. Sundsfjord, A.; Spein, A.R.; Lucht, E.; Flaegstad, T.; Seternes, O.M.; Traavik, T. Detection of BK virus DNA in nasopharyngeal aspirates from children with respiratory infections but not in saliva from immunodeficient and immunocompetent adult patients. J. Clin. Microbiol. 1994, 32, 1390–1394, doi:10.1128/jcm.32.5.1390-1394.1994.
7. Knowles, W.A.; Pipkin, P.; Andrews, N.J.; Vyse, A.; Minor, P.; Brown, D.W.G.; Miller, E. Population-based study of antibody to the human polyomaviruses BKV and JCV and the simian polyomavirus SV40. J. Med. Virol. 2003, 71, 115–123, doi:10.1002/jmv.10450.
8. Hirsch, H.H.; Steiger, J. Polyomavirus BK. Lancet Infect. Dis. 2003, 3, 611–623, doi:10.1016/s1473-3099(03)00770-9.
9. Bohl, D.L.; Brennan, D.C. BK Virus Nephropathy and Kidney Transplantation. Clin. J. Am. Soc. Nephrol. 2007, 2, S36–S46, doi:10.2215/cjn.00920207.
10. Wunderink, H.F.; De Brouwer, C.S.; Gard, L.; De Fijter, J.W.; Kroes, A.C.M.; Rotmans, J.I.; Feltkamp, M.C.W. Source and Relevance of the BK Polyomavirus Genotype for Infection After Kidney Transplantation. Open Forum Infect. Dis. 2019, 6, ofz078, doi:10.1093/ofid/ofz078.
11. Demey, B.; Tinez, C.; François, C.; Helle, F.; Choukroun, G.; Duverlie, G.; Castelain, S.; Brochot, E. Risk factors for BK virus viremia and nephropathy after kidney transplantation: A systematic review. J. Clin. Virol. 2018, 109, 6–12, doi:10.1016/j.jcv.2018.10.002.
12. Mallat, S.G.; Tanios, B.Y.; Itani, H.S.; Lotfi, T.; McMullan, C.; Gabardi, S.; Akl, E.A.; Azzi, J.A. CMV and BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor–Based Regimen Versus a CNI-Based Regimen: A Syste

matic Review and Meta-Analysis of Randomized, Controlled Trials. Clin. J. Am. Soc. Nephrol. 2017, 12, 1321–1336, doi:10.2215/cjn.13221216.

13. Sawinski, D.; Goral, S. BK virus infection: An update on diagnosis and treatment. Nephrol. Dial. Transplant. 2014, 30, 209–217, doi:10.1093/ndt/gfu023.

14. Plafkin, C.; Singh, T.; Astor, B.C.; Parajuli, S.; Bhutani, G.; Safdar, N.; Panzer, S.E. Kidney transplant recipients with polycystic kidney disease have a lower risk of post-transplant BK infection than those with end-stage renal disease due to other causes. Transpl. Infect. Dis. 2018, 20, e12974, doi:10.1111/tid.12974.

15. Huang, G.; Zhang, L.; Liang, X.; Qiu, J.; Deng, R.; Li, J.; Chen, G.; Dong, Y.; Chen, L. Risk Factors for BK Virus Infection and BK Virus–Associated Nephropathy Under the Impact of Intensive Monitoring and Pre-emptive Immunosuppression Reduction. Transplant. Proc. 2014, 46, 3448–3454, doi:10.1016/j.transproceed.2014.08.036.

16. Sharif, A.; Alachkar, N.; Bagnasco, S.; Geetha, D.; Gupta, G.; Womer, K.; Arend, L.; Racusen, L.; Montgomery, R.; Kraus, E. Incidence and Outcomes of BK Virus Allograft Nephropathy among ABO- and HLA-Incompatible Kidney Transplant Recipients. Clin. J. Am. Soc. Nephrol. 2012, 7, 1320–1327, doi:10.2215/cjn.00770112.

17. Mannon, R.B.; Hoffmann, S.C.; Kampen, R.L.; Cheng, O.C.; Kleiner, D.E.; Ryschkewitsch, C.; Curfman, B.; Major, E.; Hale, D.A.; Kirk, A.D. Molecular Evaluation of BK Polyomavirus Nephropathy. Arab. Archaeol. Epigr. 2005, 5, 2883–2893, doi:10.1111/j.1600-6143.2005.01096.x.

18. Ito, Y.; Nishi, S.; Imai, N.; Yoshita, K.; Saito, K.; Nakagawa, Y.; Takahashi, K.; Narita, I. The case of BK virus infection in which it was difficult to differentiate from acute rejection. Clin. Transplant. 2011, 25, 44–48, doi:10.1111/j.1399-0012.2011.01481.x.

19. Menter, T.; Mayr, M.; Schaub, S.; Mihatsch, M.J.; Hirsch, H.H.; Hopfer, H. Pathology of Resolving Polyomavirus-Associated Nephropathy. Arab. Archaeol. Epigr. 2013, 13, 1474–1483, doi:10.1111/ajt.12218.

20. Nankivell, B.J.; Renthawa, J.; Shingde, M.; Khan, A. The Importance of Kidney Medullary Tissue for the Accurate Diagnosis of BK Virus Allograft Nephropathy. Clin. J. Am. Soc. Nephrol. 2020, 15, 1015–1023, doi:10.2215/cjn.13611119.

21. Vu, D.; Shah, T.; Ansari, J.; Naraghi, R.; Min, D. Efficacy of Intravenous Immunoglobulin in the Treatment of Persistent BK Viremia and BK Virus Nephropathy in Renal Transplant Recipients. Transplant. Proc. 2015, 47, 394–398, doi:10.1016/j.transproceed.2015.01.012.

22. Kable, K.; Davies, C.D.; O′connellP.J.; Chapman, J.R.; Nankivell, B.J. Clearance of BK Virus Nephropathy by Combination Antiviral Therapy With Intravenous Immunoglobulin. Transplant. Direct 2017, 3, e142, doi:10.1097/txd.0000000000000641.

23. Josephson, M.A.; Gillen, D.; Javaid, B.; Kadambi, P.; Meehan, S.; Foster, P.; Harland, R.; Thistlethwaite, R.J.; Garfinkel, M.; Atwood, W.; et al. Treatment of Renal Allograft Polyoma BK Virus Infection with Leflunomide. Transplantation 2006, 81, 704–710, doi:10.1097/01.tp.0000181149.76113.50.

24. Krisl, J.C.; Taber, D.J.; Pilch, N.; Chavin, K.; Bratton, C.; Thomas, B.; McGillicuddy, J.; Baliga, P. Leflunomide Efficacy and Pharmacodynamics for the Treatment of BK Viral Infection. Clin. J. Am. Soc. Nephrol. 2012, 7, 1003–1009, doi:10.2215/cjn.12531211.

25. Faguer, S.; Hirsch, H.H.; Kamar, N.; Guilbeau-Frugier, C.; Ribes, D.; Guitard, J.; Esposito, L.; Cointault, O.; Modesto, A.; Lavit, M.; et al. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. Transpl. Int. 2007, 20, 962–969, doi:10.1111/j.1432-2277.2007.00523.x.

26. Kuypers, D.; Vandooren, A.-K.; Lerut, E.; Evenepoel, P.; Claes, K.; Snoeck, R.; Naesens, L.; Vanrenterghem, Y. Adjuvant Low-Dose Cidofovir Therapy for BK Polyomavirus Interstitial Nephritis in Renal Transplant Recipients. Arab. Archaeol. Epigr. 2005, 5, 1997–2004, doi:10.1111/j.1600-6143.2005.00980.x.

27. Vandercam, B.; Goffin, E.; Marot, J.C.; Cosyns, J.P.; Moreau, M.; Jadoul, M. Cidofovir-Induced End-Stage Renal Failure. Clin. Infect. Dis. 1999, 29, 948–949, doi:10.1086/520475.

28. Josephson, M.A.; Williams, J.W.; Chandraker, A.; Randhawa, P.S. Polyomavirus-associated nephropathy: Update on antiviral strategies. Transpl. Infect. Dis. 2006, 8, 95–101, doi:10.1111/j.1399-3062.2006.00150.x.

29. Leung, A.Y.H.; Chan, M.T.L.; Yuen, K.-Y.; Cheng, V.C.C.; Chan, K.-H.; Wong, C.L.P.; Liang, R.; Lie, A.K.W.; Kwong, Y.-L. Ciprofloxacin Decreased Polyoma BK Virus Load in Patients Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation. Clin. Infect. Dis. 2005, 40, 528–537, doi:10.1086/427291.

30. Lee, B.T.; Gabardi, S.; Grafals, M.; Hofmann, R.M.; Akalin, E.; Aljanabi, A.; Mandelbrot, D.A.; Adey, D.B.; Heher, E.; Fan, P.-Y.; et al. Efficacy of Levofloxacin in the Treatment of BK Viremia: A Multicenter, Double-Blinded, Randomized, Placebo-Controlled Trial. Clin. J. Am. Soc. Nephrol. 2014, 9, 583–589, doi:10.2215/cjn.04230413.

31. Knoll, G.A.; Humar, A.; Fergusson, D.; Johnston, O.; House, A.A.; Kim, S.J.; Ramsay, T.; Chassé, M.; Pang, X.L.; Zaltzman, J.; et al. Levofloxacin for BK Virus Prophylaxis Following Kidney Transplantation. JAMA 2014, 312, 2106–2114, d

oi:10.1001/jama.2014.14721.

32. Tohme, F.; Kalil, R.; Thomas, C.P. Conversion to a sirolimus-based regimen is associated with lower incidence of BK viremia in low-risk kidney transplant recipients. Transpl. Infect. Dis. 2015, 17, 66–72, doi:10.1111/tid.12347.
33. Hodowanec, A.C.; Simon, D.M. BK virus screening and management practices among US renal transplant programs: A survey. Transpl. Int. 2015, 28, 1339–1341, doi:10.1111/tri.12602.
34. Pape, L.; Tönshoff, B.; Hirsch, H.H. Perception, diagnosis and management of BK polyomavirus replication and disease in paediatric kidney transplant recipients in Europe. Nephrol. Dial. Transplant. 2016, 31, 842–847, doi:10.1093/ndt/gfv392.
35. Bischof, N.; Hirsch, H.H.; Wehmeier, C.; Amico, P.; Dickenmann, M.; Hirt-Minkowski, P.; Steiger, J.; Menter, T.; Helmut, H.; Schaub, S. Reducing calcineurin inhibitor first for treating BK polyomavirus replication after kidney transplantation: Long-term outcomes. Nephrol. Dial. Transplant. 2019, 34, 1240–1250, doi:10.1093/ndt/gfy346.
36. Höcker, B.; Schneble, L.; Murer, L.; Carraro, A.; Pape, L.; Kranz, B.; Oh, J.; Zirngibl, M.; Strologo, L.D.; Büscher, A.; et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients. Transplantation 2019, 103, 1224–1233, doi:10.1097/tp.0000000000002414.
37. Schachtner, T.; Babel, N.; Reinke, P. Different risk factor profiles distinguish early-onset from late-onset BKV-replication. Transpl. Int. 2015, 28, 1081–1091, doi:10.1111/tri.12601.
38. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group Special Issue: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Arab. Archaeol. Epigr. 2009, 9, S1–S155, doi:10.1111/j.1600-6143.2009.02834.x.
39. Hirsch, H.H.; Randhawa, P.S.; AST Infectious Diseases Community of Practice BKpolyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin. Transplant. 2019, 33, e13528, doi:10.1111/ctr.13528.
40. Nankivell, B.J.; Renthawa, J.; Jeoffreys, N.; Kable, K.; O'Connell, P.J.; Chapman, J.R.; Wong, G.; Sharma, R.N. Clinical Utility of Urinary Cytology to Detect BK Viral Nephropathy. Transplantation 2015, 99, 1715–1722, doi:10.1097/tp.0000000000000642.
41. Comoli, P.; Cioni, M.; Basso, S.; Gagliardone, C.; Potenza, L.; Verrina, E.; Luppi, M.; Zecca, M.; Ghiggeri, G.M.; Ginevri, F. Immunity to Polyomavirus BK Infection: Immune Monitoring to Regulate the Balance between Risk of BKV Nephropathy and Induction of Alloimmunity. Clin. Dev. Immunol. 2013, 2013, 1–6, doi:10.1155/2013/256923.
42. Vasudev, B.; Hariharan, S.; Hussain, S.A.; Zhu, Y.-R.; Bresnahan, B.A.; Cohen, E.P. BK virus nephritis: Risk factors, timing, and outcome in renal transplant recipients. Kidney Int. 2005, 68, 1834–1839, doi:10.1111/j.1523-1755.2005.00602.x.
43. Huang, G.; Chen, L.-Z.; Qiu, J.; Wang, C.-X.; Fei, J.-G.; Deng, S.-X.; Li, J.; Chen, G.-D.; Zhang, L.; Fu, Q.; et al. Prospective study of polyomavirus BK replication and nephropathy in renal transplant recipients in China: A single-center analysis of incidence, reduction in immunosuppression and clinical course. Clin. Transplant. 2009, 24, 599–609, doi:10.1111/j.1399-0012.2009.01141.x.
44. Yoon, S.-H.; Cho, J.-H.; Jung, H.-Y.; Choi, J.-Y.; Park, S.-H.; Kim, Y.-L.; Kim, H.-K.; Huh, S.; Kim, C.-D. Clinical Impact of BK Virus Surveillance on Outcomes in Kidney Transplant Recipients. Transplant. Proc. 2015, 47, 660–665, doi:10.1016/j.transproceed.2014.11.051.
45. Park, W.Y.; Kang, S.S.; Jin, K.; Park, S.B.; Choe, M.; Han, S. Long-term prognosis of BK virus-associated nephropathy in kidney transplant recipients. Kidney Res. Clin. Pract. 2018, 37, 167–173, doi:10.23876/j.krcp.2018.37.2.167.
46. Elfadawy, N.; Flechner, S.M.; Schold, J.D.; Srinivas, T.R.; Poggio, E.; Fatica, R.; Avery, R.; Mossad, S.B. Transient versus Persistent BK Viremia and Long-Term Outcomes after Kidney and Kidney–Pancreas Transplantation. Clin. J. Am. Soc. Nephrol. 2014, 9, 553–561, doi:10.2215/cjn.08420813.
47. Chen, X.-T.; Yang, S.-C.; Li, J.; Deng, R.-H.; Chen, W.-F.; Qiu, J.; Chen, L.-Z.; Wang, C.-X.; Huang, Y. Prognosis of BK polyomavirus nephropathy. Chin. Med. J. 2019, 132, 388–394, doi:10.1097/cm9.0000000000000085.
48. Mohamed, M.; Parajuli, S.; Muth, B.; Astor, B.; Panzer, S.; Mandelbrot, D.; Zhong, W.; Djamali, A. In kidney transplant recipients with BK polyomavirus infection, early BK nephropathy, microvascular inflammation, and serum creatinine are risk factors for graft loss. Transpl. Infect. Dis. 2016, 18, 361–371, doi:10.1111/tid.12530.
49. Leeaphorn, N.; Thongprayoon, C.; Chon, W.J.; Cummings, L.S.; Mao, M.A.; Cheungpasitporn, W. Outcomes of kidney retransplantation after graft loss as a result of BK virus nephropathy in the era of newer immunosuppressant agents. Arab. Archaeol. Epigr. 2019, 20, 1334–1340, doi:10.1111/ajt.15723.