BK virus (BKV) is a member of the Polyomavirus genus, which includes BKV, JC virus, and simian virus 40. BKV has a tropism for the kidney and urinary tract, and it is now well established that it is a cause of allograft nephropathy in recipients of kidney transplants and of hemorrhagic cystitis in recipients of allogeneic hematopoietic stem cell transplants [1, 2]. The clinical significance of BKV detection in recipients of other transplants is less clear. Renal dysfunction is a recognized late complication in recipients of nonrenal solid organ transplants, particularly in recipients of heart and lung transplants, in whom it is often attributed to the long-term effects of calcineurin inhibitors. However, it is of interest to investigate whether polyomaviruses might be contributing factors to renal dysfunction after transplantation in these patients [3].

Case reports have documented the occurrence of biopsy-proven BKV nephropathy in native kidneys of recipients of nonrenal transplants [4–7]. Limaye et al. [4] described allograft nephropathy in 1 recipient of a heart transplant and 1 recipient of a stem cell transplant, utilizing histopathologic, immunohistochemistry, and PCR analysis. Schmid et al. [5] diagnosed BKV nephropathy in 1 of 13 recipients of heart transplants who underwent native kidney biopsy because of significant renal dysfunction. Milstone et al. [6] reported native kidney nephropathy due to a related virus (simian virus 40) in a recipient of a lung transplant by use of DNA detection, immunohistochemistry analysis, and neutralizing antibody testing. Randhawa et al. [8] examined recipients of liver transplants, as well as recipients of kidney transplants, in a study of BKV and JC virus and found that BKV viruria occurred in 15.9% of recipients of liver transplants, but no cases of viremia were detected in this group; Splendiani et al. [9] also noted occasional BKV viruria and 1 case of viremia among recipients of liver transplants, but no cases of renal dysfunction. However, many questions remain concerning the overall incidence and clinical significance of polyomavirus viruria and viremia in recipients of nonrenal organ transplants.

Muñoz et al. [10] have conducted a point prevalence study involving recipients of renal, liver, and heart transplants by using a nonquantitative nested PCR assay for detection of BKV in blood and urine specimens. Not surprisingly, BKV was found in urine specimens from 26.5% and blood specimens from 12.2% of the recipients of renal transplants, which is similar to findings in a previous report [11]. What is more interesting is the frequency of detection of BKV in urine and blood samples from 25.5% and 7% of heart transplant recipients, respectively. Fewer recipients of liver transplants (7.8%) had BKV detected in a urine specimen, and there was no viremia detected in any recipients of liver transplants. BKV detection in urine was associated with renal dysfunction in the heart transplantation group, but because this involved 8 viruric patients (of whom 4 had renal dysfunction), it would be desirable to confirm these results in a larger prospective study. In addition, there were only 3 recipients of heart transplants who had viremia in the study by Muñoz and colleagues, 1 of whom had another reason for renal dysfunction, so it is not possible to draw any conclusions from this regarding the clinical significance of BKV detection in blood specimens in the heart transplantation population.

The association between BKV detection and renal insufficiency among recipients of heart transplants is not necessarily causal. Both findings could be manifestations of more-intensive calcineurin inhibitor–based immunosuppression over time. To evaluate this possibility, Muñoz et al. [10] included an analysis of immunosuppressive regimens in this study. A previous randomized study by Brennan
et al. [11] compared recipients of kidney transplants receiving tacrolimus with those receiving cyclosporine; patients receiving the combination of tacrolimus/mycophenolate were significantly more likely than those receiving cyclosporine/mycophenolate to have viruria detected (46% vs. 13%; P = .005). However, BKV allograft nephropathy has also been reported among recipients of kidney transplants receiving calcineurin-free immunosuppressive regimens [12]. In the study by Muñoz and colleagues, mycophenolate use emerged as an apparent independent risk factor for renal dysfunction, with an OR of 3.5. As the authors acknowledge, differential use of mycophenolate therapy for different types of transplant recipients, in addition to the fact that this was not a randomized study, makes this finding difficult to interpret. In any event, the authors did not demonstrate any association between mycophenolate use and BKV replication.

The time after transplantation may be an important factor in BKV-associated disease. It would be of interest to perform a prospective longitudinal study involving recipients of nonrenal transplants that utilizes quantitative PCR to assess changes in viral load over time. Monitoring of BKV load after renal transplantation has now been advocated by a panel of experts [1] with the goal of early intervention to prevent graft loss. For recipients of renal transplants, decreasing immunosuppression can lead to stabilization of renal function and prevention of graft loss in some cases, and a switch to a sirolimus-based regimen has also been suggested [13]. For patients with progressive BKV allograft nephropathy, low-dose cidofovir, leflunomide, and intravenous immunoglobulin have been described in small series as potentially effective therapies [14, 15]; however, the later after transplantation that these therapies are started, the less success they are likely to have in reversing graft dysfunction. It is not yet clear what, if any, role there is for monitoring BKV load over time in recipients of nonrenal solid organ transplants, nor whether any pharmacotherapeutic intervention should be undertaken for these patients. The intriguing findings of Muñoz and colleagues should prompt further research to address these unanswered questions.

Acknowledgments


References


Note added in proof. A recently published study by Razonable and colleagues also found BK virus or JC virus DNAemia in 7% of heart and 4% of liver transplant recipients (Razonable RR, Brown RA, Humar A, Covington E, Alecock E, Paya CV. A longitudinal molecular surveillance study of human polyomavirus viremia in heart, kidney, liver, and pancreas transplant patients. PV1600 Study Group. J Infect Dis 2005; 192:1349–54).