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Helanterä, Ilkka

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Case report

Simultaneous BK Polyomavirus (BKPyV)-associated nephropathy and hemorrhagic cystitis after living donor kidney transplantation

Ilkka Helanterä[a,*], Hans H. Hirsch[b,c], Marion Wernli[b,c], Fernanda Ortiz[d], Marko Lempinen[a], Anne Räisänen-Sokolowski[e], Eeva Auvinen[f], Laura Mannonen[f], Irmeli Lautenschlager[f]

[a] Transplantation and Liver Surgery, University of Helsinki and Helsinki University Hospital, PO Box 372, FI 00029HUS, Helsinki, Finland
[b] Transplantation and Clinical Virology, Department of Biomedicine, University of Basel, Petersplatz 10, CH-4009 Basel, Switzerland
[c] Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
[d] Department of Nephrology, University of Helsinki and Helsinki University Hospital, PO Box 372, FI 00029HUS, Helsinki, Finland
[e] Department of Pathology, University of Helsinki and Helsinki University Hospital (HUSLAB), PO Box 400, FI 00029HUS Helsinki, Finland
[f] Department of Virology, University of Helsinki and Helsinki University Hospital (HUSLAB), PO Box 400, FI 00029HUS, Helsinki, Finland

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ABSTRACT

BK polyomavirus (BKPyV) commonly reactivates after kidney transplantation, and can cause polyomavirus-associated nephropathy (PyVAN), whereas after allogeneic stem cell transplantation the most frequent manifestation of BKPyV is polyomavirus-associated hemorrhagic cystitis (PyVHC). Despite high-level BKPyV replication in both, the pathogenesis and manifestation of both BKPyV entities appears to differ substantially. We describe an unusual case of simultaneous PyVAN and PyVHC presenting with acute symptoms in a BKPyV-IgG positive recipient eight months after kidney transplantation from a haploidentical living donor, who was BKPyV-IgG negative. Symptoms of cystitis and viremia subsided rapidly after reduction of immunosuppression.

1. Why this case is important

Viral infections commonly complicate the clinical course of kidney transplant patients, and several viruses are able to infect and damage the transplanted kidney [1]. BK polyomavirus (BKPyV) reactivates after kidney transplantation with BKPyV DNAemia in 10–25%, and proven polyomavirus-associated nephropathy (PyVAN) in one half of affected patients [2–5]. Due to recommendations to routinely screen for BKPyV replication, PyVAN has become a less frequent cause of early graft loss, as timely reduction of immunosuppression can prevent the development of severe nephropathy [6]. No uniform consensus of optimal screening and treatment exists, however, compared to other guidelines as those for Epstein-Barr virus or Cytomegalovirus (CMV), the recommended steps of reducing immunosuppression for BKPyV replication are quite explicit [7,8]. Reconstitution of immune control after reduction of immunosuppression may be slow, and clearance of viremia ranges from 4 to 12 weeks, depending on the BKPyV peak viral loads [6,9]. Polyomavirus-associated hemorrhagic cystitis (PyVHC) caused by BKPyV, on the other hand, is typically reported in 5–20% of patients after allogeneic stem cell transplantation [10–14], whereas only a few cases have been described after solid organ transplantation [15,16]. Despite high-level BKPyV replication in both, nephropathy and hemorrhagic cystitis, the pathogenesis and manifestation of both BKPyV entities appears to differ substantially [17]. Here, we present an unusual case of simultaneous PyVAN and PyVHC after living donor kidney transplantation.

2. Case description

We describe a male patient with IgA nephropathy (HLA type A2, A3, B12, B13, DR4, DR 16), who at the age of 27 years received a kidney transplant from his father (58 yrs, HLA type A2, B13, B15, DR 4, AB/DR mismatch 1/0). The patient was CMV seronegative and the donor was CMV seropositive, and valganciclovir prophylaxis was used for 6 months after transplantation. Primary immunosuppression consisted of cyclosporine (CsA), enteric-coated mycophenolate sodium (EC-MPS), and steroids. No induction was given. Early postoperative course was unremark-

* Corresponding author. Fax: + 358 9 471 76661.
E-mail address: Ilkka.helantera@helsinki.fi (I. Helanterä).

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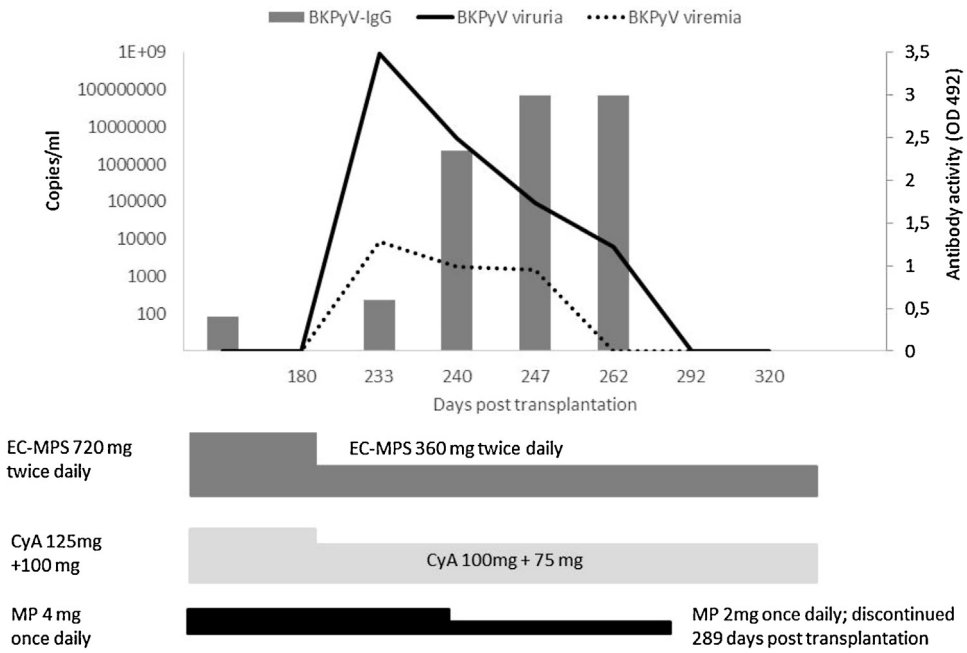

Fig. 1. BKPyV viral loads in urine and plasma in relation to BKPyV IgG antibody response to virus like particles (VLP) analyzed by enzyme immunosorbent assay for sera diluted in 1:200 using the cut-off value for positive antibody response 0.1 OD_{492}. The time related immunosuppression is demonstrated in detail. BKPyV = BK polyomavirus, EC-MPS = enteric-coated mycophenolate sodium, CyA = Cyclosporine A, MP = Methylprednisolone.

able, and estimated GFR (eGFR) was 60 ml/min at three months after transplantation. The six-month protocol biopsy showed normal histology of the kidney, and no IgA in immunofluorescense. At six months, CsA C0 concentration was 136 ng/mL (within target), eGFR was 59 ml/min, and BKPyV PCR from both blood and urine were negative.

Eight months posttransplant the patient presented with acute hematuria Grade II–III and severe dysuria. The eGFR was decreased (28 ml/min), the urine sample showed red and white blood cells, but urine bacterial culture was negative. Quantitative BKPyV PCR [18] showed 9.25×10^8 (8.97 $\log_{10}$) copies/ml in urine, and 8700 copies/ml (3.94 $\log_{10}$) in plasma. No JC polyomavirus (JCPyV) or adenovirus was detected in urine by PCR. No CMV DNAemia was detected and viral culture from urine was negative at the time of acute cystitis. The kidney biopsy showed signs of interstitial nephritis (Banff inflammation score 2, tubulitis 1) and SV40 T antigen staining was positive in tubular cells confirming BKPyV nephropathy (PyVAN grade B1). IgA in immunofluorescence was negative.

At this stage, CsA dosing was reduced from 225 mg/day to 175 mg/day (trough levels reduced from 157 μg/l to 97 μg/l), and EC-MPS from 1440 mg/day to 720 mg/day. One week after the first detection, BKPyV viremia already started to decline (1800 copies/ml; 3.26 $\log_{10}$ copies/ml), and 30 days after the first sample, plasma BKPyV PCR was negative. Symptoms of cystitis and hematuria subsided in parallel with declining urine BKPyV loads during 30 days after diagnosis, and graft function improved to eGFR 44 ml/min. Urinary BKPyV viral load has remained low, but detectable during 1 year follow-up (latest viral load 5068 copies/ml), and BKPyV PCR from plasma has remained negative. JCPyV from urine has remained negative during follow-up, but no further testing for adenovirus has been performed.

Subsequently, late-onset primary CMV infection occurred after discontinuing valganciclovir prophylaxis at 8 months after transplantation, and following diagnosis and surgical excision of a malignant melanoma skin tumor, immunosuppression was switched to sirolimus and low-dose steroid. Graft function has remained stable since (eGFR is 60 ml/min 46 months posttransplantation) and the patient is doing well. Serology [19,20] showed that the patient was BKPyV-seropositive before transplantation, but IgG titers were rising as viremia declined. Remarkably, donor sera were BKPyV-IgG negative suggesting that this clinical manifestation represented a primary infection of the donor renal transplant presumably by endogenous reactivation of the recipient virus. Fig. 1 represents schematically the evolution of the virological findings and immunosuppression.

3. Other similar cases in the literature

Although PyVHC complicates 5–15% of allogeneic hematopoietic stem cell transplantation [8], only a few cases have been reported after solid organ transplantation. A case of a pediatric lung transplant patient and another case of an adult heart transplant recipient developing BKPyV associated hematuria and cystitis have been described [21,22]. The first reported case of biopsy proven PyVHC in an adult renal transplant patient was diagnosed two months after transplantation together with a positive staining for SV40 large T-antigen histologically demonstrating proven PyVAN [15]. After discontinuing mycophenolate, hematuria subsided and the renal function stabilized. Drake et al. reported two cases of pediatric kidney transplant patients with hematuria [16], one with high BKPyV viral loads in urine (>10,000,000 copies/ml) and cystitis. A few weeks later BKPyV was also detected in plasma (7600 copies/ml). Serum creatinine remained stable and no evidence of PyVAN was found in the renal biopsy. Mycophenolate and cyclosporine doses were reduced and ciprofloxacin and leflunomide were prescribed. The patient recovered over a period of 8 weeks and the viral replication subsided. Another pediatric case demonstrated microscopic hematuria, proteinuria and leukocyturia together with high urine BKPyV loads (>10,000,000 copies/ml) followed by plasma PCR positivity (4200 copies/ml) after 8 weeks. Serum creatinine was somewhat increased, but a histological diagnosis of PyVAN was not available. Mycophenolate was discontinued and leflunomide and ciprofloxacin were administered, although the role of the latter agents is undefined in the treatment of high-level BKPyV replication, particularly since in a recent randomized con-

trolled trial, the use of levofloxacin was not even effective as BKPyV replication prophylaxis [23].

4. Discussion

Here, we describe an unusual case of BKPyV replication after kidney transplantation, which presents as histologically confirmed PyVAN with simultaneous signs and symptoms of hemorrhagic cystitis. Other possible relevant causes of cystitis, such as CMV, adenovirus, and bacterial infections, were ruled out, and the patient was successfully treated by reducing immunosuppression as currently recommended. Interestingly, simultaneous PyVAN and PyVHC presented fairly late after transplantation and signs and symptoms or both PyVAN and PyVHC resolved rapidly in parallel with declining viral load within 4–6 weeks. This might reflect the BKPyV seropositive status of the patient and the relatively mild initial cyclosporine based immunosuppression. Importantly, the donor was BKPyV-IgG seronegative, which is infrequently encountered and strongly suggests that it took some time for BKPyV to infect and colonize the renal allograft as suggested by the late and extensive manifestation with PyVAN and PyVHC. The origin of the virus remains undefined and could be either exogenous or endogenous re-infection. Exogenous re-infection with BKPyV seems less likely as in that case haematogenous seeding to renal allograft would have to be postulated in an IgG seropositive patient subsequent to oral or respiratory contact. A more likely hypothesis is reactivation of the recipient virus with urinary shedding and backwash to the transplant kidney. Similar to the more common cases, the definitive diagnosis of BKPyVAN was based on high viral loads in urine and plasma together with histology and immunohistochemistry showing positive staining for large T-antigen using cross-reacting anti-SV40 antibodies corresponding to PyVAN grade B1 [24]. Rapid immune reconstitution inflammatory syndrome (IRIS) in this haploidentical HLA context of living kidney donation may explain both, the clinical manifestations of hemorrhagic cystitis and the quick recovery. A significant increase in BKPyV-IgG serology confirmed the diagnosis. There was no biopsy to histologically confirm PyVHC due to absence of other etiologies and the quick response to decreased immunosuppression. As hematuria also subsided, no cystoscopy was indicated.

Our case is only the second renal transplant recipient with simultaneous BKPyVAN and BKPyHC described so far [15]. In the first described case ureteral stent was inserted routinely intraoperatively, which might increase the risk of BK viremia [25] whereas in our present case, no ureteral stent was used. The pathogenesis of PyVAN has been described previously [9,26], but the mechanism of developing this unusual combination is unknown. BK polyomavirus is known to replicate in uroepithelial cells and asymptomatic BKPyV associated hematuria has been reported in pediatric renal transplant patients [27]. BKPyHC is thought to result from cytopathic damage and mucosal denudation caused by high-level viral replication in the urothelial cell layer and is association with the impaired immunological conditions [10]. High viral load in urine (>7 $\log_{10}$ copies/ml) and only moderate viral loads in plasma, similar to our case, are among the diagnostic findings of PyVHC [11].

In the present case, BKPyV viremia subsided rapidly after reduction of immunosuppression. Current guidelines recommend reduction of immunosuppression as the treatment of BKPyV viremia and PyVAN, but the most effective strategy to reduce immunosuppression remains to be established [7,8]. In our BKPyV IgG seropositive case, reduction of mycophenolate and CsA doses was sufficient to be followed by rapidly declining levels of viremia. Most cases of PyVHC occur after stem cell transplantation, and reduction of immunosuppression is usually not possible due to concurrent threat of graft-versus host disease.

5. Conclusions

An unusual simultaneous BKPyV-associated nephropathy together with hemorrhagic cystitis was seen in a BKPyV-IgG Donor negative/Recipient positive kidney transplant recipient. The clinical course was fairly late after transplantation presenting acutely, and symptoms and viremia subsided rapidly after reduction of immunosuppression.

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Ethical approval

The study was approved by the Institutional Review Board and the Ethics Committee of Helsinki University Hospital.

Conflict of interest

No financial or other conflicts of interest exist with any of the authors of this article.

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