Emerging Polyomavirus Infections: A New Burden for Transplant Recipients and a New Challenge for Transplant Physicians

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Abstract

Polyomavirus is the sole genus of viruses within the Polyomaviridae family [1]. Until 2006, BK virus (BKV) and JC Virus (JCV), first isolated in 1971 [2,3], were the only two human Polyomaviruses known although some evidence suggested that also the Simian Virus 40 (SV40) could be associated to some human tumours [4]. JCV and BKV usually infect the human population during early childhood and primary infection is often asymptomatic. These viruses can remain latent in the kidney cells of the host until reactivation which occurs primarily during immunodepression. JCV causes Progressive Multifocal Leuкоencephalopathy (PML) in cases of severe immunodeficiency, generally due to HIV infection, whereas BKV causes a severe nephropathy in kidney transplant recipients [5,6].

In 2007, two new Human Polyomaviruses were independently described: the KI PolyaVirus (KIV) at Karolinska Institute and the WU PolyaVirus (WUV) at Washington University [7,8]. In 2008, a fifth polyoma virus, Merkel cell PolyaVirus (MCyPV) was isolated from the skin of a patient affected by Merkel Cell carcinoma (MCC) showing its ability to cause most of the Merkel skin cancers [9]. Another virus, the Malawi PolyaVirus (MWyPV) was isolated by two different groups from human stool sample of healthy subjects and from stool sample of a patient affected by WHIM syndrome(Warts, Hypogammaglobulinemia, Infections and Myelokathexis) [10,11].

Three other Polyomaviruses were isolated from non-tumoral skin, the Human Polyomavirus 6 and 7 (HPyV6, HPyV7) and the Trichodysplasia Spinulosa-associated Virus (TSPyV) [12,13]. The Human PolyaVirus 9 (HPyV9), closely related to LPV, was also identified from the blood and urine of asymptomatic renal transplant recipients [14]. Finally, the latest discovered polyomavirus the STLPyV [15], was isolated from stool specimen of patients in Gambia and in United States.

All the viruses that belong to the Polyomaviridae family are small and non-enveloped. They haveicosahedral capsids, measuring 40.5-44 nm in diameter, and circular, double-stranded super coiled DNA genomes of approximately 5 Kb. Primary infections with human Polyomaviruses are usually asymptomatic and very common with a reported incidence of zero prevalence varying from 20% to 100% [16]. Although classic and newly discovered Polyomaviruses show some differences in cellular/tissue tropisms, pathogenesis and clinical manifestations of the diseases, they share the peculiarity of giving rise to a latent infection in the host. The mechanisms through which Polyomaviruses manage to avoid the immune recognition and remain latent in human host are not known at the present whereas viral reactivation seems to be closely related to an impairment of the immunological state of the host.

Based on these observations, Organ Transplantation represents a typical situation at high risk for Polyomavirus reactivation, due to the deep-induced immunosuppression to prevent rejection and prolong graft survival. In particular, kidney transplant recipients are at the highest risk given the selective tropism of BK and JCV for the urological system. It is well known that BKV reactivation may be associated with the onset of Polyomavirus Associated Nephropathy (PVAN), a serious complication of transplantation whose range of severity varies from an asymptomatic viremia until graft loss [17]. Moreover, infection by JCV has been observed in renal allograft recipients, but only few cases of nephropathy have been attributed to JCV [18].

Consequently, the introduction of newer and more selective immunosuppressive drugs and the increasing number of patients who will benefit from an organ transplant or a bone marrow transplant in...
the coming years will lead to an inevitable increase in polyomavirus infections in this particular setting. A different type of Polyomavirus that has recently caught the attention of many researchers is the MCPyV which has been associated with the development of MCC, a neuroectodermal tumour arising from the Merkel Cell, amechano receptor, present in the skin of limbs and face and around hair follicles. MCC is a rare and aggressive skin cancer, very rare before age of 50, with an incidence rate of 0.44 cases per 100,000 subjects in the USA. However, the incidence of MCC is dramatically increasing, tripling from 1986 to 2001. The risk factors for the development of MCC include excessive UV light exposure, age > 50 years old and immunosuppression of the host [19]. This explains why the reported incidence of MCC is higher in immunosuppressed organ transplant recipients in HIV/AIDS patients rather than in healthy individuals. Feng et al. were able to isolate from MCC samples, the genome sequency of Merkel Cell Polyomavirus integrally within the host genome in a clonally pattern and in its episomal form in samples of normal tissues obtained from the same patients [19].

Two studies have been published so far focused on the potential association between MCPyV replication and transplantation. [20, 21]. Husseiny et al. collected serum and urine samples from three different cohorts of patients: a group of prospectively enrolled renal transplant recipients, a group of transplant recipients who developed BKV-associated nephropathy and a group of healthy donors. The results indicated a very low level of MCPyV shedding in the urine of normal subjects (15%) and of renal transplant recipients and no shedding in the urine of PVAN patients [20]. Very recently, Baez and colleagues investigated the presence of MCPyV DNA in the saliva and oral biopsies obtained from 60 kidney allograft recipients and 75 non-transplanted individuals. They detected the viral genome in the oral mucosa of both groups but only in the saliva obtained from the transplanted group [21].

Our preliminary experience of case–control study carried on in pediatric and adult renal transplant recipients show a higher prevalence of MCPyV excretion in the urine of the patients compared to the controls, and also compared to the JCV and BKV excretion (unpublished data). Interestingly, the trend seems more pronounce in the pediatric population rather than in the adult group.

In conclusion, the Polyomaviridae family is expanding very rapidly and the ubiquity and the natural history of their infections make almost all of them potential pathogens in a setting of immunosuppression, and in particular for immunomodulatory therapies following transplantation. However, further studies are needed in order to monitor either the human Polyomaviruses primary infection or reactivation following kidney transplant and to confirm these preliminary observations that suggest the potential risk associated with infections caused by the most recently identified Polyomaviruses.

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