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Is Isolation of Human Herpesvirus 6 in Kidney Transplant Recipients Clinically Significant?

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Human herpesvirus-6 (HHV-6), a ubiquitous β-herpesvirus that can infect the majority of humans, has been recognized as a cause of infection in kidney transplant recipients for more than 20 years now [1]. The incidence of HHV-6 infection varies widely, depending on the study and method of testing and is estimated to be 23–55% in kidney transplant recipients [2,3]. After primary infection, HHV-6 persists in a latent state in the host in various cells, mainly in those of monocyte and macrophage origin [4] and can reactivate later in life, especially after transplantation. The incidence of HHV-6 reactivation peaks at 2–4 weeks after transplantation, but late infections that occur months or years after transplantation may occur [1,5]. Infection is most likely to result from reactivation of recipient's endogenous HHV-6 but the virus may also be transmitted through organ transplantation [5]. Kidney transplant recipients receiving an allograft from the same donor can have the same HHV-6 isolate [2]. Thus, HHV-6 may be transmitted with the donor kidney allograft and reactivation after transplantation could be attributable to the HHV-6 strain of either the recipient or donor origin.

HHV-6 may persist in kidney allografts [6]. HHV-6 specific antigens have been detected by immunohistochemistry in kidney biopsies of patients with acute and chronic rejection or cyclosporine-related nephropathy while high viral loads in renal tissue have been correlated with significant illness owing to HHV-6 infection of pediatric kidney transplant patients [1,5,7]. Nucleic acid testing has also allowed for detection of chromosomally integrated HHV-6 (CIHHV-6) in kidney transplant recipients [8]. However the significance of the persistent HHV-6 regarding transplant outcome remains uncertain [8].

In addition to the direct effects of HHV-6, numerous indirect effects have also been reported or suggested since HHV-6 is considered to be an immunomodulatory virus [1,5]. HHV-6 has been associated with a higher risk of CMV disease, and concomitant or recent CMV infection may induce the clinical symptoms [9]. Concurrent intragaft infections of HHV-6 and CMV have been found both in kidney transplants [6]. Finally, both HHV-6 and HHV-7 infections are associated with the development of chronic allograft nephropathy [10].

Although HHV-6 infection in kidney transplant recipients is mostly subclinical, symptomatic or even fatal HHV-6 infections have been described. Pure HHV-6 infections are limited to small case series describing fever, elevated creatinine levels, liver dysfunction, and colitis [1,5]. The few fatal cases of HHV-6 disease were characterized by hemophagocytic syndrome, encephalitis, pancytopenia, severe hepatitis, or colitis [11].

The diagnosis of clinically significant HHV-6 infection is challenging. HHV-6 infections after kidney transplantation were mainly diagnosed based on serological analysis or isolation of the virus from blood specimens and were usually asymptomatic [12]. Serology has limited diagnostic value due to high seroprevalence rate (over 95%) in adult transplant patients. Viral culture of HHV-6 is laborious, is not routinely used in diagnostic laboratories, and the turn-around time is too slow to be of use in guiding the management in real-time clinical practice. Recently, several virus detection methods have been developed, that demonstrate the presence of HHV-6 in the tissue specimens [13].

Detection of HHV-6 in the clinical specimen does not necessarily implicate the virus as the etiology of a specific illness, and the differentiation between latent and active infection is not always possible. Demonstration of HHV-6 specific antigens in tissue specimens may be more informative than the demonstration of viral DNA in the blood [13]. Quantitative methods are needed to diagnose an active systemic HHV-6 infection and the quantification of HHV-6 DNA using real-time PCR, is currently the most common tool to diagnose an active HHV-6 infection [13]. However the methods are not standardized and no clear cut-off levels exist to differentiate asymptomatic viral replication from symptomatic clinical disease. Finally although novel molecular methods for the detection of HHV-6 have been developed to distinguish between latent and active infection in transplant patients, these tests are not in general use [8].

In conclusion, HHV-6 is a common infection after kidney transplantation. However, HHV-6 diagnostics is not routinely performed and the clinical role of HHV-6 infection might be underestimated. Although the reactivation rate is high, clinical disease is estimated to occur in only 1% of patients. Although HHV-6 surveillance after transplantation is not routinely performed in clinical practice, the diagnosis of HHV-6 is now commonly made using nucleic acid testing. Antiviral prophylaxis and preemptive therapy are not recommended for HHV-6 [5]. Foscarnet, ganciclovir, and cidofovir may be used for treatment in established end-organ disease such as encephalitis [5]. Current diagnostic methods need to be standardized whereas larger prospective studies with long durations of follow-up are needed to evaluate the significance of isolation of HHV-6 in kidney transplant recipients.

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