Kaposi’s Sarcoma Associated with Previous Human Herpesvirus 8 Infection in Heart Transplant Recipients

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Received 19 November 2001/Returned for modification 6 February 2002/Accepted 27 March 2002

The aim of this study was to evaluate the seroprevalence of human herpesvirus 8 (HHV-8) in a group of 150 patients awaiting heart transplants and to detect HHV-8 seroconversion after transplantation. Four patients were HHV-8 seropositive before transplantation, and one of them developed Kaposi’s sarcoma. One patient converted to seropositive HHV-8 status after transplantation.

Human herpesvirus 8 (HHV-8; also known as Kaposi’s sarcoma [KS]-associated herpesvirus) has been associated with all forms of KS, human immunodeficiency virus-positive primary effusion lymphomas (PEL), and multicentric Castleman disease (2). Viral DNA and serum antibodies to HHV-8 appear to have predictive value for the onset of KS, especially in patients with compromised immune systems (i.e., with AIDS or after kidney transplantation) (2, 3, 6–8). HHV-8 is not, however, restricted to KS patients. Higher-than-average seroprevalence has been reported for patients from certain geographic areas such as central and southern Italy and Africa, where classical KS is also more frequent than in other parts of the world (1, 9). A strict association between HHV-8 and KS has been demonstrated in transplant recipients. With kidney transplantation, two mechanisms have been described: HHV-8 contamination from the donor to the recipient and HHV-8 reactivation in patients who were infected before the graft (3, 6, 7, 11, 17, 19). With heart transplantation, KS and PEL were found to be associated with HHV-8; in some patients, this association led to patient death (4, 5, 10). But it is still unclear whether posttransplantation KS is due to HHV-8 reactivation as a result of immunosuppressive treatment or to HHV-8 primary infection transmitted via organ transplantation.

The aim of this study was to evaluate HHV-8 seroprevalence in a group of patients awaiting heart transplant, the risk of HHV-8 transmission via heart transplantation, and the subsequent development of KS- or other HHV-8-related diseases.

One hundred and fifty patients (115 men and 35 women) who underwent heart transplantation in the Pitié-Salpêtrière Hospital Transplant Unit (Paris, France) from 1995 to 2001 were included in this study. The mean age of transplant patients was 47.4 years (range, 18 to 68 years), and most of the patients lived in France. Patients whose sera prior to and 3 months after transplantation were not available and patients lost to follow-up were excluded (minimum duration of clinical follow-up, 3 years). Follow-up visits were scheduled every month during the first year after transplantation and every 3 months subsequently. Diagnosis of KS was made clinically during physical examination by Transplant Unit physicians and hospital dermatologists and confirmed by histological examination.

Serum samples were collected the day before and 3 months after heart transplantation. Antibodies to latent nuclear antigen 1 of HHV-8 were detected by immunofluorescence assay of a PEL cell line (BC-3). The immunofluorescence assay was performed as previously described with a serum dilution of 1/100 (20).

Among the 150 pretransplant serum samples, 4 (2.7%) were positive for HHV-8 antibodies (Table 1). HHV-8 antibody titers, before and after surgery, are presented in Table 2. There was a trend for HHV-8-infected patients to be older (median age, 60 years) than non-HHV-8-infected patients (median age, 48 years) ($P = 0.08$). One of the 4 patients who were HHV-8 seropositive before transplantation developed KS at month 7, corresponding to an incidence of KS of 25%, while none of the 146 seronegative patients (0%) developed the disease (Table 1). The HHV-8-seropositive patients who developed KS had skin KS without any extradermatological manifestations. The three remaining seropositive patients did not develop any HHV-8-related disease during the clinical follow-up, but one of them harbored a hepatitis with persistent cytolysis without a demonstrable viral, immunological, or drug-related etiology.

Follow-up testing of the 150 patients from 1 day before to 3 months after transplantation showed that of the 146 patients who had tested negative for HHV-8 antibodies before transplantation, only 1 seroconverted (0.68%) (Table 2). This patient did not develop any HHV-8-related disease during 3 years of follow-up after transplantation. Three months before testing positive for HHV-8 antibodies, this patient had a fever (39°C) for 1 week and a major and persistent asthenia for 3 months. Routine cultures and serologic tests for common bacterial, fungal, and viral pathogens were negative, with the exception of a 3-day period of human cytomegalovirus-positive pp65 antigenemia corresponding to the first 3 days of asthenia and fever. Ganciclovir therapy was started immediately, and...
the pp65 antigenemia became negative within 2 days, but asthena persisted for up to 3 months.

In this study, the overall seroprevalence of HHV-8 in heart transplant patients was 2.7%, a rate close to that observed for healthy subjects in Paris (2%) (13). HHV-8 seroprevalence was unaffected by pretransplant therapeutic regimens, a finding supported by other studies showing a low rate of parenteral HHV-8 transmission (7, 12, 16). One of the 150 patients (0.67%) developed iatrogenic KS after heart transplantation. This relatively low rate could be explained by the fact that HHV-8 is not endemic in France. The patient who developed KS was HHV-8-seropositive before transplantation, corresponding to a incidence of KS of 25% that is very similar to that previously described for kidney allograft recipients and that recipients of other organs (i.e., heart transplant patients) are also at risk for HHV-8-related disease, even those living in an area in which the disease is not very prevalent.

One patient (0.67%) seroconverted for HHV-8 after transplantation, suggesting that seroconversion due to transplantation is relatively rare, at least in countries where the prevalence of HHV-8 is low. This is concordant with previous studies of kidney transplant recipients and with the fact that, in our center, most of the donors were French cadavers (17–19). This patient did not develop any HHV-8-related disease but harbored a major and persistent asthena during 3 months before HHV-8 seroconversion, which was previously described (14). These results suggest that heart transplant recipients are, overall, epidemiologically similar to kidney transplant recipients and that the pathogenesis of KS and its relation to HHV-8 are very similar in both transplantation types.

In conclusion, our study suggests that antibody detection in the context of heart transplantation is a useful means of detecting patients at high risk for KS or other HHV-8-related disease, at least in areas where HHV-8 infection is common. The main interest would be to take HHV-8 serostatus into account, especially in cases where atypical clinical symptoms are present that could be predictive of the onset of a KS (i.e., edema of the legs). Previous studies suggested that ganciclovir represented a prophylaxis against HHV-8-related disease (15).

In terms of prophylaxis, the benefit of some drugs, such as valganciclovir, should be evaluated in all HHV-8-infected organ transplant recipients.

This work was partly supported by grants from Association pour la Recherche sur le Cancer (ARC), Sidaction, and ARVD. We thank Chris Boschoff (University College of London, London, United Kingdom) for providing us with the BC-3 cell line.

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