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Seroprevalence of Antibodies against Human Herpesvirus 8 in a Population of Renal Transplant Recipients at Hôtel-Dieu de Québec Hospital

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We conducted a seroepidemiologic study to determine the prevalence of anti-human herpesvirus 8 antibodies in a renal transplant population at Hôtel-Dieu de Québec Hospital. Testing for immunoglobulin G antibodies against lytic and latent antigens was performed on serum samples from 150 renal transplant patients. Human immunodeficiency virus-positive patients with confirmed Kaposi's sarcoma were used as positive controls. None of the renal transplant patients tested positive.

Human herpesvirus 8 (HHV-8) is a member of the *Herpesviridae* family. This virus belongs to the *Gammaherpesvirinae* subfamily (7) and was identified for the first time in 1994 from the skin lesions of a patient with Kaposi's sarcoma (KS) (3). Evidence points to a role for HHV-8 in oncogenesis (2, 8, 11).

Iatrogenic KS is a complication of organ transplantation and is observed predominantly in kidney allograft recipients (10). It is still unclear whether posttransplantation KS may be due to the reactivation of HHV-8 or to HHV-8 transmission via organ transplantation (1, 5, 9). Recently, HHV-8 infection has also been implicated in the development of a nonneoplastic illness manifested by cytopenia in renal allograft recipients and in a patient receiving an autologous peripheral-blood stem cell transplant (6).

The seroprevalence of HHV-8 in the general population ranges from <5% in North America, northern Europe, and Asia to 10 to 20% in certain Mediterranean countries to >50% in some African regions (4, 12).

The potential role of HHV-8 in the development of both oncogenic and nononcogenic illnesses in transplant patients led us to investigate the prevalence of anti-HHV-8 antibodies in renal transplant recipients at Hôtel-Dieu de Québec Hospital.

Between February 1997 and January 2000, serum samples were collected from 150 renal transplant recipients approximately 1 year after transplantation and tested for HHV-8 antibody. Twenty-four serum samples from 24 HIV-positive patients who were confirmed by biopsy to have KS were used as positive controls. These serum samples were collected between September 1992 and January 2000. Finally, three serum samples obtained from a 1986 renal transplant recipient who later developed KS were also tested. All serum samples were preserved at −20°C.

Serum samples were tested with two commercially available immunoenzymatic assays in order to detect most HHV-8 antibody–positive samples. The first assay (HHV-8 whole virus lytic immunoglobulin G [IgG] enzyme-linked immunosorbent assay [ELISA]; Advanced Biotechnologies Inc., Columbia, Md.) measures IgG antibodies against lytic antigens and uses an extract prepared from sucrose gradient-purified HHV-8 whole virions isolated from the KS-1 cell line. The second assay (HHV-8 ORF-73 IgG ELISA; Advanced Biotechnologies Inc.) uses a recombined protein fragment of the major latent nuclear antigen, encoded by open reading frame (ORF) 73, and detects antibodies to HHV-8 latency-associated nuclear antigen (LANA). The experiments were performed according to the manufacturer's instructions.

All HIV-positive patients were men who reported having had sex with other men at least once. Twenty-two (92%) of these 24 HIV-positive patients with KS tested positive for antibodies against lytic antigens (Fig. 1), while 14 (58%) tested positive for antibodies to LANA. Two HIV-positive patients who tested negative for lytic antigens also tested negative for LANA antigens.

Serum samples from renal transplant recipients were obtained 3 to 16 months posttransplantation (mean, 10.66 months). As shown in Fig. 1, none of the 150 renal transplant patients tested positive for antibodies against HHV-8.

Over 1,070 renal transplantations have been performed at our institution. Only one of our transplant recipients went on to develop KS after her transplantation. This woman developed a biopsy-confirmed KS 3 months posttransplantation. The results of her antibody tests are shown in Table 1. Serologic testing confirmed that she had been infected with HHV-8 prior to kidney transplantation.

There are currently no data available for estimation of the exact prevalence of HHV-8 antibody in the Canadian population. Clinical complications of HHV-8 infection, however, have occurred only in settings in which patients have been immunosuppressed, such as those involving HIV infection or organ transplantation. The most common clinical manifestation of HHV-8 infection is the development of KS, although a nonneoplastic illness in posttransplant patients was recently described (6). Between 1997 and 2000, the prevalence of HHV-8 antibodies detected in renal transplant recipients at Hôtel-Dieu de Québec Hospital was 0%. This result is in line with

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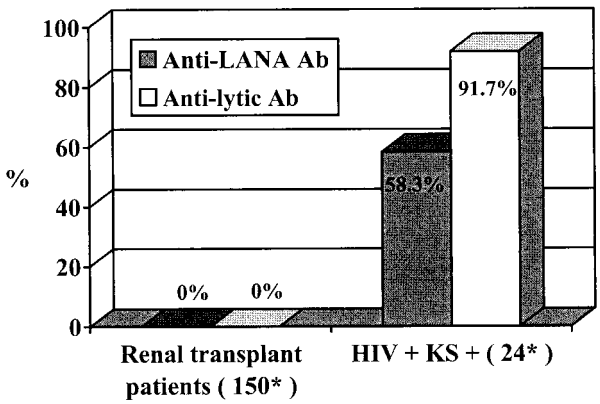

FIG. 1. HHV-8 seropositivity among renal transplant patients and HIV-positive patients with a KS diagnosis according to the type of antigen used for detection. Ab, antibody; *, number of patients.

previous reports that the prevalence of these antibodies in U.S. blood donors was <5% (12).

Two different ELISAs were used for antibody detection. Antibodies against lytic antigens were detected in the majority of HIV patients with KS (92%) and in the only renal transplant recipient who developed KS posttransplantation (100%). These antibodies were detected more frequently than antibodies against LANA (58 and 0%, respectively). During HHV-8 latency, viral expression is minimized, limiting potential targets for host immune responses. Our results are consistent with the fact that our HIV patients with KS probably had HHV-8 infection in a mostly active replication phase, as opposed to a latency phase. It is also possible that the difference in prevalence of antibodies against lytic and latent antigens in HIV-positive patients could reflect the lack of sensitivity of the ORF-73 kit.

The pre- and posttransplant sera obtained from the only transplant patient with KS were both positive for antibodies against lytic antigens. However, neither was positive for anti-LANA HHV-8 antibodies, indicating either poor ORF-73 ELISA kit sensitivity, high levels of circulating antigens in the patient samples (which may have neutralized those antibodies that were present), or the absence of such antibodies in the sera. Unfortunately, we did not verify the circulating-antigens possibility while attempting treatment to dissociate immune complexes.

TABLE 1. Results of antibody testing of a renal transplant recipient who developed KS 1 year posttransplantation[a]

Antibody target	Antibody detection at:		
	1 yr pretransplantation	1 yr posttransplantation	9 yr posttransplantation
Lytic antigen	+	+	+
LANA	−	−	−

[a] The patient tested positive for the detection of antibodies against lytic antigens 1 year posttransplantation. She also tested positive with the same kit prior to both transplantation and the development of KS as well as after treatment of KS. In contrast, antibodies to LANA could not be detected in any serum sample taken from the patient.

The 0% prevalence of HHV-8 antibodies found for our renal transplant recipients is likely not attributable to levels of immunosuppression following transplantation. The immunosuppressive therapy after transplantation primarily affects cellular, not humoral, immunity. In addition, we tested our 150 renal transplant recipients for antibodies against cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (both part of the *Herpesviridae* family and closely related to HHV-8). All patients who were CMV positive (38%) and EBV positive (98%) prior to transplantation maintained detectable levels of antibodies in the posttransplantation period (data not shown). Also, 22 CMV-negative patients and 2 EBV-negative patients developed antibodies after transplantation. These results demonstrate that antibody production continues and that antibody levels were maintained in our transplant patients.

The seroprevalence of anti-HHV-8 antibodies in renal transplant recipients at the Hôtel-Dieu de Québec Hospital was <1%. The question of whether to systematically screen the hospital's kidney donors and transplant recipients for HHV-8 appears to be irrelevant in light of the results of this study. Furthermore, if a patient does develop cytopenia in the renal transplant setting, HHV-8 infection or reactivation should not be considered initially in the determination of a differential diagnosis.

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