



Seroprevalence of Human Herpes Virus-8 in Renal Transplant Recipients: A Single Center Study From Iran

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ABSTRACT

The long-term risk of malignancy among renal transplant patients is approximately 100 times that of the general population. Unlike North America and many European countries, Kaposi's sarcoma is the most common cancer after renal transplantation in most series reported from the Middle East. Human herpes virus-8 (HHV-8) has a major role in the pathogenesis of Kaposi's sarcoma. The risk of posttransplantation Kaposi's sarcoma is 23% to 28% among seropositive patients compared with 0.7% among seronegative patients. This study was conducted to investigate the seroprevalence of HHV-8 among our transplant recipients. The sera from 100 renal transplant recipients were examined by indirect immunofluorescence against latent nuclear antigen. Sixty of 100 patients were males. The overall mean age was 41.1 years (range, 17–74 years) with 17 patients older than 55 years. The mean transplantation duration was 41.6 months. Twenty-five percent of patients were seropositive for HHV-8. There was statistically significant seropositivity for HHV-8 among recipients older than 55 years ($P = .02$). Eight of 17 patients older than 55 years were seropositive (47%), whereas 17/83 patients younger than 55 years were seropositive (20%). There were no significant differences for HHV-8 seropositivity regarding sex, transplantation duration, and immunosuppressive regimen, including dose of immunosuppressive drugs and cyclosporine blood levels. In this study, we showed seropositivity for HHV-8 among a significant percentage of our renal transplant recipients, a finding which may render them at risk to develop Kaposi's sarcoma. Seropositive and seronegative patients were followed for 16 months. One HHV-8 seropositive patient (1/25) developed Kaposi's sarcoma.

THE LONG-TERM RISK of malignancy among renal transplant patients is approximately 100 times greater than the general population. Unlike North America and many European countries, Kaposi's sarcoma (KS) is the most common cancer after renal transplantation in most series reported from the Middle East.^{1,2} Human herpes virus-8 (HHV-8) or Kaposi's sarcoma associated herpes virus (KSHV) was discovered in 1994 to be a member of the gamma herpes virus group. HHV-8 has been identified by polymerase chain reaction in all types of KS, including AIDS-associated, classic, endemic African and immunosuppression-associated.³ The risk of posttransplantation KS is 23% to 28% among seropositive patients compared with 0.7% among seronegative patients. Based on seroprevalence, 3 areas have been defined: first, the regions with seroprevalence rates less than 5%, like North America and Northern Europe; the second pattern of

infection occurs in areas with intermediate prevalence, ranging from 5% to 20%, like the Mediterranean and the Middle East; the third area is Africa and the Amazon with seroprevalence rates of more than 50%.⁴ This study was performed to assess the seroprevalence of HHV-8 among our transplant recipients.

MATERIALS AND METHODS

We selected 100 consecutive patients for a cross-sectional study to assay sera for HHV-8 latent nuclear antigen by indirect immunofluorescence (IFA; Biotrin). All positive samples were checked for

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ANA because of possible cross reactivity. Informed consent was completed by all participants as recommended by the guidelines of the university ethics committee. The remainder of the serum samples was discarded.

Data variables included age, sex, duration of transplantation, immunosuppressive drugs, cyclosporine blood level, ALG induction, intensification of treatment, and hepatitis B and C infections.

Seropositive and seronegative transplant recipients were followed for 16 months for development of KS. The chi-square, Student *t* test and Fisher exact test were used. Data were analyzed by SPSS version 11. *P* < .05 was considered significant.

RESULTS

Sixty of 100 patients were males. The overall mean age was 41.1 ± 14 years (range, 17–74 years) and 17 patients were older than 55 years. The mean transplantation duration was 41.6 months (range, 1–166 months).

Twenty-four of 100 patients received ALG for an induction protocol. Ninety-eight patients were on cyclosporine (52/98 ≤3.5 mg/kg). Ninety-seven of 100 patients were on prednisolone (69/97 ≤10 mg/d). Seventy-one patients were on mycophenolate mofetil (18/71 ≤1 g/d) and 23 patients were on azathioprine (7/23 ≤75 mg/d). Forty-three of 100 patients received a steroid pulse due to acute allograft dysfunction. Twenty-five of 100 patients were seropositive for HHV-8 assayed by IFA. None of them was ANA positive. Demographic data of seropositive and seronegative recipients are shown in Table 1.

There was statistically significant seropositivity for HHV-8 among recipients older than 55 years (*P* = .02). Eight of 17 patients older than 55 years were seropositive

(47%), whereas 17/83 patients younger than 55 years were seropositive (20%). Mean duration of transplantation in recipients older than 55 years was 50.8 months; for those younger than 55, 40.7 months, a difference that was not significant. There were no significant differences for HHV-8 seropositivity regarding sex, transplantation duration, HBV and HCV infections, immunosuppressive regimen, immunosuppressive drug dose, induction with ALG, and cyclosporine (CsA) blood levels.

Seropositive and seronegative patients were followed monthly or bimonthly after the study for evidence of KS by regular visits to our renal transplant clinic for 16 months. During this period, 1 of the seropositive patients (1/25) developed KS (4%). She was a 36-year-old women transplanted 10 years ago. Her immunosuppression had been intensified by courses of methylprednisolone due to deterioration of allograft function. The lesions which were confined to the skin regressed upon cessation of her immunosuppressive drugs. There was no significant difference in immunosuppressive dose reduction with respect to HHV-8 serology among seropositive or seronegative groups.

DISCUSSION

The incidence of HHV-8 seropositivity among our renal transplant recipients was 25%, which was close to that observed in the Middle East and the Mediterranean region.² Seropositivity in our study was higher among the older age population, a finding similar of Stein et al⁵ and Kouri et al⁶ and a study from Burkina Faso.⁷

In some studies, the seroprevalence of HHV-8 among renal transplant patients was higher than in the general population. For instance, in the study by Regamey and coworkers,⁸ the seroprevalence of HHV-8 among graft recipients increased from 6.4% on the day of transplantation to 17.7% at 1 year after transplantation.

The mode of transmission is not well known. Possible routes of transmission include virus reactivation after transplantation, transmission via the transplanted organ, sexual contacts, and saliva. The seroprevalence of HHV-8 in our general population and among kidney donors is not known, but there is wide distribution between 0% to 56% in various parts of the world.^{9–13}

Studies suggest that in areas in which HHV-8 is endemic, KS among transplant recipients is primarily due to reactivation of virus during immunosuppression. In areas in which the virus is not endemic, transplantation-associated KS is often transmitted from the donor.^{13,14}

We did not observe any association between the kind and the dose of immunosuppressive drugs and the seroprevalence of HHV-8, a finding which was similar to other studies,^{2,15} but the cross-sectional design of our study had limitations in this regard. In conclusion, in this study we showed seropositivity for HHV-8 among a significant percentage of our renal transplant recipients, a finding that may render them at risk to develop KS.

Table 1. Demographic Data and Clinical Characteristics of Seropositive and Seronegative Patients

	HHV-8 Negative	HHV-8 Positive
No.	75	25
Mean age (y)	39 ± 13	45 ± 15
Age >55 y	9/75	8/25
Sex (M/F)	45/30	15/10
Transplantation duration (months), mean	40.6 ± 43	44.8 ± 42.3
Hbs Ag	3/75	0/25
Anti-HCV ELISA	1/75	0/25
Cyclosporine (mg/d)	228 ± 69	222 ± 45
Cyclosporine >3.5 mg/kg	35/75	11/25
Cyclosporine blood level (ng/mL), mean	210 ± 109	195 ± 48
Mycophenolate mofetil	55/75	17/25
Mycophenolate mofetil (mg/d), mean	1627 ± 566	1196 ± 747
Azathioprine	17/75	6/25
Azathioprine (mg/d), mean	78 ± 27	88.9 ± 31
Azathioprine >75 mg	10/75	6/25
ALG	18/75	6/25
Prednisolone	73/75	24/25
Prednisolone >10 mg	23/75	5/25
Prednisolone (mg/d), mean	14.5 ± 10.8	12.9 ± 8.3
Patients receiving steroid pulse	33/75	10/25

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