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Seroprevalence of Human Herpesvirus 8 and its Impact on the Hemoglobin Level in Patients of End Stage of Renal Diseases

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Abstract

The incidence of Kaposi's sarcoma (KS) is increasing among renal transplant recipients. Patients with end-stage renal disease (ESRD) are immunocompromised and are candidates for renal transplantation, but HHV8 seroprevalence in ESRD patients has not been well documented. A cross-sectional study of 286 ESRD patients and 281 matched subjects without kidney disease was conducted at the First People's Hospital of Huzhou, Zhejiang province to explore the epidemiologic features of HHV8 among ESRD patients in China. Blood samples were collected and HHV8 antibodies and serologic indices were measured. The seroprevalence of HHV8 was 15.3% for ESRD patients and 8.9% for the comparison group. A significant difference in the geometric mean titer (GMT) of the HHV8 antibodies was detected between ESRD patients and the comparison group (617.1 vs. 291.7; $P=0.042$). The average level of hemoglobin was 11.56 ± 1.78 g/dl for the ESRD group and 13.73 ± 1.42 g/dl for the comparison group, ($P>0.05$). Multiple linear regression revealed a negative association between HHV8 infection and plasma hemoglobin concentration ($\beta=-0.682$, $P=0.036$). We found a higher HHV8 prevalence and a higher level of HHV8 antibody GMT in ESRD patients than the comparison group, which indicate a high risk of post-transplantation KS.

Keywords

Human herpesvirus 8; Prevalence; End-stage renal disease

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Introduction

Human herpesvirus 8 (HHV8), also known as Kaposi's Sarcoma Associated Herpesvirus (KSHV), is the etiologic agent of Kaposi's sarcoma, primary effusion lymphoma (PEL) and of multicentric Castelman's disease (MCD)¹. Previous studies have demonstrated an elevated HHV8 prevalence among HIV positive individuals or patients practiced transplantation²⁻⁵. Meanwhile, transplant recipients have been found as the high-risk population for Kaposi's sarcoma (KS), which may partly due to immunosuppression therapy^{6,7}. HHV8 antibodies however, were frequently detected before the initiation of immunosuppressive therapy⁸, indicating an early infection of HHV8 in patients with end-stage renal disease (ESRD)⁹⁻¹¹. A high prevalence of HHV8 was found in ESRD patients undergoing hemodialysis^{12,13}, whom were candidates for renal transplantation and are usually under an immunodeficient state¹⁴⁻¹⁶. To a certain extent, HHV8 infection may increase the disease burden of ESRD patients and the risk for KS development after renal graft.

In a multicenter cross-sectional study, the prevalence of chronic kidney disease (CKD) was estimated to be 10.8% (119.5 million patients) in China¹⁷. Another study reported there were a total of 65,074 ESRD patients in China, with an annual increasing rate of prevalence to be 52.9%¹⁸. An inevitable and frequent complication of CKD is anemia, which in turn affects the CKD progression and patient survival, and the low hemoglobin level was detected to be associated with elevated KS antibody titer and the risk of KS development¹⁹⁻²². Moreover, HHV8 infection may have an impact on the hematologic factors.

China has a high disease burden of CKD. So far there has been limited information on HHV8 infection and its impact among ESRD patients. Therefore, we conducted a cross-sectional study of ESRD patients to detect the HHV8 prevalence and its potential impact on biochemical indices as compared with a group of patients with no kidney disease.

Material and methods

Study participants

The present study was conducted during the period from Jan 2015 to Dec 2016 in Huzhou, Zhejiang, China. ESRD patients were recruited from the First People's Hospital of the city, and were those who had an estimated glomerular filtration rate (eGFR) of 16 ml/min using the Modification of Diet in Renal Disease (MDRD) formula. Meanwhile patients free of kidney diseases with matched gender, age and ethnicity were recruited from the same hospital as controls. The clinical and demographic data were obtained from their medical records on standardized forms, which were linked to patient samples by numerical code.

Blood collection

Venous blood was collected from participants by professional nurses using disposable sterile needles and tubes. Serum samples were stored at -80°C for further serological testing. Specimens were coded by unique identification numbers and were analyzed without knowledge of the personal identity of the study participants. The study protocol was reviewed and approved by the Institutional Review Board of Fudan University, China. All study participants provided written informed consent.

Laboratory testing

HHV8 serology: An immunofluorescence assay (IFA) was performed to detect the presence of lytic or latent antigen specific antibodies, as previously reported²³. Briefly, *Spodoptera frugiperda* clone 9 cells infected with baculovirus expressing ORF65 antigen (lytic antigen) or the ORF73 (latent nucleic antigen, LANA) were harvested, fixed, and spotted individually on separate slides for further sample testing. All serum samples were then tested at 1:40 dilution. Sera from KS patients and healthy individuals, who were previously tested seropositive and seronegative, respectively were used as controls. Only those sera scoring positive by both assays were characterized as HHV8 seropositive. Each slide was read independently by two experienced laboratory workers. To determine geometric mean titer (GMT) of HHV8 antibody, HHV8 seropositive subjects were further tested by IFA on serially diluted samples ranging from 1:40 to 1:10240²⁴.

The CRP (C-reactive protein) level was measured with a fluorescence polarization immunoassay (TDxFLEX analyzer; Abbott Laboratories). All other laboratory tests were performed using standard clinical assays.

All the above serological tests were performed by two experienced technicians from the key laboratory of Fudan University, according to the manufacturers' standard protocols.

Statistical analysis

Both medical recorders and laboratory testing results were double-entered and managed in EpiData 3.1. All data were subsequently transferred to SAS database for further management and statistical analysis. Continuous variables were expressed as mean $\pm$ standard deviation or median and interquartile range (IQR). Categorical variables were described as numbers or proportions. Associations between categorical variables were tested using *Chi-square test* or *Fisher's exact test*, whichever was appropriate. Non-parametric tests (*Mann-Whitney U test*) was used to assess the difference in geometric mean titer (GMT) of KSHV antibodies between different groups.

Simple and multiple linear regression analyses were used to examine the determinants of hemoglobin level. Coefficients of regression and corresponding 95% confidence interval (CI) were calculated and used to determine whether a variable was associated with the hemoglobin level. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, NC) and GraphPad Prism 5.0 (GraphPad, La, Jolla, CA, USA). A two-sided p-value of 0.05 or less was considered statistically significant.

Results

Characteristics of the study patients

A total of 286 ESRD patients and 281 controls without renal disease were included in the present study (Table 1). The ESRD group and the comparison group were similar in terms of ethnicity, gender (male: 48.2% vs. 47.6% male, respectively) BMI (22.5 $\pm$ 3.60 vs. 23.1 $\pm$ 3.92) and smoking history (21.0% vs. 19.8%). For the ESRD group, the most common underlying

disease was chronic glomerulonephritis (n=141, 49.3%), followed by hypertensive renal damage (n=42, 14.7%) and diabetic nephropathy (n=38, 13.3%).

The seroprevalence of HHV8 and the distribution of HHV8 antibodies titer in the patients

Meanwhile, the overall seroprevalence of HHV8 was 15.3% (95% CI: 10.7%-18.6%) for ESRD patients and 8.9% (95% CI: 5.4%-12.0%) for the control group. The geometric mean titers (GMT) of antibodies against HHV8 were further compared, the GMT of HHV8 antibody was 617.1 (95% CI: 349.2-885.1) for ESRD group and 291.7 (95% CI: 205.9-377.4) for the control group. A significant difference in the GMT of HHV8 antibodies between ESRD and control groups was detected (Mann-Whitney U=355.5, P=0.042, Figure 1).

The distribution of hemoglobin among patients

The average hemoglobin concentration level was 11.56 ± 1.78 g/dl and 13.73 ± 1.42 g/dl for the ESRD and comparison group, respectively ($P > 0.05$). We further compared the average hemoglobin concentration across different groups. Among patients with ESRD, the average hemoglobin concentration was significantly lower in HHV8 seropositive patients as compared to HHV8-negative patients (9.36 g/dl vs. 10.00 g/dl $P = 0.038$). Meanwhile, within the control group, the average hemoglobin concentration was significantly lower in HHV8 seropositive individuals compared to HHV8-negative individuals (12.67 g/dl vs. 13.47 g/dl; $P = 0.011$; Figure 2).

Multivariate analysis on the correlates of hemoglobin Level

Additionally, we explored the potential predictors for the average Hb concentration among study subjects. A multivariate linear regression analysis was performed to identify independent predictors of Hb concentration level, and the results showed that gender, ESRD status ($\beta = -3.319$, $P < 0.001$), HHV8 status ($\beta = -0.682$, $P = 0.036$) and CRP ($\beta = -0.224$, $P = 0.033$) were independently and negatively associated with Hb level among participants. While diabetes, PTH and hypertension were not correlated with Hb level (Table 2). These results indicate that for the first time, an significant association was found between HHV8 seropositivity and hemoglobin level in patients with ESRD.

Discussion

Previous reports have shown that the incidence of KS increase substantially in patients after organ transplantation. While, KS risk increases only in patients infected with HHV8 prior to transplantation, which suggests that KS was associated with a reactivation of HHV8 infection due to immunosuppression²⁵. To be able to understand HHV8 epidemiology among ESRD patients, which are candidates for kidney transplantation, is of paramount importance for KS prevention during post-transplantation. In contrast to the relatively abundant information regarding HHV8 epidemiology in ESRD patients worldwide, there is a particularly significant unmet need to understand HHV8 prevalence among patients with ESRD in China. To our knowledge, this is the first epidemiological study to examine HHV8 infection among ESRD patients in mainland China.

In the present study, we found a relatively high prevalence of HHV8 (15.3%) among ESRD patients from eastern China and the prevalence was significantly lower in the comparison group (8.9%). The result is consistent with the previous reports that patients with uraemia or hemodialysis had a high prevalence of HHV8 compared to healthy controls^{11,12,26}. The underlying causes of ESRD, the presence of the uremic status as well as the application of dialysis, which may undermine the immune system of individual, were the potential risk factors for HHV8 infection in ESRD patients²⁷. Furthermore, patients undergoing long-term ESRD are candidates for renal transplantation, a relatively high prevalence of HHV8 in ESRD patients with or without hemodialysis implies a high KS risk after transplantation. A myriad of studies have corroborated that HHV8 is relatively ubiquitous among transplant recipients²⁸⁻³⁰. However, the moderate seroconversion rate of HHV8 detected in these patients may indicate an early infection of HHV8^{31,32}, which was considered to be a risk factor for post-transplantation KS.

Results from the present study further demonstrated a significant difference in the GMT of the HHV8 antibodies between the ESRD and comparison groups (617.1 vs. 291.7; $P=0.042$). Previous epidemiologic studies from African countries revealed higher antibody titers against KSHV in patients with KS compared to the controls. Meanwhile, longitudinal studies from North America and Northern Europe have reported that elevated antibody titers against HHV8 antigens LANA and/or K8.1 were present prior to the onset of clinically evident KS^{33,34}. Increased KSHV titers in ESRD patient in the current study might indicate that they could have an elevated risk for developing KS.

Additionally, we found a lower hemoglobin level among HHV8 positive individuals than HHV8 negative ones in either ESRD patients or the control groups. Multiple liner regression revealed a significantly negative association between hemoglobin level and HHV8 seropositivity, CRP level and ESRD status. This suggested that HHV8 infection may have an unfavorable impact on the hemoglobin level among CKD patients. A number of early studies have documented the association between hemoglobin level and herpesvirus infection. Michael et al. reported a lower plasma hemoglobin concentration in CKD patients infected with cytomegalovirus (CMV), and the presence of CMV raised the dosage of recombinant human erythropoietin in ESRD patients³⁵. In addition, there was also a lower hemoglobin concentration in those who were Epstein-Barr virus (EBV) DNA positive at diagnosis³⁶. Moreover, a high HIV viral load was associated with a lower concentration of hemoglobin³⁷, and blood hemoglobin measurement has been viewed as a predictive indicator for the progression of immunosuppression³⁸. Previous data have also shown that low hemoglobin was a risk factor for KS development in kidney transplant recipients²¹. All of these findings indicate a latent relationship between viral infection and plasma hemoglobin level, which could serve as a disease predictor. Our data suggest that HHV8 infection may affect hemoglobin level, and low hemoglobin level and HHV8 infection could interact as a composited risk factor for KS after transplantation. These results suggest that low hemoglobin level in patients with CKD in China needs to be addressed more proactively, HHV8 positive individuals in particular.

A few limitations of the present study should be noted. First, the participants were recruited from a single hospital; the results may not be representative of the overall situation in China

or elsewhere in the world. Second, the geographic information for the study subjects were not systematically collected, caution is therefore warranted when interpreting the data. Third, all ESRD patients included in this study were not undergoing hemodialysis, which may lead to an underestimation of HHV8 prevalence in ESRD patients.

In conclusion, the HHV8 prevalence was higher in ESRD patients than people free of renal diseases, so was the GMT of HHV8, an efficient predictor for KS. We also found a negative association between HHV8 and hemoglobin concentration. Given the fact that chronic kidney disease poses a heavy disease burden on China³⁹⁻⁴¹, there is an important challenge to prevent the development of KS in HHV8+ kidney recipients and to prevent HHV8 reactivation by close monitoring of ESRD patients.

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Figure 1.
The titer distribution of HHV8 among the ESRD and comparison groups.

Figure 2. The titer distribution of hemoglobin across groups. Participants were grouped according to their HHV8 serostatus into HHV8-seronegative and HHV8-seropositive subjects. Individual hemoglobin levels are plotted.

Table 1
Sociodemographic characteristic of participants

Characteristics	ESRD group (N=286)	Comparison group (N=281)
Gender ratio (M/F)	138/148	134/147
Age (yr; IQR)	42 (30-57)	41 (32-61)
BMI (kg/m²)	22.5±3.60	23.1±3.92
Ethnicity (Han)	286 (100.0)	281 (100.0)
SBP, mmHg	143.61±22.45	122.26±16.55
DBP, mmHg	82.61±14.15	76.03±10.91
History of smoking (%)	21.0	19.8
Kidney diseases		
Chronic glomerulonephritis	141 (49.3)	--
Hypertensive renal damage	42 (14.7)	--
Diabetic nephropathy	38 (13.3)	--
Polycystic kidney disease	18 (6.3)	
Others	47 (16.4)	--
Hb, g/dl	11.56±1.78	13.73±1.42
Ferritin, ng/mL	137.2 (67.8-235.7)	80.77 (44.8-166.7)
Transferrin saturation (%)	34.77±17.2	25.76±15.4
CRP concentration (mg/L; median IQR)	1.0 (1.0-10.0)	1.0 (1.0-4.0)

Note: IQR: interquartile range; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CRP: C-reactive protein.

Table 2
Multiple linear regression analysis of determinants for the hemoglobin level among participants

Variable	β	95% Confidence interval	P
Gender	-0.760	-1.231 to -0.289	0.002
Age	-0.010	-0.026 to 0.005	0.193
Occupation	-0.008	-0.084 to 0.068	0.838
Education	0.004	-0.171 to 0.179	0.964
Smoking	-0.055	-0.572 to 0.461	0.833
Body mass index (kg/m ²)	0.020	-0.036 to 0.076	0.482
ESRD status	-3.319	-3.957 to -2.681	<0.001
PTH	0.184	-0.084 to 0.452	0.178
Diabetes	0.229	-0.357 to 0.814	0.442
HHV8 serostatus	-0.682	-1.317 to -0.046	0.036
CRP	-0.224	-0.429 to -0.018	0.033
Hypertension	-0.331	-0.913 to 0.252	0.265

Note: PTH, parathyroid hormone; CRP, C-reactive protein. Serum concentrations were log-transformed for analysis