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Short Communication

Prevalence and risk factors of human pegivirus type 1 infection in hematopoietic stem cell transplantation patients

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ABSTRACT

Objectives: To investigate the prevalence, risk factors, and genotypes of human pegivirus type 1 (HPgV-1) in hematopoietic stem cell transplantation (HSCT) patients.
Methods: One hundred and eighty-eight HSCT patients and 694 healthy blood donors were investigated retrospectively, including their demographic information and HPgV-1 infection status.
Results: When compared with healthy blood donors, a significantly higher HPgV-1 prevalence (18.6% vs. 2.3%) and a high risk of HPgV-1 infection (odds ratio 9.7) were observed in HSCT patients ($p < 0.05$). The number of transfusions in patients with RNA test conversions (negative to positive) was significantly higher than the number in patients without conversions (negative to negative) (median 10 vs. 1) ($p < 0.05$). Although HPgV-1 infection is independent of age, sex, blood type, hepatitis B virus infection, hepatitis C virus infection, marriage status, and type of hematological malignancy ($p > 0.05$), race might be a risk factor for infection ($p < 0.05$). The great majority (95.7%) of HPgV-1-positive patients were infected with genotype 3.
Conclusions: HPgV-1 is highly prevalent in HSCT patients, and blood transfusions can significantly increase the risk of HPgV-1 infection. Thus, HPgV-1 screening is recommended in HSCT patients to reduce the potential impact of infection on survival, as well as in their blood and stem cell donors to reduce the risk of infection after transfusions, unless the beneficial effects of HPgV-1 infection in immunocompromised patients are clearly confirmed.

Introduction

Human pegivirus type 1 (HPgV-1) was first discovered in 1995 and was originally named GB virus C (GBV-C) or hepatitis G virus (HGV) (Chivero and Stapleton, 2015). Epidemiological investigations showed that 1–5% of blood donors in developed countries and approaching 20% of blood donors in developing countries were HPgV-1 viremic at the time of blood donation (Chivero and Stapleton, 2015). Unlike hepatitis C virus (HCV), HPgV-1 is lymphotropic, establishes a subclinical infection, and does not cause hepatitis.

Although HPgV-1 has not been shown to cause any human diseases, it might increase the risk of non-Hodgkin lymphoma (Chivero and Stapleton, 2015). Interestingly, it might slow disease progression and reduce mortality in HIV-infected and Ebola virus-infected individuals (Chivero and Stapleton, 2015; Lauck et al., 2015).

This retrospective study was performed to investigate the prevalence, risk factors, and genotypes of HPgV-1 in 188 hematopoietic stem cell transplantation (HSCT) patients.

Materials and methods

This study analyzed 188 HSCT patients who attended the HSCT centre of a tertiary care hospital (5th Medical Center of PLA General

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Hospital; 1500 beds) from June 4, 2011 to December 26, 2017. Their demographic information, including age, sex, blood type, marriage status, race, hepatitis B surface antigen (HBsAg) status, antibody to HCV (anti-HCV) status, type of hematological malignancy, and HPgV-1 RNA test results, were recorded and analyzed. A total of 694 healthy blood donors without hepatitis B virus (HBV), HCV, *Treponema pallidum*, or HIV infection were tested for HPgV-1 and included as controls.

HPgV-1 RNA was detected using the HGV Real-Time RT-PCR Kit (Liferiver Biotech). Patients who were tested more than twice for HPgV-1 RNA during their hospitalization were only included once, as follows: if all tests were negative, they were considered negative; if one test was positive, they were considered positive.

The 5′-UTR (untranslated region) sequences of HPgV-1 were amplified as described previously (Smith et al., 2000), and purified amplification products were directly sequenced using an ABI 3730XL automated DNA analyzer. Genotypes were then determined by maximum-likelihood (ML) phylogenetic tree using the TREE-PUZZLE program (Schmidt et al., 2002).

Results

The overall prevalence of HPgV-1 was 2.3% (16/694) in healthy blood donors and 18.6% (35/188) in HSCT patients; a strong association was found between HPgV-1 infection and HSCT patients (odds ratio 9.7, 95% confidence interval 5.2–18.0) ($p < 0.05$). The prevalence of HBV was 4.8% (9/187) and of HCV was 0.5% (1/186), but no patient was found to be co-infected with HPgV-1/HBV, HPgV-1/HCV, or HPgV-1/HBV/HCV.

As shown in Tables 1 and 2, age, sex, blood type, HBV or HCV infection, marriage status, and type of hematological malignancy were not associated with HPgV-1 infection ($p > 0.05$), which suggests that these were not factors associated with the risk of acquiring HPgV-1. However, the prevalence of HPgV-1 in Han (the largest ethnic group in China) (17.4%, 32/184) was significantly lower than that in Man (a minority ethnic group in China) (100%, 3/3) ($p < 0.05$), which suggests that race might be a risk factor for HPgV-1 infection.

Six patients were initially negative and then tested positive for HPgV-1 RNA. During the time from the first negative HPgV-1 RNA test to the first positive HPgV-1 test, the number of transfusions (platelets, washed red blood cells, suspended red blood cells, and plasma) (median 10, interquartile range (IQR) 5–17) was significantly higher in these patients than the number of transfusions given to the 40 patients during the time from the first negative HPgV-1 RNA test to the last negative HPgV-1 RNA test (median 1, IQR 0–9) ($p < 0.05$).

Sequencing was performed for 65.7% (23/35) of the HPgV-1-positive patients, and 95.7% (22/23) were phylogenetically confirmed to be infected with genotype 3; the remaining patient (4.3%, 1/23) was infected with genotype 2. All isolated HPgV-1 strains of genotype 3 showed over 97% identity at the nucleotide level with strain LZ4 (GenBank accession number U86151) isolated in the 1990s in northwestern China (An et al., 1997), which suggests that genotype 3 might have been circulating in China for over two decades. All 28 5′-UTR sequences from the 23 HPgV-1-positive patients were deposited in GenBank under accession numbers **MK936428**–**MK936455**.

Table 1
Clinical and demographic characteristics of healthy blood donors.

	HPgV RNA		*p*-Value
	Positive	Negative	
Age (years), median (IQR)	37.5 (30–42)	34 (28–43)	>0.05
Sex			>0.05
Male	14	605	
Female	2	73	
Blood type			>0.05
A	7	174	
AB	0	78	
B	4	224	
O	5	202	

HPgV, human pegivirus; IQR, interquartile range (25–75%).

Table 2
Clinical and demographic characteristics of HSCT patients.

	HPgV RNA		*p*-Value
	Positive	Negative	
Age (years), median (IQR)	34 (25–41)	32 (24–45)	>0.05
Sex			>0.05
Male	20	110	
Female	15	43	
Blood type[a]			>0.05
A	11	40	
AB	4	19	
B	13	45	
O	7	48	
HBsAg[b]			>0.05
Positive	0	9	
Negative	35	143	
Anti-HCV[c]			>0.05
Positive	0	1	
Negative	35	150	
Marriage			>0.05
Married	27	109	
Unmarried	8	44	
Race			<0.05
Han	32	152	
Man	3	0	
Hui	0	1	
Diseases			>0.05
Acute lymphocytic leukemia	11	39	
Acute myeloid leukemia	18	72	
Myelodysplastic syndrome	2	21	
Aplastic anemia	1	5	
Multiple myeloma	0	3	
Chronic myelocytic leukemia	0	7	
Lymphoma	0	6	
Hemophagocytic syndrome	1	0	
Primary myelofibrosis	0	1	
Plasma cell leukemia	0	1	

HSCT, hematopoietic stem cell transplantation; HPgV, human pegivirus; IQR, interquartile range (25–75%); HBsAg, hepatitis B virus surface antigen; Anti-HCV, antibody to hepatitis C virus.
[a] The blood type of one patient was not available.
[b] The HBsAg result of one patient was not available.
[c] The anti-HCV results of two patients were not available.

Discussion

The results of this study showed that HSCT patients had a significantly higher prevalence of HPgV-1 than healthy blood donors (18.6% vs. 2.3%). The prevalence among HSCT patients is similar to that reported in other studies (29.5–42%) (Corbi et al., 1997; Rodriguez-Iñigo et al., 1997; Vu et al., 2019). A high prevalence of HPgV-1 (24–37%) has also been reported previously in HIV-1 patients (Lau et al., 1999; Ryt-Hansen et al., 2006). Despite the high prevalence in healthy and at-risk populations, the US Food and Drug Administration does not recommend blood screening for HPgV-1. However, we recommend HPgV-1 screening in immunocompromised patients because there are no data suggesting a beneficial effect of HPgV-1 infection on survival. Also, it might be necessary to screen HPgV-1 in their blood and stem cell donors to reduce the risk of infection after transfusion.

In this study, it was found that more transfusions were given to HSCT patients with HPgV-1 RNA test conversions (negative to positive) than to those who did not convert, providing strong evidence that transfusion significantly increases the risk of HPgV-1

infection. Of note, race might be a risk factor for HPgV-1 infection, although this needs to be investigated further in a larger-scale study.

In conclusion, HPgV-1 (mainly genotype 3) is highly prevalent in HSCT patients, and blood transfusions can increase the risk of HPgV-1 infection. Although HPgV-1 infection is independent of age, sex, blood type, HBV infection, HCV infection, marriage status, and type of hematological malignancy, race might be a risk factor. Thus, HPgV-1 screening is recommended in HSCT patients to reduce the potential impact of infection on survival, as well as in their blood and stem cell donors to reduce the risk of infection after transfusion, unless the beneficial effects of HPgV-1 infection in immunocompromised patients are clearly confirmed.

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Ethical approval

The study was approved by the Ethics Committee of the 5th Medical Center of PLA General Hospital and informed consent was waived for this retrospective study (No. KY-2019-5-21).

Conflict of interest

We declare no competing interests.

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