Chromosomally integrated human herpesvirus-6 in kidney transplant recipients

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Abstract

Background. During primary infection, human herpesvirus-6 (HHV-6) may become integrated into the chromosome. This entity, termed chromosomally integrated HHV-6 (CIHHV-6), is often mistaken as active infection and treated unnecessarily. The prevalence of CIHHV-6 in kidney transplant recipients is not known.

Methods. We performed quantitative HHV-6 polymerase chain reaction assay on whole blood samples collected from 47 kidney recipients. CIHHV-6 was defined as HHV-6 DNA levels >1 × 10⁶ genomes/mL.

Results. One of 47 kidney recipients was found to have CIHHV-6. The prevalence of CIHHV-6 was calculated at 2.1% (95% confidence interval, <0.01–12.1%). Despite an increase in HHV-6 DNA level after transplant, the patient did not develop clinical HHV-6 disease.

Conclusions. CIHHV-6 may be observed in kidney transplant recipients. Clinicians should be aware of this entity so as not to provide unnecessary treatment to asymptomatic patients with CIHHV-6.

Keywords: chromosomal integration; human herpesvirus-6; infection; kidney transplantation; prevalence

Introduction

Instead of existing as a separate circular DNA, human herpesvirus 6 (HHV-6) may become integrated into the host chromosome. This is known as chromosomally integrated HHV-6 (CIHHV-6). Both variants HHV-6A and HHV-6B have the ability to integrate into the chromosome [1]. Because they are found in germ lines, CIHHV-6 may be transmitted vertically from mother to child [2,3]. As a consequence of the presence of the viral genome in every nucleated cell, patients with CIHHV-6 have very high baseline levels of the virus in blood and tissues [4].

The clinical significance of CIHHV-6 is not known, and there is very limited data on its prevalence after transplant-
Table 1. Demographic and clinical characteristics of 47 kidney transplant recipients

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplant, median years (range)</td>
<td>55 (20–75)</td>
</tr>
<tr>
<td>Male gender</td>
<td>24 (51)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>37 (79)</td>
</tr>
<tr>
<td>Donor age at transplant, median years (range)</td>
<td>46 (26–70)</td>
</tr>
<tr>
<td>Living donor</td>
<td>47 (100)</td>
</tr>
<tr>
<td>Related</td>
<td>24 (51)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>23 (49)</td>
</tr>
</tbody>
</table>

Indication for transplantation

- Glomerular disease (primary and secondary) 12 (26)
- Autosomal dominant polycystic kidney disease 11 (23)
- Diabetic nephropathy 10 (21)
- Hypertensive nephrosclerosis 4 (9)
- Diabetes and hypertension 4 (9)
- Other 6 (13)

Type of transplantation

- Kidney 46 (98)
- Kidney after pancreas 1 (2)
- Retransplantation 5 (11)

Induction immunosuppressive therapy

- Thymoglobulin 44 (94)
- Anti-interleukin 2 antibodies 3 (6)

Maintenance immunosuppressive therapy

- Prednisone 47 (100)
- Mycophenolate mofetil 47 (100)
- Tacrolimus 45 (96)
- Sirolimus 3 (6)

CMV serostatus

- D+/R+ 17 (36)
- D+/R 16 (34)
- D+/R– 14 (30)

Follow-up duration, median days (range) 1755 (122–1999)

Posttransplant event

- Acute rejection, humoral 3 (6)
- Acute rejection, cellular 4 (9)
- CMV viremia (>1000 copies/mL) 9 (19)
- CMV disease 5 (11)
- Death 7 (15)

aCMV, cytomegalovirus; D, donor; R, recipient.

bValues are presented as number of patients (percentage), unless otherwise specified.

Discussion

Based on the study of healthy blood donors [7], the prevalence of CIHHV-6 is 0.8% (95% CI, 0.2–2.1%). There is limited data on the prevalence of CIHHV-6 in the transplant population. In two prior studies, three (5%; 95% CI, 1.2–14.3%) of 60 liver [9] and one (1.9%; 95% CI, <0.01–11.1%) of 52 kidney recipients had HHV-6 loads >1 × 10^6 genomes/mL of whole blood [10] and could be assumed to have had CIHHV-6. In a recent study of 205 transplant patients, the prevalence of CIHHV-6 was 1.0% (95% CI, 0.5–3.5%) [5]. In this third study, one (1.4%; 95% CI, <0.01–8.4%) of 70 hematopoietic stem cell and one (0.7%; 95% CI, <0.01–4.5%) of 135 solid organ transplant recipients had CIHHV-6 [5]. Our study is consistent with these reports since we observed the prevalence of CIHHV-6 in kidney recipients at 2.1% (95% CI, <0.01–12.1%).

There are nine publications describing 12 cases of CIHHV-6 after transplantation (11 after hematopoietic stem cell and 1 after small bowel transplantation) [5,11–18]. None of 13 patients, including our case, with CIHHV-6 developed definite HHV-6 disease after transplantation. Our case had skin rash and neurologic manifestations, which are typical manifestations of HHV-6 disease; however, these were clinically diagnosed as seborrheic dermatitis and embolic phenomenon, respectively. In addition, CSF analysis was normal, while patients with HHV-6 encephalitis typically have lymphocytic pleocytosis. In four previously reported patients with high HHV-6 levels, antiviral therapy with ganciclovir, valganciclovir, foscarnet or cidofovir was used despite lack of symptoms [12,15–18], but these did not result in reducing HHV-6 levels. In our patient, HHV-6 load increased at 2 weeks, potentially signifying HHV6 reactivation despite valganciclovir prophylaxis, but there were no symptoms related to the viral illness.

In summary, this study defines the prevalence of CIHHV-6 in kidney recipients at 2.1%. Our review of our case and those of the literature demonstrates that patients with CIHHV-6 may not develop active clinical HHV-6 disease despite high baseline viral loads. Clinicians should be aware of this entity of CIHHV-6 so that misdiagnosis and unnecessary treatment can be avoided.

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Conflict of interest statement. None declared.

References

13. Hubacek P, Hynčíková K, Muziková K et al. Disappearance of pre-existing high HHV-6 DNA load in blood after allogeneic SCT. Bone Marrow Transplant 2007; 40: 805–806

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