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Herpes simplex virus 1 rhombencephalitis in a patient with chromosomally integrated human herpesvirus-6A

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ABSTRACT

Central nervous system infection caused by Herpes simplex virus 1 remains a significant cause of morbidity and mortality in transplant patients. Additionally, the clinical implications of the recently discovered Human herpesvirus 6A are still under investigation.

Hereby, we report a clinical case of an immunosuppressed patient following kidney transplantation and with chromosomally integrated human herpesvirus-6A (CIHHV-6A) that developed rhombencephalitis due to herpes virus simplex 1.

This case highlights the importance of investigating the CIHHV-6 status in the differential diagnosis whenever a human herpesvirus is detected in the cerebrospinal fluid.

Background

Viral infections remain a significant cause of morbimortality in transplanted patients.

The herpes simplex virus 1 is a well-recognized and threatening cause of encephalitis. Treatment with acyclovir has reduced mortality from 70 % to almost 16 %. However, even with early diagnosis and prompt therapy, more than 50% remain with significant neurologic sequelae [1]. In immunocompromised hosts, the disease has a faster course of progression and may present with atypical clinical manifestation, which delays the diagnosis and negatively impacts the prognosis [2].

In contrast to HSV-1, human herpesvirus 6 (HHV-6) pathophysiology and clinical implications are still under investigation.

HHV-6 was accidentally isolated from the peripheral blood leukocytes of patients with Acquired Immune Deficiency Syndrome (AIDS) and lymphoproliferative disorders in 1986. Shortly after, two different molecular and biologically variants were identified. In 2012, they were classified by the International Committee on Taxonomy of Viruses as two distinct species, HHV-A and HHV-B. They belong to the *Herpesvirales* order, *Herpesviridae* family, *Betaherpesvirinae* subfamily, *and Roseolovirus* genus [3].

This virus is transmitted mainly through saliva, although vertical transmission and organ transplantation are confirmed infectious pathways. There is no reported transmission after a blood transfusion or breastfeeding [3,4].

HHV-6B is a universal virus responsible for the condition known as the exanthema *subitum* and its complications. The primary infection occurs in the first years of life and its prevalence reaches more than 90 % in adults [3–5].

In contrast to HHV-6B, HHV-6A's prevalence is higher in regions where AIDS is endemic in Sub-Saharan Africa but is infrequent in developed countries. When it occurs, it presents later in life, mainly as an asymptomatic disease [3–5]. Therefore, its clinical features are still largely unknown. HHV-6A is a neurotropic virus with proinflammatory properties that may play a role in neuroinflammatory diseases like multiple sclerosis and rhombencephalitis [6,7].

These viruses, HHV-6A and HHV-6B, have a distinctive mechanism to establish a lifelong latency. They integrate their genome into the telomeres of the host cell chromosomes [7]. The integration can occur in somatic cells (chromosomally integrated HHV-6) or gametes (inherited chromosomally integrated human herpesvirus 6). The chromosomally integrated human herpesvirus (CI-HHV-6) has a prevalence of 0.2 %–1.5 % in the general population [7] and 2.1 % in kidney transplant recipients [8]. These patients will have a high viral load in all body specimens such as whole blood, cerebrospinal fluid (CSF), and plasma when tested by quantitative polymerase chain reaction (PCR) assays. Currently, the laboratory differentiation between infection and CIHHV-6 status is not clearly defined nor internationally standardized. It is generally accepted that a viral load in whole blood higher than 5.5 $\log_{10}$

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copies/mL or higher than 3.5 $\log_{10}$ in serum is consistent with ici-HHV-6 positive status [9].

Recognition of patients with CIHHV-6 is mandatory to not over-diagnose HHV-6 infection or overtreat these patients.

Clinical case

A 60-year-old kidney transplant man presented to the emergency room with psychomotor slowing, marked dysarthria, dysphonia, dysphagia, and signs of cerebellar dysfunction – left dysmetria and ataxic gait. These symptoms occurred with gradual onset after a flu-like syndrome. The patient's medical history included a kidney transplant after accidental electrocution, arterial hypertension, and dyslipidemia. The immunosuppressive therapy consisted of everolimus (0.75 mg + 0.25 mg), mycophenolic acid (360 mg), and prednisolone (10 mg). Blood chemistry showed chronic graft failure and therapeutic levels of immunosuppressive drugs. The cranial computed tomography scan was normal. A lumbar puncture was performed, and the CSF analysis revealed: proteins - 60 mg/dL, glucose - 73 mg/dl, leukocytes - 12/mm3 (mononuclear predominance), erythrocytes 34 cells/mm3, and Gram-staining was negative. The brain magnetic resonance imaging showed diffuse high signal intensity on T2-weighted, and T2 shine through signal in diffusion-weighted imaging at the mesencephalon, ponto-mesencephalic transition, and protuberance. This clinical picture is compatible with rhombencephalitis.

He was empirically started on ampicillin and acyclovir. Immunosuppression therapy was adjusted with mycophenolic acid withdrawal and dose-decreasing of prednisolone and everolimus. Autoimmunity studies, serology, and CSF cultures were negative, but CSF-PCR was positive for HSV-1 and HHV-6. After 15 days of treatment with acyclovir, the CSF-PCR was negative for HSV-1 but remain positive for HHV-6. At this point, a quantitative real-time PCR was performed and showed 7855 copies/mL in the CSF and 6234 copies/mL in the plasma for variant HHV-6A (RealStar® HHV-6 PCR Kit 1.0; Hamburg, Germany). He was then treated with ganciclovir (10 mg/Kg per day) for fifteen days, but no neurologic improvement was noticed. Not surprisingly, the CSF-PCR was still positive for HHV-6A after the antiviral therapy conclusion. While hospitalized, the patient received physical rehabilitation and speech therapy. However, he was discharged with mild dysarthria and ataxic gait.

Discussion

So far, there is no evidence-based disease linked to HHV-6A infection. A recent study proved that HHV-6A may reach the central nervous system through the olfactory pathway after infection of nasal glial cells [10]. Its association with neuroinflammatory diseases such as encephalitis or multiple sclerosis remains controversial.

This clinical case of rhombencephalitis in an immunosuppressed patient raised some questions at the time of diagnosis. Specifically, if there was an HSV-1 and HHV-6 CNS co-infection or an HVS-1 infection in an ici-HHV-6 patient.

After the antiviral treatment with acyclovir, the quantitative and qualitative PCR study of CSF and plasma identified the HHV-6 variant A with 7855 copies/mL (3.8 Log_{10}) in the CSF and 6234 copies/mL (3.7 $\log_{10}$) in the plasma. Accordingly, to the Ward KN and colleagues' study [9], HHV-6 DNA levels detected in CSF of patients with primary infection differ from those due to chromosomal viral integration. In this retrospective study, the median viral DNA detected in the CSF of the primary infection was 2.4$\log_{10}$ copies/mL and 4$\log_{10}$ copies/mL in Ici-HHV6 patients. The previous HHV-6 status in the patient or kidney graft was unknown. Nevertheless, the high viral DNA levels detected in our patients CSF and plasma were inconsistent with HHV6 primary CNS infection. On the other hand, there are no international defined diagnostic criteria for CIHHV-6, and the persistence of neurologic symptoms and the lack of significant difference between the log values of viral loads between plasma and CSF favored reactivation of CIHHV-6.

There are no international approved guidelines for clinical treatment of HHV-6 infection. The American Society of Transplantation and Infectious Diseases Guidelines [11] recommend the initiation of antiviral therapy in cases of probable HHV-6 encephalitis. However, there are no antiviral agents formally approved for HHV-6 treatment. HHV-6A is resistant to acyclovir but susceptible to ganciclovir, foscarnet, and cidofovir [12]. After ganciclovir therapy, CSF-PCR was still positive for HHV-6A. The absence of clinical improvement or virologic response to antiviral therapy is consistent with CIHHV-6A status.

In conclusion, we report a rare clinical case of rhombencephalitis due to VHS-1 acute infection in an ici-HHV-6A and immunosuppressed patient. We emphasize the importance of keeping in mind that CIHHV-6 status is the leading diagnosis whenever human herpesvirus-6A is detected in the CSF [3,9,13,14]. The CIHHV-6 patients will have higher viral DNA in all samples.

Because of the possible consequences, HHV-6 should be systematically screened in the grafts and patients eligible for transplants, and a quantitative PCR test should be done in all positive patients.

Declaration of Competing Interest

The authors report no declarations of interest.

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