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PROBABLE HHV-6 LIMBIC ENCEPHALITIS AFTER LIVER TRANSPLANTATION: DIAGNOSTIC OVERLAP WITH TACROLIMUS NEUROTOXICITY AND REFRACTORY STATUS EPILEPTICUS

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ABSTRACT

Human herpesvirus 6 (HHV-6) encephalitis is an uncommon but severe post-transplant complication. A 64-year-old woman developed confusion, behavioural changes, and staring episodes 6 months after liver transplantation. Cerebrospinal fluid (CSF) multiplex testing was positive for HHV-6, and magnetic resonance imaging showed bilateral hippocampal and mesial temporal abnormalities, later involving the bitemporal and insular regions. Her course was complicated by refractory status epilepticus, cardiac arrest, kidney injury, prolonged ventilation, pancytopenia, recurrent HHV-6 positivity, and death. This case highlights the challenge of interpreting CSF HHV-6 positivity amid competing diagnoses and the treatment burden imposed by antiviral and antiseizure drug toxicity.

KEYWORDS

Human herpesvirus 6, HHV-6 encephalitis, liver transplantation, status epilepticus, Immunosuppression

LEARNING POINTS

- Human herpesvirus 6 (HHV-6) limbic encephalitis should remain an important diagnostic consideration in solid organ transplant recipients presenting with otherwise unexplained encephalopathy or temporal-lobe seizures, even months after transplantation and without a classic meningoencephalitic presentation.
- A positive cerebrospinal fluid HHV-6 result should not be interpreted in isolation. Internists should integrate the clinical syndrome, magnetic resonance imaging distribution, electroencephalogram findings, immunosuppression, and competing diagnoses such as tacrolimus neurotoxicity when determining whether HHV-6 is pathogenic.
- Management may be as challenging as diagnosis: probable severe HHV-6 limbic encephalitis can require prolonged antiviral and antiseizure therapy, while nephrotoxicity, marrow suppression, bradycardia, and hepatic dysfunction may substantially limit treatment and require repeated reassessment.

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INTRODUCTION

Human herpesvirus 6 (HHV-6) reactivation is well recognized after transplantation, but clinically apparent end-organ disease remains uncommon in solid organ transplant recipients[1]. When central nervous system (CNS) involvement occurs, encephalitis is one of the most serious manifestations, and it may present with confusion, memory impairment, seizures, and rapid neurologic deterioration[2]. Post-transplant HHV-6 encephalitis has been linked to limbic system involvement, with electroencephalographic abnormalities and temporal lobe signal changes on magnetic resonance imaging (MRI) providing important diagnostic support[3].

Detection of HHV-6 deoxyribonucleic acid (DNA) in cerebrospinal fluid (CSF) is clinically useful, but the result must be interpreted in the context of symptoms, neuroimaging, electroencephalography (EEG), and the broader transplant setting because viral detection alone does not always establish causality[4]. In addition, MRI findings may evolve over time, and early studies can be nondiagnostic[5]. These issues are especially relevant in solid organ transplant recipients, in whom reported cases remain limited[5].

Here we present a case of probable HHV-6 limbic encephalitis in a woman 6 months after liver transplantation who developed altered mental status, limbic-predominant MRI abnormalities, and refractory status epilepticus.

CASE DESCRIPTION

A 64-year-old woman with history of hepatitis B complicated by cirrhosis and hepatocellular carcinoma presented with altered mental status 6 months after orthotopic liver transplantation. Two days before presentation, her family noted new confusion and inappropriate behaviour including multiple staring episodes, and progressive behavioural changes prompted her family to bring her to the hospital. Her home medications included prednisone 10 mg daily, tacrolimus 3 mg daily and entecavir 0.5 mg daily, and she was reportedly adherent to treatment without any regimen changes. On presentation, she had tachycardia with heart rate at 111 beaths/minutes, but other vital signs were stable. Initial laboratory testing showed normal liver function panel, stable kidney function at her baseline and normal lactic acid levels *(Table 1)*.

MRI showed bilateral hippocampal and mesial temporal fluid-attenuated inversion recovery hyperintensities *(Fig. 1A)*. Diffusion-weighted imaging showed hyperintense signal in the bilateral hippocampi, mesial temporal lobes, limen insulae, and insular cortices, without corresponding apparent diffusion coefficient restriction *(Fig. 1B and 1C)*. Empiric acyclovir was started and later changed to ganciclovir 5 mg/kg twice daily and ceftriaxone.

Lumbar puncture on hospital day (HD) 2 showed mild lymphocytic pleocytosis: CSF leukocyte count 8/µl with 86% lymphocytes, glucose 154 mg/dl, and protein 74 mg/

Laboratory test	Result
Hematology	
WBC (/µl)	6,650
Neu (%)	95.7
Eos (%)	0.2
Lym (%)	2.3
Hb (g/dl)	11.8
Hct (%	34.5
Plt (/µl)	18.4×10^4
Biochemistry	
T-Bil (mg/dl)	0.9
AST (U/l)	23
ALT (U/l)	9
ALP (U/l)	70
BUN (mg/dl)	29
Cre (mg/dl)	1.2
Na (mEq/l)	132
K (mEq/l)	5.3
Cl (mEq/l)	97
Glucose (mg/dl)	324
Lactic acid (mEq/l)	1.8
TSH (µIU/ml)	0.62
Ammonia (µmol/l)	30
Coagulation	
PT-INR	<1
APTT (s)	24.5
Drug	
Tacrolimus (ng/ml)	6
Urine toxicology	Negative
Infection test	
SARS-CoV-2 PCR	Negative
Influenza A/B Antigen	Negative
Blood culture	Negative
Urine culture	Negative
Sputum culture	Negative
Urine hCG	Negative

Table 1. *Laboratory data of the patient on admission. Abbreviations: WBC, white blood cell; Neu, neutrophils; Eos, eosinophil; Mono, monocytes; Lym, lymphocytes; Hb, hemoglobin; Hct, hematocrit; Plt, platelet; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cre, creatinine; TSH, thyroid stimulating hormone; PT-INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; hCG, human chorionic gonadotropin.*

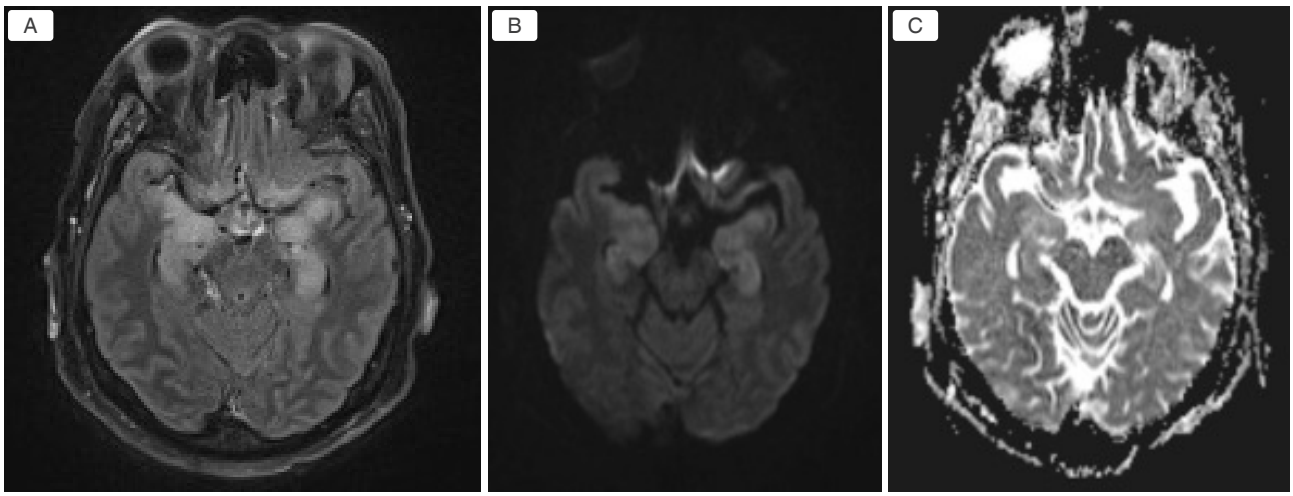


Figure 1. *Brain magnetic resonance imaging findings.*
A) Fluid-attenuated inversion recovery imaging demonstrated hyperintense signal in the bilateral hippocampi and mesial temporal lobes, raising concern for human herpesvirus 6 encephalitis, immune-mediated limbic encephalitis, or seizure-related/peri-ictal changes. Diffusion-weighted imaging showed hyperintense signal in the bilateral hippocampi, mesial temporal lobes, bilateral limen insulae, and insular cortices (B), without corresponding low signal on apparent diffusion coefficient mapping (C).

dl. Cerebrospinal fluid culture showed no growth, but the multiplex polymerase chain reaction assay (FilmArray Meningitis/Encephalitis Panel; BioFire Diagnostics, Salt Lake City, UT, USA) was positive for HHV-6 *(Table 2)*. Other infectious studies were negative.

She developed refractory status epilepticus with persistent rhythmic movements of the right arm and foot, and pulseless electrical activity arrest on HD 4. The cardiac arrest was considered secondary to hypercapnic respiratory failure in the setting of status epilepticus. She required endotracheal intubation, mechanical ventilation, and transfer to the intensive care unit. EEG was performed on the same day which demonstrated left temporal lateralized periodic discharges on the ictal-interictal continuum, prompting escalation from propofol-based sedation to a midazolam infusion. Initial seizure control was achieved by HD 6 with levetiracetam and sedation.

Quantitative HHV-6 PCR in plasma or CSF was not available, and HHV-6A/B subtyping and formal testing for chromosomally integrated HHV-6 were unavailable. Therefore, the diagnosis was adjudicated as probable HHV-6 limbic encephalitis based on the concordance of acute encephalopathy, temporal-lobe seizures, limbic-predominant MRI abnormalities, immunosuppressed transplant status, and CSF HHV-6 detection, while recognizing that qualitative CSF HHV-6 detection alone does not establish causality. Tacrolimus-associated neurotoxicity was considered because the patient was receiving tacrolimus and presented with encephalopathy and seizures. The tacrolimus trough level was 6 ng/ml on HD 1, followed by 7.9 ng/ml on HD 2 and 8.4 ng/ml on HD 3. Tacrolimus was held on HD 4 due to possible dynamic kidney function change and concern for neurotoxicity causing seizure, and subsequently restarted at a reduced dose, with later levels generally within or below the institutional target range rather than persistently supratherapeutic. Brain MRI did not show a typical posterior-predominant vasogenic oedema pattern of posterior reversible encephalopathy syndrome (PRES); instead, abnormalities were centred in the bilateral hippocampi and mesial temporal lobes. Together with

Laboratory test	Result
WBC (/mm^3)	8
Neu (%)	1
Lym (%)	86
Mono (%)	13
RBC (/mm^3)	33
Protein (mg/dl)	74
Glucose (mg/dl)	154
Multiplex PCR	
Haemophilia influenza	Negative
HSV-1	Negative
HSV-2	Negative
HHV-6	Positive
HPeV	Negative
Listeria monocytogenes	Negative
Neisseria spp.	Negative
Streptococcus agalactiae	Negative
Streptococcus pneumoniae	Negative
Varicella	Negative
Cryptococcus	Negative

Table 2. *Cerebrospinal fluid analysis.*
Abbreviations: WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Mono, monocyte; RBC, red blood cell; PCR, polymerase chain reaction; HSV, herpes simplex virus; HHV, human herpes virus; HPeV, human parechovirus.

CSF HHV-6 detection and temporal lobe epileptiform activity on EEG, these findings favoured probable HHV-6 limbic encephalitis over isolated calcineurin-inhibitor toxicity. However, the bilateral mesial temporal and hippocampal abnormalities were not specific to viral limbic encephalitis. Seizure-related or peri-ictal MRI changes could not be excluded, particularly because staring episodes preceded admission and refractory status epilepticus was documented later during hospitalization. Similarly, tacrolimus neurotoxicity could not be fully excluded because calcineurin-inhibitor neurotoxicity can occur without a classic posterior-predominant PRES pattern. Therefore, the subsequent neurologic course was interpreted as multifactorial rather than attributable to ongoing HHV-6-mediated injury alone.

On HD 11, another seizure like activity was noted and the patient received multiple antiseizure medications, with serial adjustments because of treatment-related adverse effects, including bradycardia, liver dysfunction, hypotension, and metabolic acidosis. Lacosamide was discontinued because of bradycardia, and valproate was loaded but not continued because of worsening liver function. Fosphenytoin was loaded on HD 12, but the patient developed hypotension and was therefore transitioned to phenytoin. Clobazam was started at 5 mg twice daily on HD 13 and later increased, while topiramate was loaded at 400 mg on HD 14 and continued at 100 mg twice daily. Also, the ganciclovir dosage required adjustment to 2.5 mg/kg two times a day because of acute kidney injury. Foscarnet was added on HD 14 for severe CNS disease and concern for ongoing viral activity but was discontinued on HD 21 because of acute kidney injury. Because her clinical presentation and neuroimaging findings also raised concern for limbic encephalitis, she received an empiric 5-day course of intravenous immune globulin from HD 12 to HD 16. Formal autoimmune/paraneoplastic encephalitis antibody testing was not performed. Deep sedation remained necessary for seizure control for the following 2 weeks requiring ventilatory support. Multiple antiseizure medications were gradually tapered under EEG monitoring after no further seizures were detected by HD 22. Antiseizure medications continued to require modification because of adverse events; phenytoin was discontinued because of hypotension on HD 18, and topiramate was also discontinued because of worsening metabolic acidosis on HD 21. Repeat brain MRI showed persistent bitemporal and bilateral insular T2 hyperintensities with slight interval improvement. Follow-up CSF analysis on HD 24 was negative for HHV-6.

However, her clinical course was complicated by worsening lethargy which prompted repeat continuous EEG monitoring and repeat lumbar puncture. EEG showed a right temporal lobe seizure and periodic lateralized epileptiform discharges in the left posterior quadrants and the patient required further modification of antiseizure medications with increasing the dosage of Levetiracetam, clobazam and resuming topiramate. Lumbar puncture showed positive CSF for HHV-6 on HD 45 despite being on ganciclovir 2.5 mg/kg twice daily. Quantitative viral load testing, HHV-6A/B subtyping, and testing for chromosomally integrated HHV-6 were unavailable, but this was considered as recurrence and the dosage of ganciclovir was increased to 5 mg/kg two times daily.

Her cytopenias evolved during the prolonged stay in the intensive care unit. Leukopenia and neutropenia were present early, partially recovered, and later recurred with profound leukopenia and severe neutropenia in the final hospital course. Thrombocytopenia also worsened over time, with platelet counts declining from initially preserved values to severe thrombocytopenia near the end of hospitalization, though she did not require any platelet transfusion by HD 52. Hemoglobin levels remained approximately 7–9 g/dl for most of the hospitalization without evidence of active bleeding, but later declined to 5.9 g/dl on HD 52, requiring three red blood cell transfusions by HD 55. She underwent bone marrow biopsy on HD 53, which showed markedly hypocellular

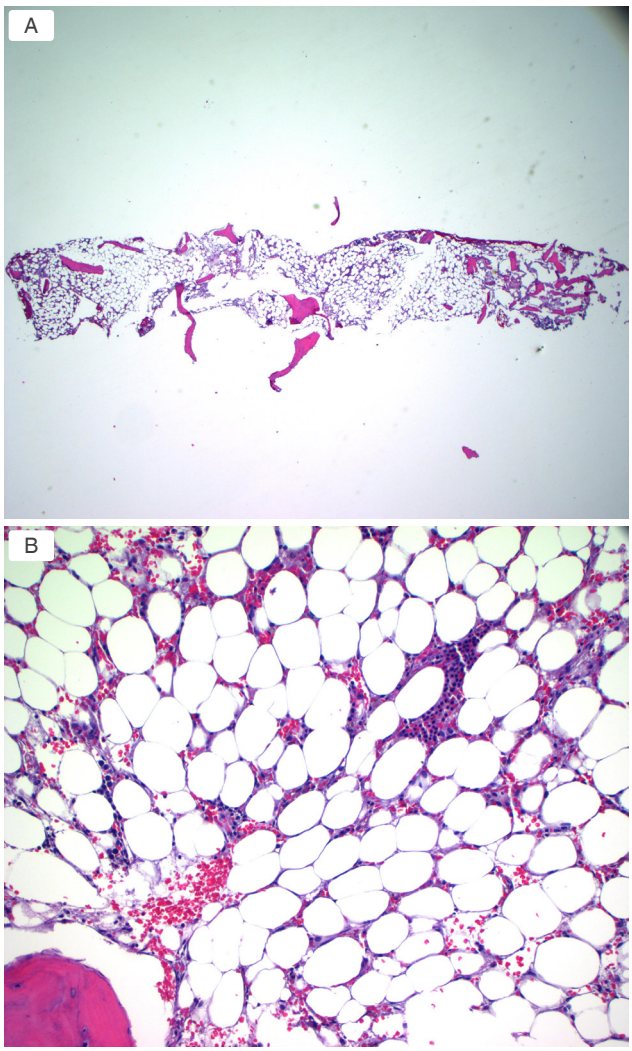


Figure 2. *Bone marrow biopsy. Bone marrow biopsy revealed a markedly hypocellular marrow for age (estimated cellularity <5%) with limited hematopoiesis 2A) H&E, 20X; 2B) H&E, 200X.*

Hospital day	Neurologic status and EEG findings	CSF and neuroimaging findings	Antiviral, immunosuppressive, and antiseizure treatment	Major complications and interpretation
Before admission	Two days of confusion, inappropriate behavior, and multiple staring episodes	—	Home medications included prednisone, tacrolimus, and entecavir prophylaxis	—
Presentation	Presented with altered mental status and focal seizure-like episodes	Brain MRI showed bilateral hippocampal and mesial temporal FLAIR hyperintensities. DWI showed hyperintense signal in the bilateral hippocampi, mesial temporal lobes, limen insulae, and insular cortices without corresponding ADC restriction	Empiric acyclovir and valganciclovir were initially administered. Entecavir prophylaxis was continued. Tacrolimus trough was 6 ng/ml	MRI findings supported limbic involvement but were not specific for viral encephalitis
HD 2	Persistent encephalopathy and concern for CNS infection	Lumbar puncture showed mild lymphocytic pleocytosis, elevated protein, and HHV-6 positivity on a multiplex meningitis/encephalitis panel. CSF culture and other infectious studies were negative	Acyclovir and valganciclovir were stopped, and ganciclovir was started at 5 mg/kg twice daily. Tacrolimus trough was 7.9 ng/ml.	Quantitative HHV-6 PCR, HHV-6A/B subtyping, and testing for chromosomally integrated HHV-6 were unavailable
HD 3	Ongoing encephalopathy	—	Tacrolimus trough was 8.4 ng/ml	Early tacrolimus trough levels were not supratherapeutic
HD 4	Developed refractory status epilepticus with rhythmic right arm and foot movements. EEG showed left temporal lateralized periodic discharges on the ictal-interictal continuum	MRI distribution remained limbic-predominant rather than a classic PRES pattern	Required intubation, mechanical ventilation, ICU transfer. Tacrolimus was held and later restarted at a reduced dose. Tacrolimus levels were within or below the target range for the rest of the hospital course	Pulseless electrical activity arrest was attributed to hypercapnic respiratory failure during status epilepticus. Probable HHV-6 limbic encephalitis was favoured, but peri-ictal MRI changes and tacrolimus neurotoxicity could not be excluded
HD 5–HD 6	EEG continued to show seizures	—	Levetiracetam and lacosamide were initiated. Lacosamide was discontinued because of bradycardia. Valproate was loaded but not continued because of worsening liver function. Levetiracetam was continued	Antiseizure therapy was limited by bradycardia and liver dysfunction, though controlled under EEG after modification
HD 11–HD 12	Recurrent seizure-like activity occurred, and EEG confirmed seizures	—	Fosphenytoin was loaded, but hypotension developed, prompting transition to phenytoin. Clobazam was started. High-dose propofol and midazolam were used for seizure control. Topiramate was loaded and continued. Propofol and midazolam were required for deep sedation. Five-day course of intravenous immunoglobulin was started	Deep sedation and prolonged mechanical ventilation were required for seizure control
HD 13-21	Seizure control improved, allowing gradual weaning of deep sedation	—	Foscarnet was added for severe CNS disease and concern for ongoing viral activity on HD 14. Ganciclovir dose was reduced to 2.5 mg/kg twice daily on HD 15. Phenytoin was discontinued because of hypotension on HD 18. Topiramate was discontinued because of worsening metabolic acidosis on HD 21. Foscarnet was discontinued on HD 21 due to acute kidney injury. Levetiracetam and clobazam were continued.	Foscarnet was limited by kidney injury. Antiseizure medications required repeated adjustment because of adverse effects
HD 22	No further seizures were detected	Repeat brain MRI showed persistent bitemporal and bilateral insular T2 hyperintensities with slight interval improvement	Propofol and midazolam were discontinued under EEG monitoring Levetiracetam and clobazam were continued	The subsequent neurologic course was interpreted as multifactorial rather than attributable to ongoing HHV-6-mediated injury alone
HD 24	No recurrent electrographic seizures reported	Follow-up CSF testing was negative for HHV-6	Ganciclovir was continued at 2.5 mg/kg twice daily.	Virologic improvement did not translate into meaningful neurologic recovery
Later recurrent encephalopathy/ seizure phase (HD 45–HD 50)	Worsening lethargy prompted repeat continuous EEG. Subsequent EEG showed recurrent right temporal seizure activity and periodic lateralized epileptiform discharges	Repeat CSF testing later became positive again for HHV-6 despite ongoing ganciclovir therapy	Ganciclovir was increased to 5 mg/kg twice daily on HD 45. Levetiracetam and clobazam were continued. Topiramate was reloaded and continued. Lorazepam was administered for recurrent seizures. Clobazam and levetiracetam were later increased.	Recurrent qualitative HHV-6 positivity was interpreted cautiously because quantitative viral load testing, HHV-6A/B subtyping, and chromosomally integrated HHV-6 testing were unavailable. Medication-related sedation complicated neurologic assessment
HD 53	Persistent critical illness	Bone marrow biopsy showed markedly hypocellular marrow with limited haematopoiesis	Levetiracetam, clobazam, topiramate were continued Ganciclovir was continued during the prolonged course	Severe pancytopenia developed. The etiology of marrow hypocellularity remained indeterminate
HD 58	Clinical deterioration despite supportive care	—	Care was transitioned to comfort measures after goals-of-care discussions	Death on hospital day 58. Autopsy was offered but declined by the family

Table 3. *Chronological summary of the clinical course.*

Abbreviations: HD, hospital day; ADC, apparent diffusion coefficient; CNS, central nervous system; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; HHV-6, human herpesvirus 6; ICU, intensive care unit; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PRES, posterior reversible encephalopathy syndrome.

Note: Ganciclovir dosing was directed by the Infectious Diseases service. Ganciclovir was started at 5 mg/kg twice daily, reduced to 2.5 mg/kg twice daily because of kidney injury, and later increased to 5 mg/kg twice daily after recurrent qualitative CSF HHV-6 positivity. Entecavir prophylaxis was continued throughout hospitalization. Other antibacterial and antifungal agents were adjusted according to infectious concerns and kidney function under the guidance of the Infectious Diseases service.

marrow with limited haematopoiesis. The etiology remained indeterminate, with possible contributors including HHV-6–associated marrow suppression, ganciclovir toxicity, critical illness, and transplant-related factors *(Fig. 2A and 1B)*. The patient became hypotensive, and she developed multi-organ failure. Eventually, her care was transitioned to comfort measures only and she passed away on HD 58. Autopsy was offered but declined by family members. A chronological summary of the neurologic, virologic, radiologic, therapeutic, and systemic events is provided in *Table 3*.

DISCUSSION

We describe a case of probable HHV-6 limbic encephalitis occurring six months after liver transplantation. HHV-6 encephalitis should remain in the differential diagnosis of transplant recipients with subacute encephalopathy and temporal lobe seizure features, even in the absence of a classic meningoencephalitic presentation. Both diagnosis and treatment required repeated reassessment, and therapeutic strategy should be modified in response to adverse drug effects. These findings are important because HHV-6 reactivation is recognized after transplantation, yet clinically apparent end-organ disease is uncommon in solid organ transplant recipients, and published experience remains much smaller than in the hematopoietic stem cell transplant population.

The first major lesson from this case is diagnostic recognition. The presented case is compatible with the recognized limbic phenotype of post-transplant HHV-6 encephalitis[6,7]. Prior reports have described HHV-6-associated limbic encephalitis after transplantation, including in liver transplant recipients, which supports the clinical possibility of HHV-6 as the principal diagnosis in this case[3,8]. At the same time, HHV-6 positivity in CSF cannot be interpreted solely. In suspected HHV-6 encephalitis, viral detection must be correlated with the clinical picture because incidental detection, viral reactivation without tissue-invasive disease, and chromosomally integrated HHV-6 can complicate interpretation[9–11]. In our patient, the combination of compatible symptoms, positive CSF HHV-6 testing, limbic-predominant MRI abnormalities, immunosuppressed transplant status, and temporal-lobe epileptiform activity supported probable HHV-6 limbic encephalitis. However, this interpretation remained probabilistic because qualitative CSF HHV-6 detection alone cannot establish causality[12,13]. Furthermore, tacrolimus neurotoxicity remained an important competing diagnosis, but the limbic distribution and CSF HHV-6 detection favoured probable HHV-6 encephalitis rather than isolated calcineurin-inhibitor toxicity. Early trough levels were not supratherapeutic, and subsequent levels were generally within or below the institutional target range. This pattern made sustained tacrolimus overexposure less likely, but it did not exclude calcineurin-inhibitor neurotoxicity. This practical implication highlights the importance of comprehensive work up especially for the patients with solid organ transplant.

The second major lesson is that this case also illustrate the management burden of probable severe HHV-6 limbic encephalitis. Intravenous ganciclovir and foscarnet are the principal antiviral agents used for HHV-6 encephalitis in transplant recipients, but neither regimen is supported by randomized comparative data in solid organ transplant recipients. In this patient, foscarnet was added because of severe CNS disease with refractory status epilepticus and concern for ongoing viral activity. This decision required repeated reassessment because foscarnet was limited by kidney injury, whereas ganciclovir was a potential contributor to marrow suppression[14,15]. Our patient developed acute kidney injury during foscarnet therapy, while antiseizure treatment was further limited by bradycardia with lacosamide and avoidance of valproic acid because of liver dysfunction. The subsequent pancytopenia and hypocellular marrow could not be attributed to a single cause. Potential contributors included HHV-6–associated marrow suppression, ganciclovir toxicity, critical illness, and transplant-related factors. These limitations are clinically important because seizure control in HHV-6 limbic encephalitis may require aggressive and evolving treatment, but aggressive treatment should be balanced with toxicity with close monitoring[5], though the existing literatures are limited.

In summary, this case suggests that HHV-6 encephalitis should be considered early in solid organ transplant recipients with altered mental status and temporal lobe seizure features. Also, treatment may require repeated adjustment because of antiviral and antiseizure drug toxicity, and the relevant outcome extends beyond virologic or electrographic improvement to include functional recovery after critical illness. Further reports in solid organ transplant recipients are needed to better define the diagnostic weight of CSF HHV-6 positivity and the most effective management strategies in patients with overlapping infectious and limbic encephalitic features.

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