CASE REPORT

HSV-1 Encephalitis With Progressive Outer Retinal Necrosis in an HIV-infected Patient

Rinusha Manogaran[1,2], Nur Hanani Ahmad[2], Hasni Mahayidin[3], Fadia Sharmin Binti Fauzi[2,4], Karthiban Thanalingam[5], Niazlin Mohd Taib[1]

[1] Department of Medical Microbiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
[2] Department of Pathology, Hospital Sungai Buloh, Ministry of Health Malaysia, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia
[3] Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
[4] Department of Medical Microbiology & Parasitology, Faculty of Medicine, Universiti Teknologi MARA, 47000 Sg. Buloh, Selangor, Malaysia
[5] Department of Ophthalmology, Hospital Sungai Buloh, Ministry of Health Malaysia, Jalan Hospital, 47000, Sungai Buloh, Selangor, Malaysia

ABSTRACT

Herpes simplex virus type 1 (HSV-1) is a leading cause of viral encephalitis, with increased severity in immunocompromised individuals. While HSV-1 encephalitis is well documented, its association with progressive outer retinal necrosis (PORN) is rare, as PORN is typically linked to varicella-zoster virus (VZV). A 53-year-old man with HIV infection developed right-sided weakness, unsteady gait, and slow speech. He had a history of cryptococcal meningitis, and initial cerebrospinal fluid (CSF) analysis showed hypoglycorrhachia, elevated protein, and persistent cryptococcal antigen positivity. Despite antifungal therapy, persistent neurological symptoms prompted further CSF analysis, which confirmed HSV-1 encephalitis via QIAstat-Dx Meningitis/Encephalitis Panel. Further ophthalmologic evaluation revealed an incidental diagnosis of PORN, with HSV-1 DNA detected in vitreous fluid. Despite intravenous acyclovir and intravitreal ganciclovir, he developed bilateral retinal detachment and remained neurologically disabled. This case highlights the need for early diagnostics and ophthalmologic screening in HSV-1 encephalitis.
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Keywords: Herpes simplex virus type 1 (HSV-1), Encephalitis, Progressive outer retinal necrosis (PORN), Human immunodeficiency virus (HIV), QIAstat-Dx Meningitis/Encephalitis (ME) Panel

Corresponding Author:
Niazlin Mohd Taib, MPath
Email: niazlin@upm.edu.my
Tel: +603-97692364

INTRODUCTION

HSV is a major cause of viral encephalitis especially in immunocompromised individuals. While HSV-1 commonly causes central nervous system (CNS) infections and certain ocular complications, such as acute retinal necrosis (ARN), its role in progressive outer retinal necrosis (PORN) is rare as PORN is typically linked to varicella-zoster virus (VZV). PORN is characterized by rapidly progressing retinal necrosis, minimal inflammation, and poor response to therapy. We present a case of HSV encephalitis (HSVE) complicated by PORN in a patient with well-suppressed HIV, highlighting the need for heightened clinical suspicion and early molecular diagnosis in unusual presentations.

CASE REPORT

A 53-year-old man with HIV on antiretroviral therapy with virological suppression presented with two days of right-sided weakness, jerky movements, unsteady gait, and sluggish speech. He was febrile (38°C), but other vital signs were unremarkable. Neurological examination revealed right-sided hypertonia, hyperreflexia, and intermittent low-amplitude jerky movements. Routine blood investigations were normal (Table 1). His most recent CD4 count was 254 cells/uL, and HIV-1 RNA viral load was undetectable two months prior.

Contrast-enhanced computed tomography (CT) scan showed mild acute communicating hydrocephalus with periventricular seepage (Figure 1). Lumbar puncture revealed an opening pressure of 24 cm H_2O, hypoglycorrhachia, reduced CSF-to-serum glucose ratio (0.55), and elevated total protein (Table 1). While India ink staining was negative, cryptococcal antigen was

detected. Given his history of cryptococcal meningitis and fungemia a year prior, he was treated for presumed recurrent cryptococcal meningitis with intravenous flucytosine and amphotericin B.

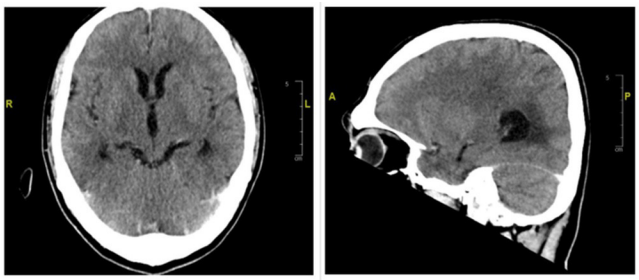

Figure 1: CECT of the brain showing mildly acute communicating hydrocephalus with periventricular seepage

Table I: Summary of Laboratory Investigations

Investigations	Results	Reference range
White blood cell	5.86	(4-10) x 10^9/L
Hemoglobin	13.4	13-17 g/dL
Platelet	324	(150-410) x 10^9/L
Urea	3.9	3.2-8.2 mmol/L
Creatinine	91	62-115 µmol/L
C-reactive protein	0.4	0.0-1.0 mg/dl
CSF findings:		
Appearance	Clear	
Opening pressure	24 cmH_2O	
Cell count RBC	< 5 x 10^6 cells/L	
Cell count WBC	< 5 x 10^6 cells/L	
Glucose	1.90	2.20-3.90 mmol/L
Protein	0.88	0.15-0.45 g/L
Gram stain	No pus cells or organisms seen	
India ink	No encapsulated yeast seen	
Cryptococcal antigen (LFA)	Detected (Titer 1:20)	

RBC = Red blood cell; WBC = White blood cell; LFA = Lateral flow assay

On day four, he developed a generalized tonic-clonic seizure, prompting further evaluation. Electroencephalography showed generalized slowing with periodic discharges in the left parietotemporal-occipital region, raising suspicion of subacute sclerosing panencephalitis (SSPE) or viral encephalitis. A second lumbar puncture was performed for measles and rubella polymerase chain reaction (PCR), CSF-venereal disease research laboratory (VDRL) test and rapid meningoencephalitis multiplex PCR. Intravenous acyclovir was empirically initiated.

Concern for SSPE related complications prompted an ophthalmologic evaluation. Pupils were sluggish (2 mm) bilaterally, with cataractous lenses, swollen optic discs, dull and pale maculae bilaterally, generalized retinal haemorrhages, necrotic retina in the left eye, and peripheral vasculitis in the right eye, and no vitreous inflammation. A diagnosis of bilateral PORN was made, and intravitreal ganciclovir was started. Vitreous fluid was sent for PCR testing for cytomegalovirus (CMV), VZV, and HSV, as well as for culture and sensitivity. The QIAstat-Dx ME Panel done on day six of admission confirmed the presence of HSV-1 DNA in the CSF, while a real-time PCR testing of vitreous fluid from both eyes also detected HSV-1 DNA but were negative for VZV and CMV. Brain magnetic resonance imaging (MRI) scan revealed multifocal infarcts of varying ages with minimal leptomeningeal enhancement, initially suggestive of septic emboli or meningoencephalitis (Figure 2). However, after correlation with CSF HSV-1 PCR findings, HSV-1 encephalitis complicated by infective vasculitis and watershed infarctions was confirmed. Further testing for CSF-VDRL, measles and rubella PCR, and mycobacterial DNA were negative. Despite cryptococcal antigen positivity, the absence of encapsulated yeast on microscopy and negative CSF cultures lead to discontinuation of antifungal therapy.

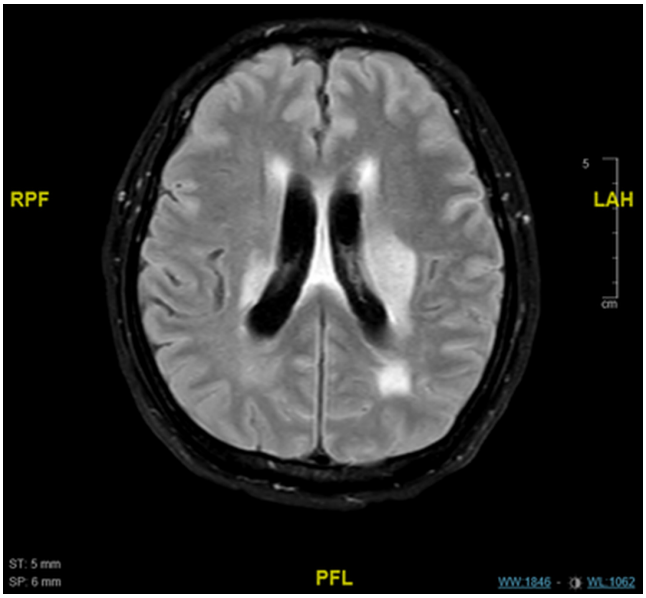

Figure 2: MRI Brain (FLAIR) showing multifocal infarcts with minimal leptomeningeal enhancement

The patient completed three weeks of intravenous acyclovir and six weeks of intravitreal ganciclovir. Despite aggressive treatment, he developed bilateral retinal detachment and remained bedbound with a guarded visual prognosis. He was discharged with ongoing rehabilitation follow-up.

DISCUSSION

HSV remains a significant aetiology of viral encephalitis, causing severe morbidity and mortality. Beyond the neonatal period, HSV-1 accounts for the majority of cases, while HSV-2 is responsible for fewer than ten percent. HSV-1 may reach the brain via the trigeminal or olfactory nerves following a primary oropharyngeal infection, by reactivating in the trigeminal ganglia and spreading to the temporal and frontal lobes, or through in situ reactivation within the brain (1). In immunocompromised patients, especially those with HIV, the clinical picture may deviate from the typical presentation or progress more rapidly, delaying diagnosis as presented in this case.

In viral encephalitis, leukocyte counts are usually mildly elevated (<250/μL) with a predominance of lymphocytes, though neutrophils may be seen early in infection. Normal cell counts can occur in a subset of patients, particularly early in HSV-1 encephalitis (2). CSF protein is typically mildly elevated, and glucose levels are generally normal, though hypoglycorrhachia has been reported in HSV and other viral infections, especially in immunocompromised patients (2).

The QIAstat-Dx ME Panel has been shown to have high positive and negative percent agreement for a wide range of CNS pathogens, demonstrating performance comparable to other multiplex PCR platforms such as the BioFire FilmArray ME Panel (3). Although valuable for rapid pathogen detection, they have known limitations in sensitivity for certain organisms, including Cryptococcus neoformans/gattii, particularly in cases with low fungal burden or prior antifungal therapy (3). Cryptococcal antigen testing remains the most sensitive method for diagnosing cryptococcal meningitis, although positivity can persist long after pathogen clearance (3). In this case, the negative PCR result, together with clinical correlation, helped avoid unnecessary prolonged antifungal therapy, and the patient's symptoms improved following initiation of acyclovir, confirming HSV as the true aetiology. This underscores the importance of interpreting cryptococcal antigen results alongside multiplex PCR and complementary diagnostics, such as culture, to guide management and optimize patient outcomes.

HSVE can present with nonspecific neurological symptoms and may mimic acute ischemic stroke. While initial CT scans may be unremarkable or show nonspecific findings like hydrocephalus, brain MRI is more sensitive in detecting characteristic lesions, making it a crucial diagnostic tool. Nonetheless, unusual presentations may arise, as demonstrated in this case, where the MRI revealed multifocal infarcts. This highlights the difficulty in distinguishing HSVE from stroke, necessitating a high index of suspicion.

HSV-1 is a well-known cause of ARN, but its involvement in PORN is uncommon and not well characterized, since VZV is the pathogen most frequently isolated in PORN cases (4,5). ARN typically occurs in immunocompetent individuals and is characterized by peripheral retinal involvement, marked intraocular inflammation, and gradual progression. In contrast, PORN is more often seen in immunocompromised patients and commonly caused by VZV, progresses rapidly, primarily affects the outer retina, and is associated with minimal inflammation (4,5). Notably, our patient had a CD4 count above 200 cells/uL and virologically suppressed HIV, whereas previously reported cases of PORN have primarily occurred in individuals with CD4 counts below 200 and uncontrolled viral replication (4). This challenges the conventional understanding that PORN is exclusively associated with profound immunosuppression and suggests that additional factors such as localized immune dysregulation or viral neurotropism may contribute to its pathogenesis. The patient did not report any eye symptoms, which is characteristic of PORN. The lack of significant inflammation in PORN often delays the onset of symptoms, leading to late diagnosis (5). Despite appropriate treatment, this patient developed retinal detachment. The primary cause of retinal detachment in PORN is the extensive and rapid destruction of the outer retinal layers, which weakens the structural integrity of the retina. The absence of early warning signs, such as pain or significant visual changes, further contributes to this complication (5). Unlike ARN, where inflammation often prompts earlier clinical attention, the silent progression of PORN can result in widespread retinal damage before it is clinically apparent.

The detection of HSV-1 in both CSF and vitreous fluid in our patient underscores the importance of high index of suspicion and a comprehensive diagnostic approach when evaluating viral infections affecting both CNS and ocular structures. Previous case reports have utilized detection of viral DNA in intraocular fluid to confirm necrotizing herpetic retinopathy (4,5). Molecular testing can aid in confirming the diagnosis and guiding targeted antiviral therapy in patients with suspected PORN and encephalitis.

CONCLUSION

This case underscores the diagnostic challenges of HSV-1 encephalitis with ocular complications in immunocompromised patients. Persistent cryptococcal antigen positivity should not be interpreted as active infection, and HSV-1-associated PORN should be considered in HIV patients even with well-controlled disease. Molecular diagnostics are essential for guiding timely and appropriate management in such complex presentations.

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REFERENCES

1. Bello-Morales R, Andreu S, Lypez-Guerrero JA. The Role of Herpes Simplex Virus Type 1 Infection in Demyelination of the Central Nervous System. Int J Mol Sci. 2020 Jul 16;21(14):5026. doi: 10.3390/ijms21145026. PMID: 32708697; PMCID: PMC7404202.
2. Benninger F, Steiner I. Handbook of Clinical Neurology: CSF in acute and chronic infectious diseases. 187–206; 2017. https://doi.org/10.1016/b978-0-12-804279-3.00012-5
3. Sundelin T, Bialas J, de Diego J, Hermanowski M, Leibhan H, Ponderand L, et al. Evaluation of the QIAstat-Dx Meningitis/Encephalitis Panel, a multiplex PCR platform for the detection of community-acquired meningoencephalitis. J Clin Microbio 2023; 61:e00426-23. https://doi.org/10.1128/jcm.00426-23
4. Tseng C, Chen S, Hwang J, Lin C, Chen H. Progressive outer retinal necrosis associated with occlusive vasculitis in acquired immunodeficiency syndrome. Journal of the Formosan Medical Association; 2012; 114(5), 469–472. https://doi.org/10.1016/j.jfma.2012.04.005
5. Vasudevan A, Rojas-Moreno C, Tarun T. Acute retinal necrosis secondary to Varicella Zoster Virus. ID Cases; 2019; 18, e00585. https://doi.org/10.1016/j.idcr.2019.e00585