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Beyond Opportunistic Infections: Unmasking CD8+ Encephalitis in Virologically Suppressed HIV Patient

Yasmeen Aboussaf[1*] and Yaroslav Buryk[2]

[1]Fourth-year Medical Student, American University of the Caribbean School of Medicine, Miami, FL, USA

[2]Assistant Professor of Clinical Medicine, University of Miami. Department of Pulmonary, Critical Care, and Sleep Medicine, USA

[*]**Corresponding author:** Yasmeen Aboussaf, Fourth-year Medical Student, American University of the Caribbean School of Medicine, Miami, FL, USA. E-mail: YasmeenAboussaf@students.aucmed.edu

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Abstract

CD8+ encephalitis is a rare inflammatory process of the central nervous system (CNS) commonly seen in virologically suppressed diseases, like HIV. This condition is characterized by the infiltration of CD8+ cytotoxic T-lymphocytes into brain parenchyma and often mimics opportunistic infections and CNS malignancies, leading to diagnostic delays. We report a 56-year-old male with well-controlled HIV and undetectable viral load, who developed new-onset generalized tonic-clonic seizures, followed by aphasia and focal motor activity. Neuroimaging revealed multifocal hyperintensities without acute infarction or mass effect. Cerebrospinal fluid studies, including infectious and autoimmune panels, were negative. Based on complete absence of infectious, neoplastic, or structural etiologies, as well as the patient's rapid clinical improvement with corticosteroid therapy, a diagnosis of CD8+ encephalitis was made. Brain biopsy was considered to confirm the diagnosis but was ultimately deferred due to thrombocytopenia and clinical improvement. This case highlights the importance of incorporating CD8+ encephalitis in HIV patients presenting with acute or subacute neurological symptoms. While relatively rare, this presentation may occur in HIV patients with undetectable viral load. Elimination of infectious and neoplastic causes, characteristic radiological appearances, and favorable response to corticosteroids can help support the diagnosis of CD8+ encephalitis when histopathological confirmation is lacking.

Keywords: CD8 Encephalitis; HIV-associated encephalitis; PML-IRIS; CNS lymphoma; Opportunistic infections; CNS inflammation

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Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus identified in the late 1970s. Ever since, it has been the causative agent of one of the most devastating infectious diseases in modern history, Acquired Immunodeficiency Syndrome (AIDS) [1]. While HIV mainly targets the immune system, it can also have a catastrophic effect on the nervous system leading to a wide spectrum of severe neurological disorders, particularly in the setting of untreated infection or progression to AIDS [2]. HIV affects the nervous system by targeting glial cells that support and protect neuronal function, thereby placing brain function and cognition at risk [3].

As a result, individuals with HIV become susceptible to life-threatening neurological complications from CNS malignancies to opportunistic infections such as toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), and rarer conditions like CD8+ encephalitis [4-6].

CD8+ encephalitis is a rare but severe inflammatory disease of the CNS occurring in patients with HIV [7] characterized by intraparenchymal infiltration of CD8+ cytotoxic T-lymphocytes in the brain tissue. It is often difficult to diagnose, as its neurological presentation overlaps with other differential diagnoses including PML, primary CNS lymphoma, and opportunistic CNS infections like toxoplasmosis or cryptococcal meningitis to name a few [7]. Symptoms that should raise suspicion for CD8+ encephalitis commonly include impaired cognitive function, dizziness, headache, confusion, memory impairment, drowsiness, and seizures [8].

The diagnostic approach to suspected CD8+ encephalitis involves a combination of patient clinical history, neurological presentations, laboratory findings, neuroimaging, cerebrospinal fluid (CSF) analysis, and, in select cases, brain biopsy. Magnetic resonance imaging (MRI) typically reveals bilateral, confluent, and symmetrical T2/FLAIR hyperintensities, often demonstrating gadolinium enhancement in a perivascular distribution. CSF analysis commonly demonstrates lymphocytic pleocytosis with elevated protein levels, while immunophenotyping usually reveals predominance of CD8+ T-lymphocytes in up to 90% of cases [9].

Additionally, HIV RNA quantification frequently reveals CSF viral escape, characterized by a disproportionately high viral load within the CSF relative to the plasma, further implicating CNS-specific immune activation in the disease process [9]. Notably, this condition typically arises in patients with well-controlled HIV on antiretroviral therapy, suggesting a pathogenesis linked to immune dysregulation during immune reconstitution in which cytotoxic CD8+ T-cells infiltrate the CNS and mistakenly target neural tissue [10]. However, because standard infectious and autoimmune workups lack definitive findings, brain biopsy remains the most reliable method for establishing a diagnosis. Early initiation of corticosteroid treatment is essential for preventing neurological deterioration and improving outcomes [9].

A study conducted by Lucan et al. between 2002 and 2021 reported only 53 confirmed cases of CD8+ encephalitis worldwide. Among those 53 patients, only 30 received steroid therapy; 20 of them survived, and 10 died from the disease, resulting in a 70% survival rate with steroid therapy. Only 9 cases of the 53 reported were from the USA [11]. In this report, we present a case of atypical CD8+ encephalitis in an HIV-positive patient, highlighting the importance of including this entity within the differential diagnostic list for unclear encephalopathy in patients with HIV.

Case Presentation

A 56-year-old male with well-controlled HIV on antiretroviral therapy (CD4+ count 380, viral load 0) presented to the emergency department after a witnessed generalized tonic-clonic seizure, followed by sudden-onset aphasia. On arrival, he exhibited persistent rhythmic jerking of the left lower extremity (LLE), disorientation, and preserved awareness-suggestive of focal motor seizure.

Aside from HIV, the patient's only significant medical history was a recent molar extraction in Honduras one month prior to presentation. There was no history of trauma or signs of acute systemic illness. On physical examination, the patient was awake, alert, and oriented only to person. He was aphasic with no dysarthria and was unable to name, repeat, or follow commands; however, he was able to mimic. Cranial nerves were all intact. Motor examination revealed 5/5 strength in the bilateral upper extremities and 3/5 in the bilateral lower extremities. Sensation was intact and symmetrical to pain. Coordination was difficult to assess due to aphasia. Reflexes and gait examinations were deferred. Initial laboratory evaluations including CBC, CMP, and inflammatory markers were within normal limits. Given the focal neurologic deficits, neuroimaging was obtained. Imaging of the chest and abdomen were unremarkable. A non-contrast head CT revealed multifocal hypodensities in the frontal, temporal and parietal lobes. However, subsequent CT angiography showed no evidence of large vessel occlusion or critical stenosis. Although brain MRI demostrated multifocal abnormalities, acute infarcts could not be confirmed due to the absence of significant diffusion restriction (Figure 1).

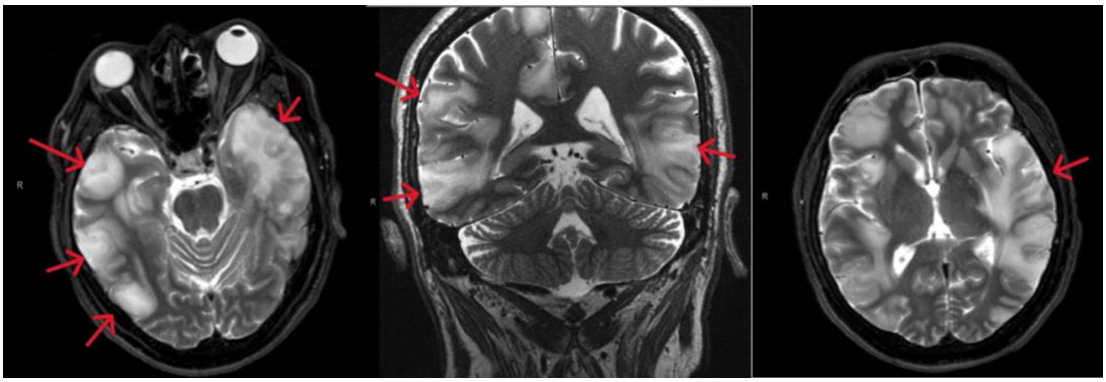

Figure1: MRI of the brain showing multifocal hyperintense lesions in the frontal, temporal and parietal lobes (Red arrows) with surrounding vasogenic edema observed on T2 sequence. Adapted from Patient.

EEG demonstrated epileptiform discharges in the right frontotemporal region (F4, C4, F8, T8, CZ) corresponding with the LLE movements. The background showed generalized theta-delta slowing with triphasic discharges and absence of the posterior dominant rhythm. CSF analysis showed normal glucose and protein levels, with no evidence of acute infection or bleeding. Testing for Epstein-Barr Virus (EBV), HSV, Cytomegalovirus (CMV), JC virus, and VDRL in the CSF was negative. Serologic testing showed positive Toxoplasma IgG with negative IgM. Upon hospital admission, the patient was started on levetiracetam for seizure control. By hospital day 4, the patient was transferred between multiple units due to clinical instability. He had persistent seizures despite being on medication and exhibited fluctuating levels of consciousness, which prompted further evaluation and escalation of care. The patient was then placed on 1g IV methylprednisolone where he showed clinical improvement. He was then transitioned to 80 mg of oral prednisone as part of a rapid tapering regimen.

In addition to steroid therapy, the patient remained on intravenous ceftriaxone, Bactrim for prophylaxis, and was restarted on Biktarvy as part of his antiretroviral regimen. Brain biopsy was considered but ultimately deferred due to the procedure's invasiveness, the patient's clinical improvement, and thrombocytopenia (platelet count: 58-102 × 10^9/L). He was ultimately discharged on a tapering course of oral prednisone, with plans for close outpatient neurology follow-up and further evaluation, including repeat brain MRI and serologic testing for EBV and Histoplasma. Several months later, the patient experienced recurrent seizures after discontinuing his antiepileptic medication while traveling. The seizures resolved upon resumption of the medication. A five-month follow-up MRI demonstrated marked improvement in T2/FLAIR hyperintensities with small persistent areas in the right parietal and anterior temporal lobes. The patient was planned to continue his current regimen with close follow-up with the infectious disease team.

Discussion

Encephalitis is a condition that causes inflammation of the brain parenchyma and can have both infectious and non-infectious etiologies [9]. Infectious encephalitis is caused by Toxoplasma gondii, EBV, JC virus, CMV, and Cryptococcus; whereas, non-infectious encephalitis can be classified as progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome (PML-IRIS), CNS involvement by non-Hodgkin's lymphoma, and CD8+ encephalitis.

Our patient is a 56-year-old male with well-controlled HIV who presented with generalized tonic-clonic seizures, aphasia, and focal motor activity. Based on his laboratory and imaging findings, the primary differential diagnoses included: CD8+ encephalitis, PML-IRIS, CNS primary lymphoma, and toxoplasmosis. Infectious etiologies were considered early due to the patient's HIV status; however, extensive CSF analysis, including a negative meningoencephalitis panel (EBV, HSV, JCV, CMV, VDRL), and the absence of systemic signs of infection, reduced the likelihood of an opportunistic infection [6]. While Toxoplasma IgG was positive, the negative IgM confirmed prior exposure rather than active infection.

Primary CNS lymphoma, usually associated with Epstein-Barr virus (EBV), typically occurs in patients with a CD4+ count below 100 [12]. MRI findings in primary CNS lymphoma often demonstrate ring-enhancing lesions with central necrosis or hemorrhage [13] (Figure 2).

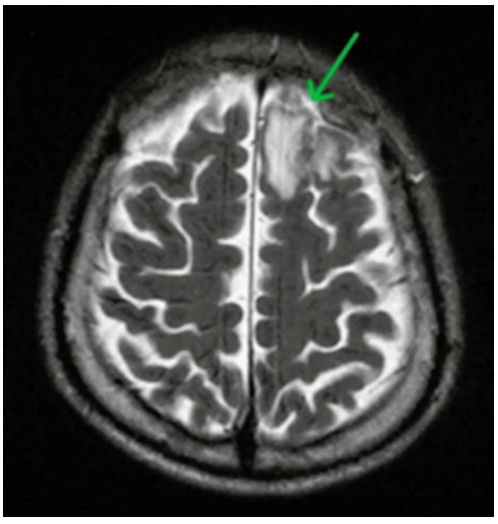

Figure 2: Example of a T2-weighted brain MRI demonstrating a hypertense signal with surrounding edema (green arrow) in the frontal paramedian cortex seen in patient with primary CNS lymphoma. Adapted from MRI imaging features of HIV-related central nervous system diseases: diagnosis by pattern recognition in daily practice.

In this case, the patient's CD4+ count remained within the 380 range, suggesting relatively preserved immune function. Moreover, his neuroimaging findings were more suggestive of an alternative etiology. Additionally, the absence of constitutional symptoms such as weight loss or night sweats, and the lack of evidence of systemic lymphoma on further evaluation, further reduced the likelihood of this diagnosis.

PML-IRIS is a severe demyelinating disorder that presents in immunosuppressed patients with a CD4+ count of less than 200. It is thought to develop in patients with advanced HIV, particularly after initiating antiretroviral (ART) therapy, which triggers immune reconstitution. IRIS has been reported to occur in HIV-PML patients between one week and 26 months following initiation of ART [14]. Patients with low CD4+ counts and high viral loads are at increased risk of developing IRIS. On MRI, FLAIR sequences show white matter lesions [15] (Figure 3).

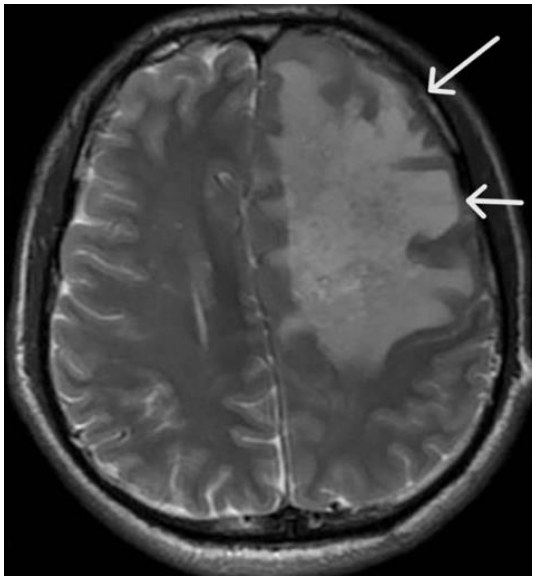

Figure 3: Example of a brain MRI of a patient with HIV associated PML-IRIS showing a confluent demyelinating lesion involving the subcortical white matter (white arrows) on T2 sequence. Adapted from PML-IRIS: Progressive Multifocal Leukoencephalopathy Immune Reconstitution Inflammatory Syndrome.

Treatment regimen for PML-IRIS usually includes discontinuation of ART, as reversal of immune indolence restores normal immune system function [14]. In this case, the patient's HIV was well controlled, as evidenced by an undetectable viral load and stable CD4+ count. Additionally, there was no clinical improvement upon cessation of ART, making PML-IRIS an unlikely diagnosis [14].

The typical presentation of CD8+ encephalitis can be either acute or subacute, with common symptoms including headache, confusion, and seizures [10]. Slurred speech and ataxia have also been reported [16]. Given the limited literature available, its pathogenesis remains unknown. However, numerous factors such as CNS infections, discontinuation of ART, and IRIS in patients with HIV can trigger an immune response leading to CD8+ encephalitis [11]. The current hypothesis states that in HIV-related illnesses, there is an imbalance between CD8+ and CD4+ T-cells, which in the presence of certain triggers, can lead to this inflammatory response with a predominance of CD8+ T-cells in the brain [11]. Additionally, CD8+ encephalitis can present in both ART-naïve and well-controlled patients [9], where it has been shown to develop without warning or evident change in the patient's viral load or CD4+ count [11].

Neuroimaging typically shows confluent T2/FLAIR hyperintensities in cortical and subcortical white matter, often demonstrating gadolinium enhancement in a perivascular distribution [9,11] (Figure 4).

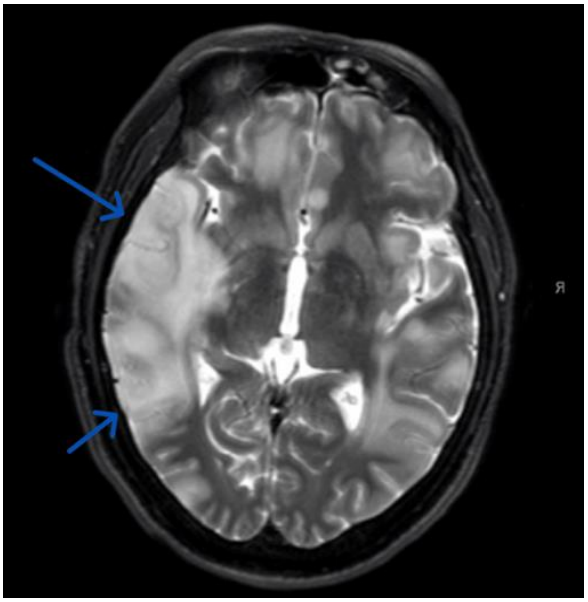

Figure 4: T2/FLAIR MRI sequence demonstrating confluent hyperintensities involving cortex and subcortical white matter with surrounding edema characteristic of CD8+ encephalitis. Adapted from patient.

Several diagnostic tools can aid in narrowing the differential diagnoses and establishing a definitive diagnosis of CD8+ encephalitis; however, brain biopsy remains the gold standard, demonstrating CD8+ T-cell infiltrates in brain tissue [9]. Furthermore, CD8+ encephalitis has shown a favorable response to corticosteroid therapy. Across reported cases, the disease consistently appears to be steroid-responsive, with marked improvements in both neurological symptoms and radiological findings following treatment [11]. Notably, Shenoy et al. reported a statistically significant association between corticosteroid use and patient survival, reinforcing its value as a therapeutic intervention [9]. The gold standard for diagnosis remains histopathological examination via brain biopsy, typically revealing numerous CD8+ T-cell infiltrates in a predominantly perivascular distribution, characteristic of CD8+ encephalitis [9].

As per neurology's recommendation, given the patient's thrombocytopenia and clinical improvement, brain biopsy was deferred. Therefore, the diagnosis of CD8+ encephalitis was based on the patient's subacute clinical presentation, negative infectious workup, characteristic MRI findings, favorable response to corticosteroids, and exclusion of alternative differential diagnoses.

Conclusion

This case highlights the importance of considering non-infectious etiologies, such as CD8+ T-cell encephalitis, in the differential diagnosis of HIV-positive patients presenting with new-onset neurological symptoms. Although rare, CD8+ encephalitis has been increasingly recognized across all HIV patients (including both well and poorly controlled viral loads). It is believed to result from a dysregulated immune response, in which cytotoxic CD8+ T cells infiltrate the central nervous system and mistakenly target neural tissue. With our patient's rapid response to steroids and clinical improvement, we emphasize the value of early recognition and timely intervention.

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