LETTER TO THE EDITOR

To The Editor

CD8 Encephalitis in a Treatment-Naive and a Virologically Suppressed Patient with HIV*

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CD8+ encephalitis (CD8E) is a recently described steroid-responsive, HIV-associated disease with marked perivascular infiltration by CD8 lymphocytes in patients receiving antiretroviral therapy (ART).[1,2] It presents with diverse neurologic findings ranging from subacute neurocognitive decline to status epilepticus. Brain magnetic resonance imaging (MRI) shows diffuse T2 FLAIR hyperintensities with punctate or linear gadolinium enhancement. Pathologically, there is an extraordinary perivascular infiltration by CD8 lymphocytes.[3] Cases of CD8E have been reported after minor infections, interruptions in ART, immune reconstitution inflammatory syndrome (IRIS), and in those who have had a good virologic response to ART in the periphery but possibly an inadequate response in the central nervous system (CNS). We report two additional cases of CD8E: one patient with untreated HIV infection and an unusually prominent meningeal inflammation, and a second patient on ART with good response and an associated cerebral vasculopathy.

A 54-year-old African American woman presented with seizures and cognitive decline in 2016. She has been known to be infected with HIV since 2006, was never on ART, and has had seizures since 2015 with poor adherence to levetiracetam. On admission, her CD4 count was 336 cells/μL and her HIV viral load (VL) was 16,700 copies/mL. Cerebral spinal fluid (CSF) analysis revealed WBC of 45 with 91% lymphocytes, glucose 53 mg/dL, and protein 93 mg/dL. Her brain MRI revealed perivascular and pachymeningeal enhancement, a subdural fluid collection, and scattered areas of supratentorial periventricular T2 FLAIR hyperintensity (Figure 1, panels A and B). An extensive evaluation for autoimmune, viral, bacterial, mycobacterial, and fungal infections in the CSF and systemically was negative. A QuantiFERON®TB Gold test was positive, and a presumptive diagnosis of tuberculous meningitis was made. She was started on rifampin, isoniazid, pyrazinamide, and levofloxacin (RIPL) therapy. ART was withheld due to concern for IRIS. Her cognition improved following seizure control, and she was discharged home. Six weeks later, she returned with fever and status epilepticus. She was adherent to RIPL but not antiepileptics. CSF parameters were unchanged. Repeat MRI brain showed progression of T2 FLAIR hyperintensities in the white matter and cortex and near resolution of the meningeal enhancement. Given the extensive negative workup, brain and meningeal biopsies were performed and revealed abundant CD8 lymphocyte perivascular and parenchymal infiltration in the white matter and cortex, including transmural inflammation and compromised vascular walls. Acid fast stains, fungal stains, mycobacterial polymerase chain reaction (PCR), and DNA probes were negative. There were no multinuclear giant cells, granulomas, or viral inclusions. Additional CSF studies showed that the CD8 cells composed 86% of lymphocytes. These results strongly favored a diagnosis of CD8E. She was started on steroids with improvement in fever and cognition. She was discharged home with plan to taper steroids and initiate ART in follow-up.

A 58-year-old Hispanic man was diagnosed with HIV (CD4 155/μL and VL 139,000 copies/mL) in 2017 and was started shortly thereafter on abacavir, lamivudine, and dolutegravir with good response (HIV VL <20 copies/mL). He presented in 2018 with a 3-month history of paresthesia, dysarthria, sensorineural hearing loss, and disorientation. He discontinued ART a month prior to presentation. CSF analysis showed WBC 2, red blood cells 57, glucose 45 mg/dL, and protein 76 mg/dL. The CSF John Cunningham (JC) virus DNA PCR was positive, and negative studies for viruses, bacteria, mycobacteria, and fungi. His brain MRI showed multiple hyperintense confluent and punctate enhancing, predominantly perivascular, foci throughout the left deep frontal and parietal lobes without diffusion restriction (Figure 1, panels C and D), and his cerebral angiogram showed medium and small-vessel vasculopathy. Given the atypical findings on MRI for progressive multifocal leukoencephalopathy (PML), a brain biopsy was performed. It showed extensive perivascular and parenchymal infiltration by CD8 lymphocytes, which accounted for >90% of the inflammatory cells present (Figure 2, panels A and B). He also had disruption of vascular

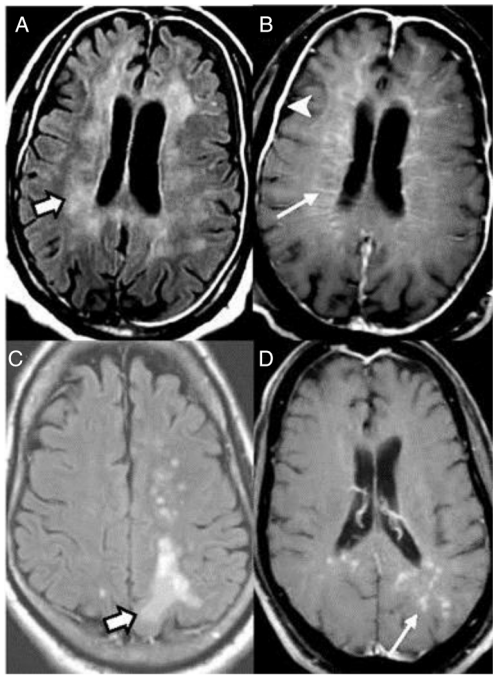

Figure 1: *Initial MRIs for case 1 (A, B) and case 2 (C, D). (A) Axial FLAIR with multiple confluent T2 white matter hyperintensities. (B) Axial T1 with gadolinium showing pachymeningeal (arrowhead) and perivascular (thin arrow) enhancement. (C) Axial FLAIR with confluent and punctate white matter hyperintensities with (D) punctate T1 gadolinium enhancement (thin arrow) seeming to follow perivascular spaces and with callosal involvement.*

*Steven Richard Dunham's affiliation has been corrected. An erratum detailing this change has also been published (doi:10.1017/cjn.2019.326).

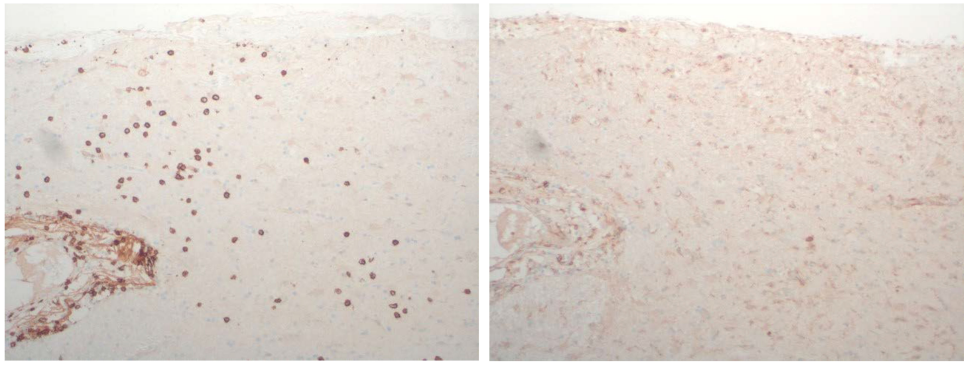

Figure 2: *Immunohistochemistry demonstrates abundant perivascular and parenchymal CD8 lymphocytes (Panel A) and very few CD4 lymphocytes (Panel B). CD8 and CD4 immunohistochemistry with hematoxylin counterstain 200x.*

integrity. There were no multinucleated giant cells, granulomata, viral inclusions, bizarre astrocytes, or organisms seen. He received a 6-month steroid taper with marked improvement.

In summary, these two cases illustrate the diagnostic difficulty in distinguishing immune-related diseases from infectious issues in HIV, and the need to pursue a pathologic diagnosis when the etiology of neurologic decline in patients with HIV infection is in question. Patient A had a presumptive CNS TB diagnosis, but the duration of neurologic decline was atypical, and patient B had a presumptive PML diagnosis, but the MRI findings were not typical. Multidisciplinary involvement of neurologists, infectious diseases experts, radiologists, and pathologists is recommended in these unusual cases.

There are other pathologies that occur in patients infected with HIV, which would be in the differential diagnosis of CD8E. HIV encephalitis is thought to arise as viral propagation in mononuclear phagocytes leads to persistent activation of CD8 lymphocytes. Biopsy of the brain usually reveals microgliosis, multinucleated giant cells, myelin pallor, and HIV p24 immunopositivity. CNS IRIS develops after initiation of ART and manifests as heightened inflammatory reactions to microorganisms. Demyelinating lesions, brain infiltration by CD8+ lymphocytes, multinucleated giant cells, and hyalinization of vessels are some of the associated changes that can be present on brain biopsy.[4] Tumefactive demyelination is usually easily distinguished from the aforementioned pathologies and is characterized by a vast area of demyelination with mass effect and ring enhancement on imaging. Perivenular inflammation, foamy macrophages, and bizarre astrocytes are often seen on histological examination.[5]

The clinical and pathological features of CD8E are not fully elucidated. Generally, CD8E manifests as acute or subacute decline in brain function. Brain MRI typically shows bilateral, diffuse abnormality on T2-weighted and FLAIR images and linear gadolinium-enhanced lesions on T1-weighted images. Multiple perivascular contrast enhancements in postgadolinium T1 sequences are strongly suggestive of CD8E. Brain pathology findings include microglial activation and reactive astrocytosis with inconsistent expression of HIV protein p24 and a diffuse, perivascular, and intraparenchymal infiltration by CD8+ T-lymphocytes. Steroid responsiveness is a feature of CD8E, though optimal dose and duration have not been defined. The etiology of CD8E has been hypothesized but never confirmed, given its recent description and the small number of patients confirmed to have CD8E. These hypotheses include a dysregulated immune response in HIV infection setting following a minor infection, CNS IRIS to HIV itself, and heightened immune response to virologic escape.[1] The occurrence of CD8E in case 1 and in one other case in the literature, who were both ART-naïve, makes virologic escape a less plausible explanation.

In summary, we present two cases of CD8E in patients on opposite ends of the spectrum of HIV control. CD8E should be in the differential diagnosis of HIV-infected patients with compatible clinical and radiologic findings, regardless of ART history, to expedite the diagnosis and receipt of appropriate therapy and to expand the medical literature and knowledge of this novel entity.

Conflict of Interest

The authors have no conflicts of interest pertaining to this manuscript.

Statement of Authorship

AC, KM, CB SRD, JCG, and HES provided clinical care for the two patients, drafted the manuscript, and provided revisions and edits to reach the submitted version.

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