CD8 Encephalitis Caused by Persistently Detectable Drug-resistant HIV

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Abstract

We herein report a 52-year-old man infected with human immunodeficiency virus (HIV) who was referred to our hospital due to the development of severe neurocognitive disorders and bilateral leukoencephalopathy. He has been treated with antiretroviral agents for 17 years, but low-level viremia has been detected consistently prior to admission. Drug resistant testing of the serum and the cerebrospinal fluid (CSF) both demonstrated a M184V mutation. A brain biopsy revealed perivascular CD8+ T-lymphocyte infiltration, leading to the diagnosis of CD8 encephalitis. The clinical symptoms improved drastically after changing to a nucleoside reverse transcriptase inhibitor sparing regimen, which subsequently decreased the HIV viral load to an undetectable level in both the serum and CSF.

Key words: HIV, CD8 encephalitis, HIV-associated neurocognitive disorder (HAND)


Introduction

The introduction of combination antiretroviral therapy (cART) has contributed to the longer survival of individuals infected with the human immunodeficiency virus (HIV). It also reduced the incidence of HIV-associated central nervous system (CNS) complications, including HIV-associated dementia (HAD), which previously was termed HIV encephalopathy or acquired immunodeficiency syndrome (AIDS) dementia complex (1). However, less severe forms of neurocognitive disorders in these individuals have started to be recognized as emerging problems in the cART era (2).

Recently, CD8 encephalitis (CD8E) was reported to be a severe CNS complication among HIV-infected individuals treated with cART (3). We herein present a case of CD8E that was presumed to have been caused by the inflammatory host immune response to drug-resistant HIV.

Case Report

A 52-year-old HIV-infected man was referred to Tokyo Metropolitan Komagome Hospital with a 2-month history of progressive memory loss and a deteriorated gait disturbance. The patient was diagnosed with HIV at the age of 35, with a nadir CD4 count was 2/μL. He did not recall any trigger before the onset of these symptoms. He had been treated with zidovudine, lamivudine and indinavir, but switched to atazanavir, ritonavir, tenofovir, and emtricitabine in order to reduce the pill burden at 45 years of age. Although the HIV viral load (HIV-VL) was well controlled initially, occasional blips were observed from 47 years of age. Several years prior to admission, the CD4 count and HIV-VL were consistently in the range of 500-600/μL and 100-700 copies/mL, respectively.

On admission, physical examination revealed mild dysarthria, clumsy diadochokinesis and an intention tremor of the left arm. The results of blood tests including a complete blood count, liver and kidney function tests were within the

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normal limits. The CD4 cell count and HIV-VL were 632/μL and 660 copies/mL, respectively. A cranial magnetic resonance image (MRI) demonstrated severe generalized brain atrophy and diffuse leukoencephalopathy on fluid attenuated inversion recovery (FLAIR) image, but no abnormal enhanced lesions on T1 weighted image (Fig. 1). No previous cranial MRI findings were available. A cerebrospinal fluid (CSF) analysis was as follows: white blood cell (WBC) count, 4/μL; protein level, 110 mg/dL; HIV-VL, 910 copies/mL. The results of staining and culture of CSF for bacteria, mycobacteria, and fungi were all negative. Polymerase chain reaction assays of CSF samples were negative for herpes simplex virus, varicella zoster virus, and cytomegalovirus.

His clinical symptoms deteriorated, and he became unable to stand up by himself only 2 weeks after admission. To make a definite diagnosis, a stereotactic brain biopsy of the right frontal lobe was performed. cART was changed to lopinavir, ritonavir, abacavir, and lamivudine because of the higher CNS penetration effective score (CPE score) of this combination which led to a partial improvement of both the motor and neuropsychological symptoms. He was thereafter able to stand up by himself, but still needed support to walk straight safely. HIV drug-resistance testing on admission revealed a M184V mutation both in the serum and CSF. Based on this result, cART was switched for the second time to raltegravir, lopinavir, and ritonavir. The findings of a CSF analysis prior to this regimen were as follows: WBC, 18/μL; protein level, 129 mg/dL; neopterin, 120 pmol/mL; HIV-VL, 1,050 copies/mL. At one month thereafter, his clinical symptoms dramatically improved: he walked without any gait disturbances, lived the same as before the onset of these symptoms, and remembered to take his medications on time. Blood and CSF tests were repeated at this time, thus demonstrating undetectable levels of HIV-VL in both the serum and CSF. In addition, WBC, protein, neopterin in the CSF decreased to 4/μL, 92 mg/dL and 50 pmol/mL, respectively. The clinical course is shown in Fig. 2.

The pathological findings of the brain biopsy are demonstrated in Fig. 3. The specimen consisted mainly of cortical and subcortical layers and partial abnormal white matter. Perivascular infiltration consisted mainly CD8+ T-lymphocytes, accompanied by CD163+ monocytes and reactive astrocytosis. Immunostaining for HIV-p24 and JC virus-VP2/VP3 was negative. From these pathological findings, the patient was diagnosed with CD8E. Corticosteroid therapy was not necessary due to the excellent clinical response to cART.

Discussion

The prevalence of HIV-infected patients with milder forms of neurocognitive disorders has increased since the pre-cART era (2, 4). During the evolution of HIV therapy, a new term named HIV-associated neurocognitive disorder (HAND) has been proposed (5). HAND is stratified into 3 categories: asymptomatic neurocognitive impairment (ANI); mild neurocognitive disorder (MND); and HAD. HAD is the most severe form of HAND, where macrophages, microglia and reactive astrocytes have been shown to play key role in its pathogenesis (6). On the other hand, the pathogenesis of milder HAND or other neurocognitive disorders in patients on cART remains unclear. It is reported that neurological symptoms can develop even in HIV-infected patients with fully suppressed plasma viremia (7, 8).

Recently, CD8E has received attention as a new type of neurocognitive disorder in HIV-infected individuals. Lescur et al. described CD8E as a “new, severe, but treatable form of HIV-related encephalitis” (3). The clinical and pathological features of CD8E have not yet been fully elucidated. The symptoms of CD8E consist of unexpected acute or subacute decline in brain function accompanied by dizziness, headache, memory disorders, confusion, and seizure. Previous reports demonstrate that minor infection, immune reconstitution inflammatory syndrome (IRIS), virological escape and cART interruption may trigger the disease. The majority
of the patients diagnosed with CD8E have been treated for a mean duration of 4.2 years, with a CD4 cell count >200/μL during the 6 months prior to disease onset (3). Cranial MRI typically shows bilateral, diffuse abnormality on T2 weighted and FLAIR images, and linear gadolinium-enhanced lesions on T1 weighted images (3, 9). Among CD8E patients, CSF analysis typically reveals pleocytosis and elevated protein levels, although there are cases without any abnormalities (3). The pathological findings include microglial activation and reactive astrocytosis with inconsistent, weak expression of HIV protein p24 and a diffuse, perivascular and intraparenchymal infiltration by CD8+ T-lymphocytes (9). Lescure et al. reported in their cohort of 14 patients in which 5 recovered completely and 5 died within a mean period of 9 months (3).

To the best of our knowledge, this is the first case of CD8E caused by persistently detectable drug-resistant HIV which was treated successfully just by switching antiretroviral agents. The characteristic pathological findings are thought to be distinct from HAD (3, 10, 11). Diagnosing CD8E may be challenging for clinicians, since a brain biopsy is essential for making a definite diagnosis. Although the previous literature demonstrates that linear gadolinium-enhanced lesions on T1 weighted images are characteristic of CD8E, our case was negative for this finding. The pathognomonic findings for CD8E are thus warranted, or this new clinical entity may continue to be regarded and mistakenly treated as HAND.

CD8E may have been triggered by persistent CNS inflammation caused by CD8+ T-lymphocytes. Previous case reports support the notion that an excessive immune reaction to HIV can be regarded as IRIS (12, 13). Switching to raltegravir, lopinavir, and ritonavir may have suppressed CNS inflammation by reducing HIV-VL. The decrease of protein and neopterin levels in the CSF supports this speculation. Sekiya et al. reported a case of HIV encephalopathy with
pathological findings revealing perivascular CD8+ T-lymphocyte infiltration. M184V/I mutation was detected, but treated successfully by changing antiretroviral therapy alone without the use of concomitant corticosteroid therapy (14).

A recent report by Fabbiani et al. described that optimized cART with confirmed genotypic susceptibility is more important than total CPE score in HIV-infected patients with HAND (15), which could be applicable to CD8E caused by drug-resistant HIV. Corticosteroids may play a key role in CD8E treatment by suppressing CNS inflammation (3), but these cases may imply that its use may be determined based on the clinical course after making a change in the cART regimen.

The new onset of neurocognitive disorders has become an emerging problem in the cART era. Most patients are presumed to be classified as HAND, but clinicians need to be aware that some may be CD8E. Continuous low-level viremia and inflammation between drug-resistant HIV and host immunity may trigger CD8E, especially in patients on cART.

The authors state that they have no Conflict of Interest (COI).

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