Case Report

HSV-1 Encephalitis Complicated by Cerebral Hemorrhage in an HIV-Positive Person

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Although herpes simplex virus type 1 (HSV-1) is the most common cause of sporadic encephalitis in immunocompetent adults, it is an unusual cause of encephalitis in patients with HIV/AIDS. We report the case of a 56-year-old man with recently diagnosed HIV infection who presented with subacute mental status changes, fever, and temporal lobe abnormalities evident on brain imaging. Results of a polymerase chain reaction assay of the cerebrospinal fluid were positive for HSV-1. His course was complicated by 2 episodes of cerebral hemorrhage. He ultimately improved after surgical decompression, treatment with acyclovir, and a switch from a protease inhibitor–based antiretroviral regimen to one including an integrase inhibitor. [AIDS Reader. 2009;19:153-155]

Key words: HIV/AIDS • Herpes simplex virus • Encephalitis • Cerebral hemorrhage • Acyclovir

Herpes simplex virus type 1 (HSV-1) is the most common cause of sporadic encephalitis worldwide. In the California Encephalitis Project, 24% of the cases of viral encephalitis were caused by HSV-1 and 3% were caused by HSV-2.[1] In addition, HIV-positive persons are at an increased risk for mucosal reactivation of HSV.[2,3] Despite these observations, HSV-associated neurological disease is surprisingly rare in HIV-infected patients. In several large studies, HSV-associated neurological disease was only found in up to 3% of patients.[4-7] We report here a case of HSV-1 encephalitis in an HIV-positive man presenting with subacute memory loss and seizure. His hospital course was complicated by intracranial hemorrhage.

CASE SUMMARY

A 56-year-old man was brought to the emergency department for evaluation after he was found with diminished responsiveness following an apparent seizure. Subsequently, he was hospitalized. He reported no fevers, headaches, neck stiffness, or photophobia. HIV infection had been diagnosed 1 month before presentation, at which time his CD4+ cell count was 185/µL and his HIV RNA level was 444,000 copies/mL. Two weeks before admission, the patient's partner noted that the patient was becoming confused, with worsening memory. The night before admission, the patient had begun antiretroviral therapy with coformulated efavirenz/tenofovir/emtricitabine.

On physical examination, the patient was found to be well nourished. His body temperature was 38.0°C (100.4°F), with other vital signs within normal limits. He had a pleasant demeanor but exhibited poor memory and word-finding difficulty. He knew his name and the date but could not state his current location. He scored 20/30 on the mini-mental state examination with, points deducted for orie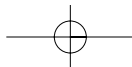ntation, poor object recall at 3 minutes, and the inability to spell the word "world" backward. The results of his neurological examination were otherwise nonfocal. There was no photophobia or nuchal rigidity. There was a small tongue laceration, but the head and neck showed no other signs of trauma. The remainder of the examination findings were normal.
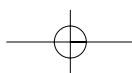
The patient's white blood cell (WBC) count was 6700/µL, and the results of other routine laboratory tests were normal. A chest radiograph and a noncontrast head CT scan showed no acute abnormalities. An electroencephalogram obtained on the day of admission showed left frontotemporal periodic lateralizing epileptiform discharges, mainly during drowsy and sleeping states. An MRI scan of the brain showed abnormal T2 signal in the medial left temporal lobe with focal areas of enhancement involving multiple vascular territories (Figure 1).

A lumbar puncture was also performed on the day of admission, with normal opening pressure. The WBC count was 30/mL (75% lymphocytes, 17% neutrophils, and 4% monocytes), red blood cell count was 9/mL, glucose level was 66 mg/dL (normal, 40 to 70), and total protein level was 87 mg/dL (normal, 10 to 44). Results of a Gram stain and bacterial culture of the cerebrospinal fluid (CSF) were negative. Polymerase chain reaction (PCR) assay of CSF was positive for HSV-1, while the results of PCR studies for HSV-2, a VDRL test, and tests for varicella-zoster virus and JC virus were negative. All blood cultures and serum treponemal antibody test results were negative.

Treatment with intravenous acyclovir was started. Because the CNS

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adverse effects associated with efavirenz could potentially complicate an assessment of the patient's neurological status, the antiretroviral regimen was switched to tenofovir, emtricitabine, and lopinavir/ritonavir.

On hospital day 6, the patient became increasingly somnolent, and a head CT scan showed an acute hemorrhage in the left temporal lobe and basal ganglia (Figure 2). Five days later, he had another precipitous mental decline and was found to have an enlarging bleed in the same area. No deficiencies were found in his platelet count, prothrombin time/partial thromboplastin time, or other coagulation studies (factor VII, VIII, XI, vWF studies; ristocetin cofactor test; and clot lysis test). The patient was taken to the operating room for urgent decompression and clot removal. Because of reports linking the use of protease inhibitors with increased bleeding risk in patients with hemophilia,[8-10] the integrase inhibitor raltegravir was substituted for lopinavir/ritonavir. After receiving a 28-day course of intravenous acyclovir, the patient was discharged on a regimen of oral valacyclovir.

Over the next several months, the patient's mental status gradually improved, although impairment in word finding, reading comprehension, and memory persisted. At his most recent outpatient visit, 3 months after admission, his CD4+ cell count was 406/µL and his HIV RNA level was undetectable.

DISCUSSION

T-cell–mediated immunity is essential for the control of HSV[11]; thus, immunosuppressed patients, including those undergoing organ transplant and chemotherapy, are at increased risk for severe HSV infections.[12] While HIV-infected persons are also at increased risk for severe mucosal HSV reactivation,[2,3] HSV encephalitis is surprisingly rare in this popula-
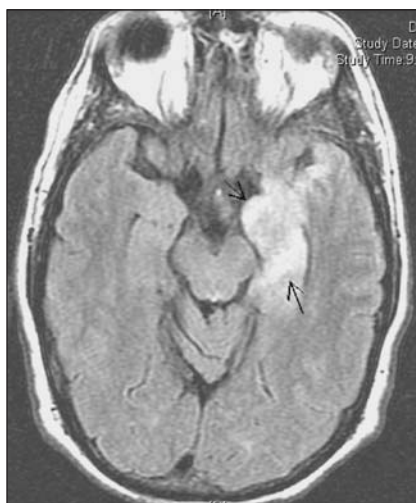

Figure 1. *MRI scan showing T2 hyperintensity in the left medial temporal lobe on hospital day 1.*

tion. In several large studies of HIV-positive patients who underwent neurological evaluation, the incidence of HSV encephalitis ranged from 0% to 3%.[4-7] On the other hand, cytomegalovirus infection and other human herpesvirus infections appear to be much more common.[4,6,13,14] Even though HSV encephalitis is not considered an AIDS-defining illness, the vast majority of case reports in the literature involve patients who have CD4+ cell counts

Figure 2. *CT scan revealing acute hemorrhage in the left temporal lobe and basal ganglia on hospital day 6.*
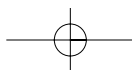
below 350/µL.[5,7,15-18] In the HIV-positive population, the relative rarity of HSV encephalitis and the increased frequency of mucocutaneous disease are puzzling and deserve further investigation.
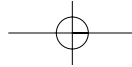
Unlike the acute meningoencephalitis seen in those with intact immune systems, HSV encephalitis in persons with HIV/AIDS can present in an atypical, subacute fashion with several days to weeks of confusion, depressive symptoms, and slowed mentation.[5,7,15,16,19,20] Our patient presented with a 2-week history of memory impairment, possibly reflecting an attenuated immunological response to HSV infection as a consequence of his underlying HIV infection. In addition, stroke-like symptoms and seizures have also been reported to be frequently encountered.[5,15,17-21]

This patient's clinical course was complicated further by 2 episodes of intracranial hemorrhage. A survey of the literature found that while radiologically apparent intracranial hemorrhage is a rare sequela of HSV encephalitis,[5] it has been well described that HSV causes a necrotizing encephalitis with evidence of hemorrhage seen in autopsy studies.[7,15,18,21]

There have been several reports linking protease inhibitor use to an increased bleeding risk in hemophiliacs.[8-10] (None of the reports have demonstrated consistent laboratory abnormalities of hemostasis, and the mechanism behind the association is still unclear.) Furthermore, the prescribing information for the protease inhibitor tipranavir cites a possible association between its use and intracranial hemorrhage,[22] which prompted a black box warning from the FDA.

These issues led us to switch this patient's ritonavir-boosted protease inhibitor to an integrase inhibitor, because we felt that a slight increase in the risk of bleeding might have converted a necrotizing encephalitis into

a clinically important bleed.

There is no consensus on the most appropriate treatment of HSV encephalitis in HIV-positive persons. In most of the previous reports in this patient population, patients were treated with 14 to 24 days of intravenous acyclovir,[7,15,16,20] a treatment similar to that given to patients without HIV infection. Given our patient's complicated recovery period, we elected to treat with an extended course of intravenous acyclovir followed by a suppressive regimen of oral valacyclovir. With this regimen, the patient has had a very good recovery, although memory deficits remain 1 year later.
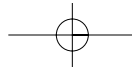
While HSV is a common cause of encephalitis in immunocompetent persons, it is a surprisingly rare cause of encephalitis in the HIV-positive population. As this case demonstrates, HSV encephalitis in the immunocompromised person can present quite atypically, with symptoms such as subacute memory loss and seizure. This case was further complicated by 2 episodes of intracranial hemorrhage after the patient began an antiretroviral regimen containing a ritonavir-boosted protease inhibitor. Clinicians should remain vigilant for bleeding complications in persons with necrotizing encephalitis caused by HSV. ☐

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