Recurrent Stroke as a Manifestation of Primary Angiitis of the Central Nervous System in a Patient Infected With Human Immunodeficiency Virus

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Context: Cerebral vasculitis in patients infected with human immunodeficiency virus (HIV) is usually related to additional or secondary infectious agents other than neoplastic diseases or HIV itself.

Objective: To describe a 31-year-old patient infected with HIV who presented with 2 recurrent, acute episodes of neurologic impairment in a 5-month period.

Design: Comparison of clinical and histologic data between the present case and previously published cases.

Setting: Community hospital.

Patient: A 31-year-old, HIV-infected patient with recurrent strokes and chronic lymphocytic meningitis.

Intervention: After ruling out cardiac embolisms and coagulation disorders, the presence of central nervous system vasculitis, probably secondary to an infectious process, was suspected based on the clinical examination and cerebrospinal fluid abnormalities.

Results: Necropsy findings suggest the diagnosis of primary angiitis of the central nervous system, and the only infectious agent that could be found was HIV.

Conclusions: Histologic studies were compatible with a diagnosis of primary angiitis of the central nervous system, but the pathogenic role of HIV in the genesis of the vasculitic process cannot be elucidated.

Arch Neurol. 2002;59:468-473

VASCULITIS INVOLVING the central nervous system (CNS) is rarely seen in patients with human immunodeficiency virus (HIV) infection if it is not related to opportunistic infections or lymphoproliferative disorders. A case report of an HIV-infected patient in whom a diagnosis of vasculitic process compatible with primary angiitis of the central nervous system (PACNS) was made at postmortem examination, 10 months after the initial neurologic symptoms began. The autopsy findings suggested vasculitis of the CNS, but any infectious or neoplastic cause of the vasculitis excluding HIV could not be determined. The clinical course and analytic, radiologic, and histologic autopsy findings are all described.

REPORT OF A CASE

A 31-year-old, HIV-infected man was admitted to the hospital because of neurologic symptoms in September 1996. He had been in good health, receiving zidovudine and zalcitabine, until 1 month before admission, when he complained of progressive headache. During the next 2 days, his symptoms progressed to dysarthria, dysphagia, and awkwardness of the right upper limb. On admission, he was afebrile. Neurologic examination showed a conscious patient with a reduced level of alertness. His visual fields were full to confrontation. The ophthalmoscopy results were normal, the pupils were reactive, and corneal reflexes were also bilaterally normal. Gaze to the right was limited. Dysarthria and asymmetric elevation of the palate and uvula were present. The remaining results of the cranial nerve examination were normal. Muscle strength, sensation, tone, and reflexes were all normal. Right dysmetria was present. Plantar reflexes were bilaterally extensors. The patients’ gait was unsteady, and he was unable to tandem walk, but there was no indication of Romberg sign. Routine blood analysis showed no abnormalities, and the CD4 count...
cell count was 309/µL. The HIV plasma viral load was not technically measurable at that moment in our hospital.

Computed tomography (CT) of the brain showed no abnormalities. Lumbar puncture revealed clear cerebrospinal fluid (CSF) with the following values: white blood cell count, 130/µL (90% lymphocytes); glucose, 38 mg/dL (2.11 mmol/L); protein, 0.27 g/dL; and adenosine deaminase, 12 U/L. The HIV-CSF viral load was not measurable at that moment. Magnetic resonance imaging (MRI) of the brain and brainstem showed areas of low intensity on T1-weighted signal and of high intensity on T2-weighted signal with no contrast enhancement within the pons, left semioval center, and left subcortical frontoparietal area. The MRI suggested rhomboencephalitis, and vascular damage or ischemic lesions could not be ruled out (Figure 1). The results of the following CSF analyses were negative: cytologic testing; VDRL test; bacterial, mycobacterial, fungal and viral cultures; Cryptococcus latex agglutination; and polymerase chain reaction (PCR) for herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), and varicella-zoster virus (VZV). In blood analysis, the results were also negative for viral cultures, CMV antigen, and Cryptococcus latex detection, as well as for serologic tests for Treponema pallidum, Brucella, Legionella, Mycoplasma, and Borrelia burgdorferi.

The patient achieved slow clinical improvement during a 3-month period until only a slight unsteady gait persisted. He was empirically treated with tuberculostatic drugs for 9 months. A follow-up MRI obtained 1 month after starting treatment was identical to the earlier one and the abnormalities of the CSF persisted. In February 1997, the patient experienced loss of muscle strength of his left side in less than 24 hours. Neurologic examination on admission revealed reduced alertness and cognition. He had horizontal nystagmus on looking to the right and flaccid left-sided hemiparesis (manual muscle test score: arm, 1/5; leg, 4/5). A CT scan of the brain showed multiple residual focal cystic-necrotic lesions within the pons, midbrain, and the region of the right basal ganglia. A third MRI revealed a retractile dilation of the right frontal horn of the lateral ventricle and progression of lesions with new areas of low signal intensity on T1-weighted images and high signal intensity on T2-weighted images within the right caudate, putamen, and globus pallidus and bilaterally in the pons and right midbrain (Figure 2). Magnetic resonance angiography showed abnormalities that suggested segmental stenosis of the supraclinoid segments of both internal carotid arteries and the distal segment of the basilar artery (Figure 3). Conventional angiography and CNS biopsy were not performed. Despite new empirical treatment with acyclovir and prednisone (60 mg/d orally) for 2 months, the patient’s neurologic status gradually deteriorated. The study findings from CSF, repeated during the next few months, remained unchanged with characteristic findings of aseptic meningitis. A CT scan of the brain in April 1997 revealed multifocal low-density areas within the midbrain and the right capsulogangliar region and obvious asymmetry on the lateral ventricle, all compatible with cerebral ischemia. The patient died in July 1997, in an impaired immunologic situation with a CD4 cell count of 105/µL, 10 months after the onset of symptoms.

A CNS-limited necropsy was performed. Macroscopically, there were multiple areas of softening and cysts of 1.5 cm in diameter within the putamen, caudate, right thalamus, and brainstem (Figure 4). The meninges were thickened at the base of the brain and cerebellum. There was segmental thickening of vessels in the Willis circle with luminal narrowing. Microscopically, the areas with softening and cysts corresponded to focuses of necrosis
with abundant macrophages and adjacent reactive gliosis. Lymphocytic vasculitis was observed in the meningeal and parenchymal vessels, mainly in nuclei at the base and brainstem. The vessels in the Willis circle showed evidence of fibrous vasculitis with focal destruction of the muscular structure, fibrosis of the intima, giant multinucleated cells, lymphoplasmocyte infiltrate, and focal fibrinoid degeneration (Figure 5). No microorganisms or cytopathic changes were observed on the usual stains. Brain bacterial and viral cultures (enteroviruses, HSV types 1 and 2, CMV, and VZV) were all negative. Immunohistochemical studies of the lymphocyte cells (pan T, pan B) did not show any monoclonality. Brain infection by CMV, HSV types 1 and 2, and VZV was also excluded by immunohistochemical studies. The necropsy findings suggested the diagnosis of PACNS, but the etiologic role of HIV could not be ruled out. Afterward, the nuclei from the base (globus pallidus and putamen) were analyzed for HIV. Using the PCR qualitative technique (Amplicor HIV; Roche, Branchburg, NJ), it was possible to demonstrate the presence of HIV-integrated DNA in the tissues studied.

**COMMENT**

Primary angiitis of the CNS is an uncommon disease in which CNS is the sole or dominant target organ of a vasculitic process, affecting the small and medium leptomeningeal and cortical arteries and, less frequently, the veins and venules. By definition, it is not associated with any process known to involve the CNS. Microscopically, it is a segmental vasculitic disease characterized by the infiltration of vascular walls by mononuclear cells that can be associated with fibrinoid necrosis. Since it was first described in 1959 by Cravioto and Feigin and until 1995, 113 histologically...
patients are given in the cerebral infarcts in some autopsy series. Ruling out second-
Cerebral Vasculitis in HIV-Infected Patients Not Associated With Infections or Tumoral Processes*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Cases</th>
<th>Age, y/Sex/CD4 Cell Count, /µL</th>
<th>Clinical Findings</th>
<th>CSF Findings</th>
<th>CNS Imaging</th>
<th>HIV in Brain or CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray et al,9 1992</td>
<td>6 (autopsy series of 11 patients)</td>
<td>28-39/4M, 2F/unknown</td>
<td>Early HIV infection (asymptomatic)</td>
<td>ND</td>
<td>ND</td>
<td>HIV IC negative in brain</td>
</tr>
<tr>
<td>Yankner et al,10, 11 1986</td>
<td>1</td>
<td>42/M/1600</td>
<td>1 mo before admission: headache, confusion, recurrent stroke, HTLV-I negative in serum</td>
<td>Lymphocytic meningitis</td>
<td>CT, angiography</td>
<td>HTLV-III positive in CSF and brain</td>
</tr>
<tr>
<td>Vinters et al,11 1988</td>
<td>1</td>
<td>40/M/severely depleted</td>
<td>Fulminant ascending myelopathy</td>
<td>Lymphocytic meningitis</td>
<td>CT</td>
<td>ND</td>
</tr>
<tr>
<td>Scaravilli et al,12 1989</td>
<td>1</td>
<td>57/M/unknown</td>
<td>6 mo before admission: confusion, leg weakness, and incontinence</td>
<td>ND</td>
<td>CT</td>
<td>ND</td>
</tr>
<tr>
<td>Rhodes,13 1987</td>
<td>8 (autopsy series of 100 patients)</td>
<td>Unknown</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Engstrom et al,14 1989</td>
<td>1</td>
<td>Unknown</td>
<td>Transient neurologic deficit</td>
<td>ND</td>
<td>Pleocytosis</td>
<td>CT</td>
</tr>
<tr>
<td>Berger et al,15 1990</td>
<td>1 (autopsy series of 154 patients)</td>
<td>28/M/unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frank et al,16 1989</td>
<td>1</td>
<td>4/M/unknown</td>
<td>Ischemic strokes (VZV skin infection)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Schwartz et al,17 1986</td>
<td>1</td>
<td>49/M/unknown</td>
<td>Recurrent episodes of visual loss</td>
<td>Lymphocytic meningitis</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mizusawa et al,18 1988</td>
<td>1 (autopsy series of 24 patients)</td>
<td>34/M/unknown</td>
<td></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Present study</td>
<td>1</td>
<td>31/M/309</td>
<td>1 mo before admission: headache, recurrent stroke</td>
<td>Lymphocytic meningitis</td>
<td>CT, MRI, magnetic resonance angiography</td>
<td>Viral culture of CSF and brain negative; HIV-DNA (PCR) of brain positive</td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus; CSF, cerebrospinal fluid; CNS, central nervous system; ND, not described; IC, immunocytochemistry; MN, mononuclear; HTLV, human T-cell lymphotropic virus; CT, computed tomography; HSV, herpes simplex virus; DXM, dexamethasone; SP, sulfadoxine-pyrimethamine; VZV, varicella-zoster virus; MRI, magnetic resonance imaging; and PCR, polymerase chain reaction.

Patients. The disease should be suspected if a patient has acute or subacute recurrent focal deficits sometimes in the presence of diffuse neurologic dysfunction, especially when abnormalities in the CSF are found and always after ruling out other causes. The combination of CSF analysis and MRI has a strong predictive value for a diagnosis that is later confirmed by angiography and brain biopsy specimens. Although magnetic resonance angiography has not been viewed until now as equivalent to conventional angiography for the detection of CNS vasculitis, the finding of vascular abnormalities in medium-sized vessels by magnetic resonance angiography, as occurred in our patient, may suggest the diagnosis and therefore could be useful whenever conventional angiography is not accessible.

The presence of HIV in the brain of the HIV-infected patients is currently evident, but clinically symptomatic cerebral primary vasculitis in these patients remains extremely rare. In primary HIV infection, it is not unusual to find evidence of neurologic manifestations, including acute meningitis. It seems that in these cases neurologic symptoms can have a strong correlation with HIV viral load in the CSF.10 The CSF viral load in our patient could not be measured because this technique was not available in our setting when the patient was examined. Nevertheless, before the use of highly active antiretroviral therapy (HAART), patients used to have very high plasma and probably CSF viral loads, and most HIV carriers remained neurologically symptom free throughout their lives; therefore, the natural history of CNS changes in HIV infection still remains poorly understood.

Our patient died in 1997 before the widespread use of HAART. Because the mortality of HIV-infected patients has considerably decreased since the introduction of this therapy, an aggressive diagnostic approach to cerebral vasculitis in these patients must be undertaken. Ulterior therapeutic decisions should be individualized in each case. If HIV had a pathogenetic role in cerebral vasculitis in these patients, the good blood-brain barrier penetration of new antiretroviral therapies could be a good therapeutic approach for this process, because it occurs in HIV-associated dementia.

Accepted for publication September 10, 2001.

Author contributions: Study concept and design (Drs Nogueras, Sala, and Cervantes); acquisition of data (Drs Nogueras, Sala, Sasal, Garcia, and Bella); analysis and interpretation of data (Drs Nogueras, Sala, Sasal, Viñas, Garcia, and Bella); drafting of the manuscript (Drs Nogueras, Sasal, Garcia, and Bella); critical revision of the manuscript for important intellectual content (Drs Sala, Viñas, Cervantes, and Segura); administrative, technical, and material support (Drs Nogueras, Garcia, Cervantes, and Segura).
and Bella); study supervision (Drs Sala, Sasal, Viñas, Bella, and Cervantes).

We thank Isidre Ferrer, MD, from the Department of Neuropathology, Hospital de Bellvitge, Barcelona, Spain, for his expert opinion and Jose Luis Perez, PhD, from the Laboratory of Microbiology, Hospital de Bellvitge, Barcelona, Spain, for the PCR analysis of HIV in the brain tissues.

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