Varicella-Zoster Virus Encephalitis in an AIDS Patient

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A 37-year-old man with a three-year history of Acquired Immunodeficiency Syndrome was admitted with impaired consciousness, seizures and fever. He was on highly active antiretroviral therapy and on neurotoxoplasmosis secondary prophylaxis. Laboratory exams from two months before showed a CD_4 cell count of 37/μL and a viral load of 230,000 copies/mL. Three months before admission he developed herpetic skin rash in the right trunk and acyclovir was added to his treatment regimen. On physical exam he was drowsy and had motor and sensory aphasia. The patient had elevated protein levels and normal pressure in the cerebrospinal fluid (CSF). Contrast enhanced computed tomography scan of the brain showed a hypodense lesion in the left parietal lobe, with poorly defined margins and no contrast enhancement. The magnetic resonance scan (MRI) showed multiple hyperintensities in T_2-weighted image in white and grey matters and hypointense products of hemorrhage in both hemispheres and in the cerebellum. He was empirically treated with intravenous acyclovir and prednisone. Viral DNA of Varicella-zoster virus (VZV) was detected in the CSF by means of polymerase chain reaction (PCR) analysis. Acyclovir was continued for 10 days and the patient became well, with improvement of aphasia.We present a case of VZV encephalitis, confirmed by nested PCR, in a patient with suggestive MRI findings, who succeeded with treatment. VZV encephalitis is a rare opportunistic infection, occurring in 0.1 to 4% of AIDS patients with neurological disease; it is related to severe immunodeficiency and has a high mortality.

Key Words: AIDS, varicella-zoster encephalitis.

Case Report

A 37-year old man was admitted to the hospital, because of a 12-hour history of impaired consciousness, seizures and fever. He was diagnosed with human immunodeficiency virus (HIV) three years before during an episode of neurotoxoplasmosis. A computed tomography (CT) scan demonstrated a left lesion in frontal and parietal lobes. Neurotoxoplasmosis prophylaxis was initiated.

Four months before admission, he developed a typical herpetic skin rash in the right trunk. The patient was given acyclovir/valacyclovir therapy for 40 days. The patient's CD_4 cell count was 28/μL and 37/μL, HIV RNA was 470,000 copies/mL and 230,000 copies/mL, 9 and 2 months previously, respectively. The patient had been treated for one year and six months with d4T, 3TC and indinavir.

On examination the patient was drowsy and pale, with no fever. Neurological examination revealed sensory and motor aphasia. There was no neck stiffness. Muscle strength was 5+ symmetrically. Optic disks and retinal vessels were normal, and no retinal hemorrhage or exudates were seen with direct fundoscopy exam.

Hematocrit was 34%, the white blood cell (WBC) count was 2,710/μL with 43% lymphocytes and 45% neutrophils. Erythrocyte sedimentation rate (ESR) was 59 mm/h. Hemocultures were negative. The cerebrospinal fluid (CSF) analysis revealed a protein concentration of 110 mg/dL and 38 mg glucose/dL.

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There were 25 cells/iL (80% neutrophils) and 15 erythrocytes/mm^3. A VDRL test and a search for cryptococcal antigens were negative. CSF cultures were negative.

A contrast enhanced computed tomography of the brain showed a left hypodense lesion in the frontal and parietal lobes, with poorly defined margins (Figure 1). No contrast enhancement or calcifications were demonstrated. There was no mass effect or edema. An MRI with gadolinium demonstrated multiple subcortical enhancing lesions in the left frontal, temporal and parietal lobes (Figures 2 and 3). Similar lesions were demonstrated in the cerebral midline and right cerebellar hemisphere.

Neurotoxoplasmosis therapy was initiated and anticonvulsant therapy with phenytoin and oxcarbazepine was added. Two days after admission, the patient presented with agraphia, visual hallucinations and diplopia.

A second CSF examination revealed varicella-zoster viral DNA by polymerase chain reaction (PCR) (Figure 4).

The patient was treated with intravenous acyclovir 30mg/Kg, 3 times/day. Intravenous prednisone was given at 1 mg/Kg/day for 3 days and 400 mg/day fluconazole per oral was added. Anticonvulsant therapy was changed to sodium valproate.

The acyclovir dosage was decreased on the 6th day because of episodic seizure. Effective seizure control was obtained by increasing the sodium valproate dosage. The highly active antiretroviral therapy (HAART) was changed to zidovudine, didanosine and efavirenz, because the patient was in clinical and laboratory failure.

In follow-up examinations the patient has demonstrated progressive improvement in aphasia. He was on oxcarbazepine and HAART. Six months later he was again in laboratory failure and HAART was changed to ritonavir, lopinavir, zidovudine and didanosine.

Discussion

Neurological complications of the reactivation of varicella-zoster virus (VZV) occur most frequently in elderly persons and immunocompromised patients [1]. Gray et al. reported varicella zoster virus infection of the CNS in more than 4% of patients with AIDS examined at autopsy. In AIDS patients, VZV tends to reactivate from multiple dorsal root ganglia levels, and the disease is often disseminated. The majority of patients are found to have disseminated skin lesions prior to the onset of CNS symptoms. Vascular and parenchymal central nervous system infections with varicella-zoster virus are rare in the absence of cutaneous lesions [2].

The most common VZV neurologic complications in immunocompetent and immunocompromised patients include myelitis, vasculopathy, encephalitis, ventriculitis, aseptic meningitis, postherpetic neuralgia and leukoencephalopathy [3,4].

Encephalitis is a rare complication of VZV and is classified in three patterns: (1) large vessel vasculopathy, (2) small vessel vasculopathy, and (3) ventriculitis and meningitis [1,3]. Large vessel encephalitis is usually associated with immunocompetent elderly patients, while small vessel encephalitis and ventriculitis develop almost exclusively in immunocompromised patients [5,6].

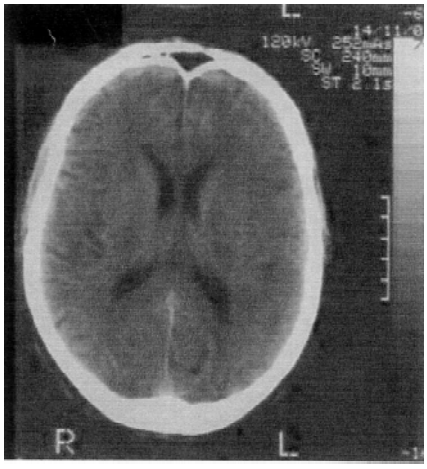
Common neurological findings in VZV encephalitis include headache, seizures, mental changes, and focal deficits [7]. In small vessel encephalitis, hemiplegia, aphasia and visual-field deficits may be present as a subacute course [1].

In this case study, the history of zoster eruption months earlier and the clinical course of seizures, impaired consciousness, aphasia, agraphia, and visual-field deficits in a HIV patient is very similar to that of other patients described previously in the literature, who were diagnosed with VZV encephalitis [4,5].

Kleinschmidt-DeMasters et al. [6] demonstrated that brain imaging in VZV encephalitis reveals bland or hemorrhagic infarctions secondary to a large vessel vasculopathy, or mixed ischemic/demyelinative lesions of deep-seated white matter as a consequence of small vessel vasculopathy.

CT and MRI findings in this patient are compatible with small vessel encephalitis. The multiple subcortical enhancing lesions are suggestive of multifocal areas of

Figure 1. Contrast enhanced brain computed tomography: left hypodense lesion in frontal and parietal lobes with poorly defined margins.



Figures 2 and 3. MRI with gadolinium: multiple subcortical enhancing lesions in left frontal, temporal and parietal lobes.

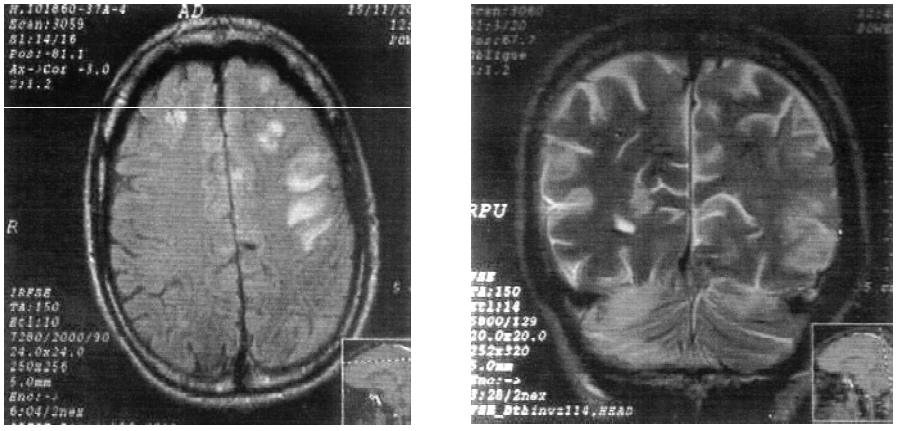
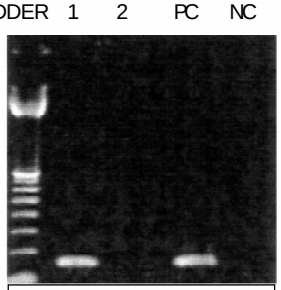


Figure 4. CSF Polymerase Chain Reaction (PCR): Varicella-zoster viral DNA.



infarction in deep ovoid lesions. Periventricular and ependymal necrosis may occur as a result of vasculopathy of subependymal vessels and secondary infection of ependymal and other glial cells in the periventricular region [1].

Early diagnosis may be established by detecting virus-specific DNA sequences in the cerebrospinal fluid (CSF), after amplification by the polymerase chain reaction (PCR), and can be confirmed by detection of intrathecally produced, specific IgG antibody [8,9]. In this patient, diagnosis was established exclusively with PCR. The predictive value of PCR in the CSF for diagnosis of VZV-associated neurological disease should take into account the patient's clinical presentation, concurrent infections and response to anti-VZV therapy. Virus isolation from CSF and antibody testing in serum are unsuitable for diagnosis [8-10].

Early acyclovir therapy (15 to 30 mg per kilogram per day, for 10 days or longer) is recommended in immunocompromised patients and those with serious disease [1,11].

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