Progressive Multifocal Leukoencephalopathy in an AIDS Patient

Ming-Hsing Lee, Yan-Zhong Chen, Lih-Shinn Wang, Pao-Sheng Yen, Yung-Hsiang Hsu*

Progressive multifocal leucoencephalopathy (PML) is a demyelinating brain disease caused by Jamestown Canyon virus (JCV). This disease is an important cause of morbidity and mortality in acquired immunodeficiency syndrome (AIDS) patients. We report a 34-year-old man infected with HIV-1 who presented with frequent general tonic clonic seizure and left side weakness for 2 months. Clinical features and magnetic resonance imaging (MRI) findings with hyperintensity on T2-weighted imaging and low density on T2 fluid attenuated inversion recovery involving multiple white matter were compatible with PML. He died of sepsis 2 months after diagnosis. Autopsy demonstrated progressive multifocal leucoencephalopathy according to characteristic histopathologic picture with multifocal demyelination, bizarre astrocytes formation and basophilic intranuclear inclusion bodies in the oligodendrocytes. JCV genome was demonstrated in the nucleus of oligodendrocytes using in situ hybridization. In conclusion, in AIDS patients with neurologic signs and typical MRI findings who present with multifocal demyelination lesions, PML should be diagnosed clinically. [J Formos Med Assoc 2007;106(3 Suppl):S24–S28]

Key Words: acquired immunodeficiency syndrome, Jamestown Canyon virus, progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (PML) is a fatal, progressive disease due to infection by the Jamestown Canyon virus (JCV). It occurs in patients with defects in cell-mediated immunity, including those with acquired immunodeficiency syndrome (AIDS) and other immunocompromised diseases. This disease is an important cause of morbidity and mortality in AIDS patients.

JCV affects oligodendrocytes almost exclusively, causing demyelination. Symptoms include progressive focal and diffuse deficits (visual, motor, cognitive deficits and memory loss, personality change), leading to death within a few months after diagnosis.¹

We report a 34-year-old HIV positive man who presented with generalized tonic clonic seizure and left side weakness for 2 months with typical magnetic resonance imaging (MRI) findings and a rapidly fatal clinical course. JCV-associated PML was diagnosed at autopsy.

Case Report

A 34-year-old man was robust before when he developed a general tonic clonic seizure, an upward gaze that lasted for 5 minutes on July 7, 2004. He underwent brain computed tomography at a local hospital, which showed a hypodense lesion suspected to be a brain tumor. On July 12, brain MRI showed multiple lesions in flare signal. No abnormal vascular lesion was detected on magnetic resonance angiography taken on July 17 in Chung Gung Memorial Hospital (CGMH).
Left side weakness and left facial palsy developed during the 1st week of August, but he did not seek treatment. On August 7, another episode of general tonic clonic seizure occurred and lasted for 2 minutes. On arrival at CGMH emergency room, he was clear but left side muscle power decreased. He was put on oral phenytoin 300 mg at bed time and was discharged. Another episode of seizure attack with general tonic clonic seizure lasting for 1–2 minutes occurred on August 21. Hemiplegia developed and he visited the neurosurgery department of CGMH on August 23. Western blot test for HIV-1 was positive. He was transferred to the neurosurgery department in Tzu-Chi Hospital for further evaluation and management on September 1.

After admission, carbamazepine 200 mg one tablet BID and phenytoin 100 mg one tablet TID were given to control the seizure and he was transferred to the infectious ward the next day. MRI showed a large area of hyperintense signal on T2-weighted image and T2 fluid attenuated inversion recovery signal change showed low density in the right fronto-tempo-parietal, left frontal, and left parietal lobes (Figure 1A). Involvement of right basal ganglia, right thalamus, right side midbrain, and pons was also noted. Contrast injection study showed no apparent abnormal enhancement (Figure 1B). Opportunistic infection including herpes simplex IgM, cytomegalovirus IgM, toxoplasma antibody, varicella IgM and IgG, Grocott’s methamine silver nitrate stain of sputum for Pneumocystis jiroveci, Treponema pallidum hemagglutination assay, Venereal Disease Research Laboratory (VDRL), cryptococcus antigen were checked and all were negative. Antiretroviral therapy including Kaletra (lopinavir 133.3 mg and ritonavir 33.3 mg/cap) three tablets two times a day and Combivir (lamivudine 150 mg and zidovudine 300 mg) one tablet two times a day were given. His CD4 cell count was as low as 40 μg/dL and prophylactic antibiotics including Baktar (sulfamethoxazole 400 mg and trimethoprim 80 mg/5 mL/1 amp) 15 mL iv every 8 hours, fluconazole (200 mg) drip daily, clarithromycin (500 mg) one tablet BID, rifabutin (150 mg) one cap two times a day, levofloxacin 500 mg one tablet daily were prescribed. Penicillin G 3MU intravenous every 6 hours was given to treat syphilis after plasma VDRL test was positive. Gancyclovir 250 mg intravenous every 12 hours was given due to suspected cytomegalovirus retinitis but discontinued after ophthalmologist consultation excluded this diagnosis. Another episode of generalized tonic clonic seizure occurred on September 10. Mannitol 20%, 50cc

Figure 1. (A) Axial T2-weighted image shows bilateral, asymmetric, patchy hyperintensities in bilateral subcortical white matter with a slightly layered lesion in the right frontoparietal lobe. (B) Postcontrast, T1-weighted image shows no apparent enhancement.
dripped every 8 hours was given to decrease intracranial pressure. He became stuporous, with exten- tion response to pain stimulation and anisocoric pupils with eyes deviated to the left. Baclofen 5 mg/tab one tablet three times a day was given for muscle rigidity. Depakine (Valproate Na 200 mg) one tablet three times a day and clonazepam (0.5 mg) one tablet every night were used for anticonvulsion. Combivir (lamivudine 150 mg and zidovudine 300 mg) was shifted to stavudine (zerit, D4T) 40 mg every 12 hours and didanosine (videx, ddl) 400 mg daily due to leukopenia developing, probably due to zidovudine. Fever and dyspnea developed on September 23 and he died on October 9.

Autopsy was performed after 24 hours. The main lesions were in the brain. Serial brain sections showed multiple softened areas involving the subcortical white matter of the right frontal, right temporal, bilateral parietal, bilateral occipital, right basal gangliar and cerebellar regions and in the brain stem (Figure 2A). Histopathology showed multifocal demyelination (Figure 2B) with foamy cell aggregation accompanied by bizarre astrocyte proliferation and characteristic basophilic intranucleus inclusion body formation in the oligodendrocytes (Figure 2C). Immunohistochemical staining failed to show JCV protein in the oligodendrocytes. JCV in situ hybridization performed as previously described demonstrated JCV genome in the nucleus of oligodendrocytes (Figure 2D).

Discussion

PML is a demyelinating disorder of the human brain caused by JCV. Up to 80% of humans express...
serum antibodies to JCV, yet only a very small percentage develop PML—predominantly those with immunosuppressive conditions. The AIDS pandemic has led to a much higher incidence of PML in the last 20 years; about 5% of all patients with AIDS develop PML.

PML is a disorder of the brain induced by the lytic infection of myelin-producing oligodendrocytes by JCV. Initial demyelination occurs as multiple foci sparsely distributed in the subcortical white matter. With disease progression, each focus grows as virus spreads from cell to cell. Ultimately, microscopic areas of necrosis become macroscopic plaque lesions up to centimeters in diameter. The three main pathologic features of PML are demyelinated lesions accompanied by abnormally large oligodendrogial nuclei with basophilic inclusion bodies and bizarre enlarged astrocytes. Macrophages are often present in PML lesions; their likely role is the removal of myelin breakdown products or damaged oligodendrocytes, as in this case.

Immunohistochemical staining and in situ hybridization have been applied to detect JCV in PML lesions. In this case, in situ hybridization showed JCV genome diffusely in the oligodendrocytes, but immunohistochemical staining was negative. In situ hybridization has proven to be more sensitive than immunohistochemistry in detecting JCV capsid proteins, as in this case. Virus is less frequently detected in astrocytes than oligodendrocytes, and neuronal loss is rare, with sparing of demyelinated axons.

MRI of PML includes high-signal lesions in multifocal white matter in T2-weighted image and no enhancement in postcontrast image, all of which were found in this case.

The multifocal nature of PML results in a variety of neurologic symptoms including visual impairment or blindness, motor dysfunction or weakness, and dementia and other cognitive abnormalities, such as personality change, memory loss, or emotional lability. These symptoms can vary in order of presentation and severity, but most patients develop all three. Less common manifestations include vertigo, headache, seizures, sensory deficits, and parkinsonism. In this case, atypical presentation with generalized tonic clonic seizure occurred. Usually, disease progression is rather rapid, with death within a year after diagnosis; some patients survive for several years.

Prior to highly active antiretroviral therapy (HAART), there was no effective therapy for PML. Since the advent of HAART, prognosis for PML has much improved; however, a significant number of patients are unresponsive to antiretroviral therapy and some worsen because of the development of immune reconstitution disease. A better understanding of the biology of JCV and its interactions with host immunity are leading to new anti-JCV-specific agents that await evaluation in randomized controlled trials. Improved diagnostic tools and the possibility of immunotherapy and gene therapy are further advancing the prospects of improved management of this condition.

References


