Progressive Multifocal Leukoencephalopathy in an Immunocompetent Taiwanese Patient

Yung-Yee Chang,† Min-Yu Lan,† Cheng-Huei Peng,† Hsiu-Shan Wu,† DeChing Chang,‡ Jia-Shou Liu†∗

Progressive multifocal leukoencephalopathy (PML) is a deadly demyelinating brain disease caused by JC virus (JCV). Genomic analysis of viral isolates in these cases often shows prototype-like JCV and its variants, which is a virulent strain compared to the latent archetype virions mostly found in the kidney. Here, we report a 57-year-old man who suffered from a subacute course of cognitive impairment and multiple neurologic deficits. Neuroimaging, pathology, and virology studies showed multifocal leukoencephalopathy and the presence of JCV deoxyribonucleic acid in the cerebrospinal fluid. The prototype type 1 (Mad-1) strain of JCV was identified on viral genotyping obtained from brain tissue. No immune deficits were found. He responded poorly to α-interferon and antiviral treatment. This case suggests that lack of immune deficiency cannot exclude the possibility of PML as a cause of subacute leukoencephalopathy. Accumulated data with respect to the disease course, pathologic feature, and viral genomic subtyping may pave the way for future treatment against this devastating disease. [J Formos Med Assoc 2007;106(2 Suppl):S60–S64]

Key Words: genotyping, JC virus, magnetic resonance imaging, polymerase chain reaction, progressive multifocal leukoencephalopathy

JC virus (JCV) is a double-stranded circular deoxyribonucleic acid (DNA) virus belonging to the family Papovaviridae and genus Polyomavirus.† It has an extremely limited host range and can only cause productive infection in humans.‡ JCV is widespread in the human population. Serum antibody to JCV could be detected in up to 80% of people beyond late childhood. It is postulated that a transient viremia period may develop following primary infection, and the virus is transported to the kidney where it resides indefinitely. Although the virus often remains inactive, in immunocompromised conditions it may be reactivated and result in viruria, chronic neurologic diseases, or a fatal demyelinating brain disease, namely progressive multifocal leukoencephalopathy (PML).§ Being first isolated from the brain tissue of a PML victim, JCV was named in 1971 after the initials of that patient. Along with the University of Wisconsin (Madison) where it was identified, the isolated strain was designated as prototype Mad-1. The Mad-1 strain differs from the latent virus that resides in the kidney (archetype) in the regulatory regions (RR) of the viral genome, with tandem repeats instead of a single unit. Other prototype-like JCV variants with tandem repeats were subsequently isolated from the brain tissue of PML patients. The particular RR DNA sequences of the prototype and its variant strains are thought to be responsible for virulence and specific neurotropism.

PML is a relentless demyelinating disorder due to lytic infection of oligodendrocytes by JCV.

©2007 Elsevier & Formosan Medical Association

†Department of Neurology, Kaohsiung Chang-Gung Memorial Hospital, Kaohsiung, and ‡Institute of Molecular Biology, National Chung-Cheng University, Chia-Yi, Taiwan.

Received: August 31, 2005
Revised: November 2, 2005
Accepted: January 10, 2006

*Correspondence to: Dr Jia-Shou Liu, Department of Neurology, Kaohsiung Chang-Gung Memorial Hospital, 123, Ta-Pei Road, Niao-Sung, Kaohsiung 833, Taiwan.
E-mail: josefliu@ms15.hinet.net
Clinically, patients may present with various neurologic deficits resulting from multifocal brain involvement. PML was once thought to be a rare disease until increasing case numbers were encountered in patients with acquired immunodeficiency syndrome (AIDS), organ transplantation, and immunocompromised status. In Taiwan, the definite diagnosis of PML has not been described and this is probably due to difficulty in virus isolation and lack of availability of necessary diagnostic tools in most hospitals. Here, we report a confirmed case of PML including the clinical course, typical neuroimaging findings, and pathologic features. Compatible virus DNA material was detected from the cerebrospinal fluid (CSF), and genomic sequencing revealed JCV prototype Mad-1 in brain tissue.

Case Report

A 57-year-old right-handed professional driver had no history of substance abuse or toxin exposure. He had an 8-year history of hypertension and hyperuricemia, which were under good medical control. Three months prior to admission, he suffered a generalized seizure but did not seek medical attention. Due to subacute onset behavior disorder and speech problems, he was admitted for further investigation. On admission, vital signs and physical examination were normal. Neurologic examination disclosed poor attention, dysphasia, visual agnosia, and generalized hyperreflexia. Laboratory studies including a complete blood cell count, biochemistry, and adrenal and thyroid hormone were all normal. Serologic tests disclosed a carrier state of hepatitis B. Serum IgMs to cytomegalovirus, herpes simplex virus types 1 and 2, and toxoplasma were all negative. Tests of antibodies to the human immunodeficiency virus 1+2, as well as reagin plasma response and treponema pallidum hemagglutination were all negative. Serial immunologic survey showed C3 142 mg%, C4 38.5 mg%, IgG 1530 mg%, IgM 90.4 mg%, and no paraprotein in the serum or CSF. Results of mononuclear cell quantitation were as follows: CD3+ 538 cells/μL, CD19+ 132 cells/μL, CD4+ 308 cells/μL, CD8+ 250 cells/μL, CD4+/CD8+ 1.23, NK 174 cells/μL. Tumor markers including carcinoembryonic antigen, carbohydrate antigen (CA) 125, CA 15-3, CA 19-9, and prostate-specific antigen were not elevated. Cytologic and biochemical analyses of CSF were within normal limits. Electroencephalography demonstrated slowing background with abundant theta and delta waves, and focal epileptogenicity in bilateral parieto-occipital areas. Cranial magnetic resonance imaging (MRI) showed high intensity lesions in the white matter of bilateral parieto-occipital lobes on T2-weighted images and fluid attenuated inversion recovery pulse sequence (Figure 1A). His consciousness deteriorated to stupor with limited eye movement, and limb jerks emerged gradually. Despite advanced laboratory survey, the definite etiology...
of the brain lesion remained obscure. Thus, leukoencephalopathy of undetermined cause was diagnosed and a stereotactic brain biopsy was performed to confirm the diagnosis and guide therapy. Microscopic examination of specimens taken from the right occipital lobe found no malignant cell or prominent inflammatory response, but abundant degenerated neurons, atypical astrocytes, foamy macrophages, and oligodendrocytes with intranuclear inclusion bodies were observed (Figure 2A). Immunohistochemical assay using anti-JCV antibody (Novocastra, Newcastle, UK) showed positive staining in the oligodendrocytes, astrocytes, and paravascular cells (Figure 2B and C). According to the clinical course, characteristic MRI picture, and specific histopathologic findings, a clinical diagnosis of PML was established.

For detecting JCV DNA, polymerase chain reaction (PCR) amplification was performed, using two different sets of specific primers. Sequences of the first set (P1: 5′-AAGTCAATATCTATATCAGATACA, P2: 5′-AGTTGCTTGGCCATTAGAG) were based on the conserved region of the major capsid protein (VP-1 region) of the JCV genome extending from base pair (bp) 1646 to 1852.12 The second set of primers applied was JBR1 (5′-CTCCACGCCCTACTACTCTTGAG) and JBR2 (5′-GTGACAGCTGGCGAAGAACCATGGC), annealing to the constant ends of RR (nucleotide −45 to −21 and 265 to 289) of the JCV.5,6 The viral DNAs coding for VP-1 structural protein were positive in urine and CSF samples (data not shown). In addition, JCV DNA bands of the non-coding RR with the expected size of 334 bp were found in urine, peripheral lymphocytes, CSF, and brain (Figure 3). To determine the specific genotype of JCV in brain tissue, the PCR product of the RR element was purified and sequenced using the fmol DNA sequencing kit (Promega, USA), and shown to be identical to Mad-1.1

The patient remained stuporous with complications of recurrent nosocomial pulmonary and urinary tract infections, the development of which were attributed to his severe neurologic condition.
His consciousness improved slightly while on recombinant α-2a interferon therapy, but later deteriorated again despite adding cytosine arabinoside (2 mg/kg body weight per day, 5 consecutive days per week for 2 weeks) to his treatment regimen. Follow-up brain MRI disclosed significant expansion of the previous lesions, and the development of new lesions in bilateral frontal white matter (Figure 1B). The patient died of severe pulmonary infection and septic shock 2 months after admission.

Discussion

JCV often causes asymptomatic infection of the kidney with intermittent viruria. Archetype JCV is the most commonly found strain in the kidney but is seldom discovered in the CNS. The nucleotide sequence of the RR is believed to play a decisive role in determining host range, virulence, and cellular tropism. Based on the sequence variation in the RR, the most often isolated strains from brain lesions are prototype Mad-1 and prototype-like variant with 98-bp tandem repeats, in contrast to the “archetype” latent strain harboring a single copy of the 98-bp tandem. In our patient, histologic examination confirmed demyelinating changes in association with inclusion bodies within oligodendroglia highly suggestive of a virus-related disease entity. Molecular studies further demonstrated that the viral genome was identical to Mad-1, a virulent strain, which attacks the nervous system.

Clinically, PML often occurs in patients with disorders involving a compromised immune system, e.g. lymphoproliferative disease, malignancy, protracted granulomatous disease, organ-transplanted status, and pandemic AIDS. It is believed that immunosuppression may lead to reactivation or mutation of latent polyomavirus. However, immune insufficiency is not a prerequisite in the diagnosis of PML. In immunocompetent individuals or those with restored immune function, PML should also be included in the list of differential diagnosis once a compatible clinical course and typical imaging findings are encountered. Immunologic surveys in our patient were normal except for a borderline CD4+ count. Low CD4 cell count per se is found in various conditions ranging from viral or bacterial infection, trauma, dementia, stroke to psychologic stress. How PML develops in immunocompetent patients is still unknown. It is possible that viremia and viral mutation could have occurred during...
an immunosuppressed period (e.g. other infection or psychologic stress).

In the past, the clinical diagnosis of PML was often a difficult task. This may have been due to insufficient imaging resolution,16 failure to perform needed brain biopsy, and difficulties in the isolation and culture of the virus.17 A definite diagnosis of PML can now be readily attained by detecting JCV DNA and antigens in brain lesions using in situ hybridization or immunohistochemistry.18,19 JCV DNA can be detected by PCR amplification in the CSF in 80–92% of biopsy-proven PML cases.20,21 This may facilitate the initial screening, reduce the need for brain biopsy, and enhance the understanding of the molecular details of the virus.

In conclusion, this is the first report of a pathologic and virology proven PML case in Taiwan. Lack of immune deficiency cannot exclude the possibility of PML as one of the causes of leukoencephalopathy. Molecular studies for initial screening and final genomic classification of the viral strain are invaluable for identifying the disease entity. Although there is still no effective therapy for PML, the gathered clinical, pathologic, and molecular information can form the basis of designing rational care and treatment for this devastating disease.

References