Detection of JC Virus Infection in Progressive Multifocal Leukoencephalopathy : The First Documented Case in Thailand

TAWEEKIAT DUJNEUNGKUNAKORN, M.D.*,
ASDA VIBHAGOOL, M.D.*,
WASUN CHANTRATITA, Ph.D.**,
JIRAPORN LAOTHAMATAS, M.D.***,
SOMNUEK SUNGKANUPARPH, M.D.*,
WANTANIT PAIROJ, M.Sc.**,
CHUTATIP SRICHUNRUSAMI, B.Sc.**,
TEERATORN PULKES, M.D.*

Abstract

Progressive Multifocal Leukoencephalopathy (PML) is a demyelinating brain disease caused by human polyoma JC virus (JCV). This disease is an important cause of morbidity and mortality in AIDS patients. Definite diagnosis currently requires a brain biopsy. PCR for JCV of CSF, an emerging diagnostic tool, has a high specificity for the diagnosis of PML in patients with characteristics on clinical and neuroradiological findings. The authors report a 36-year-old woman who presented with prolonged fever, progressive weakness, and slow speech for 2 months. Clinical features and MRI findings were compatible with PML. Qualitative PCR for JCV of CSF showed a positive result. This report emphasizes the yield of PCR, the CSF for JCV in a diagnosis of PML, which may reduce the need for a brain biopsy in such cases.

Key word : Progressive Multifocal Leukoencephalopathy, JC Virus, PCR

**DUJNEUNGKUNAKORN T,
SUNGKANUPARPH S, VIBHAGOOL A, et al
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Human polyomavirus JC virus (JCV), is known as a causative agent of the fatal demyelinating disease, progressive multifocal leukoencephalopathy (PML) that occurs mainly in HIV-infected patients. There is no report of PML in Thailand due to prior unavailability of a diagnostic test. Several studies have shown the polymerase chain reaction (PCR) to be an effective tool for detecting JCV[1-10]. Real-

* Department of Medicine,
** Department of Pathology,
*** Department of Radiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

time PCR instrument is the latest advance in nucleic acid amplification and overcomes many limitations, such as carryover and technically cumbersome PCR product detection methods[11]. Currently, PCR for JCV of a CSF specimen has a high specificity for the diagnosis in patients with characteristics on clinical and neuroradiological findings[12,13]. The authors report, herein, the first case of PML in Thailand confirmed by CSF PCR for JCV.

CASE REPORT

A 36-year-old woman presented with prolonged fever, progressive weakness, and slow speech for 2 months. The patient had otherwise been well until 2 months prior to admission when she started to have intermittent fever with occasional nausea and vomiting. She developed mild weakness of the right hand and slow speech. A month prior to admission, she had generalized malaise and went to a private hospital. Weakness became gradually progressively worse involving the right hand to left hand, left arm, and both legs. She was referred to Ramathibodi Hospital with unidentified cause of illness.

On admission, the patient was febrile (temp 37.9°C) with mild pallor. She had good consciousness but delayed verbal response. Neurological examination revealed generalized weakness, grade 4/5, with spastic tone and hyperreflexia of all extremities, and right extensor plantar response. Frontal lobe signs were noted. Other neurological and general examinations were unremarkable.

Complete blood count showed a hemoglobin of 10 g per cent with a white blood cell count of 3,000/mm^3 and 70 per cent neutrophils. Blood chemistries were normal except that the alanine aminotransferase (ALT) was 70 U/L. Serologic study demonstrated positive anti-HIV antibody, and negative for VDRL, toxoplasma antibody, and cryptococcal antigen. CD4+ cell count was 55 cell/mm^3 and HIV viral load was 685,000 copies/ml (5.84 log).

CT scan of the brain (Fig. 1) showed an ill-defined non-enhancing hypodense lesion involving the deep white matter and subcortical white matter of the bilateral frontal gyrus and superior frontal gyrus. MRI of the brain (Fig. 2) showed multiple ill-defined patchy hyposignal T1/hypersignal T2 without enhancement at the bilateral precentral and superior frontal gyrus, right parietotemporal and right frontal operculum.

Cerebrospinal fluid (CSF) examination revealed clear fluid with an open pressure of 8 cm H_2O, white blood cell count of 3/mm^3-all mononuclear cell, no red blood cells, protein of 48 mg/dl, and glucose of 65 mg per cent (serum glucose 86 mg%). The results of the CSF cryptococcal antigen, CSF PCR for TB, and CSF PCR for CMV were negative. The patient was clinically diagnosed with PML. CSF for the qualitative PCR for JCV revealed a positive result.

The patient was treated with highly active antiretroviral therapy (HAART) including zidovudine, lamivudine and indinavir. The neurological deficits

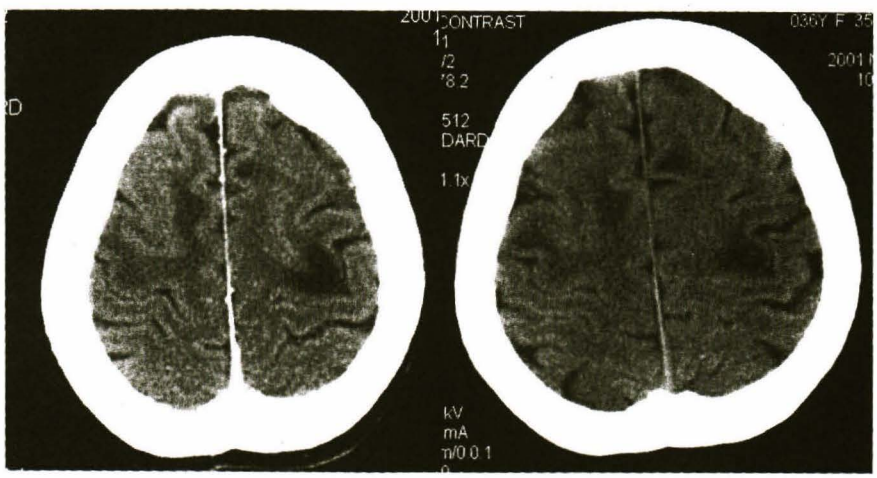

Fig. 1. CT scan of the brain (without contrast and with contrast).

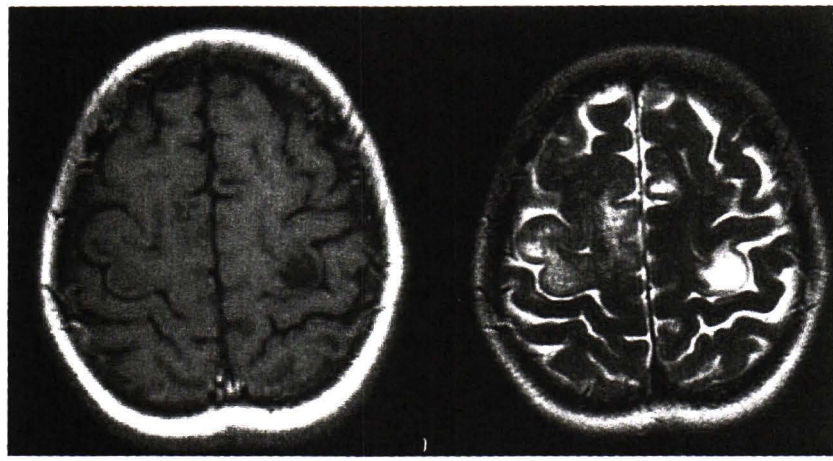

Fig. 2. MRI of the brain (T1 and T2).

were stable during the 2-week admission. The patient was discharged with HAART and co-trimoxazole for primary PCP prophylaxis. Two months follow-up at the out patient clinic showed normal speech and slightly improved muscle weakness.

DISCUSSION

Focal central nervous system involvement in patients with acquired immunodeficiency syndrome occurs frequently. Infectious cause is the most common etiology[14,15]. PML is not an uncommon cause of focal neurological disease in AIDS. In the past, typical clinical and neuroradiological features and exclusion of other more common diseases preliminarily diagnosed the disease. However, the clinical and neuroradiological findings are sometimes unable to discriminate PML from toxoplasmosis and primary CNS lymphoma[5]. A diagnostic tool to confirm the diagnosis of PML is essential since the other neurological illnesses need specific treatment.

The authors describe a patient who had a history of insidious onset of progressive multifocal weakness with speech abnormality which are the common clinical features of PML[16]. The neuroradiological study showed multiple areas of non enhancing hypodensity lesions involving the deep white matter on the CT scan of the brain and hyposignal T1/hypersignal T2 without enhancement on the MRI of the brain which are the typical findings of the neuroradiological study of PML patients[17]. Negative results of investigations including serum cryptococcal antigen, toxoplasma antibody, VDRL, CSF cryptococcal antigen, CSF PCR for TB, and CSF PCR for CMV excluded the more common neurological diseases in AIDS patients.

Although PCR for JCV of CSF has a varied sensitivity of 42-100 per cent, the high specificity of 95-100 per cent is excellent for confirmation of the diagnosis[1,2,18-20]. Positive predictive and negative predictive values of previous studies were 80-100 per cent and 88.5-95 per cent, respectively[13, 18-20]. The variability of these values may be due to methodological differences or alternatively to differences in the patients studied. Given the high positive predictive value of CSF PCR for the JCV, recovery of JCV DNA in CSF is a definite diagnosis in patients who have a high pre-test probability for PML as in the presented patient. However, the negative result of this test cannot exclude PML and brain biopsy should be performed to confirm the diagnosis[11].

There is no specific treatment for PML to date[21]. Cytarabine does not improve the prognosis of these patients[22] and cidofovir fails to demonstrate clinical benefit despite clearance of JC virus from the CSF[23]. In the era of HAART, numerous reports have shown the neurological response and improved survival in patients who receive HAART [24-28]. A combination of antiretroviral regimen including protease inhibitor reduces the progression to death by 63 per cent compared with no antiretroviral therapy[29]. Baseline CD4+ cell count is a strong independent survival prognostic factor; a higher CD4+

cell count is statistically associated with a reduction in the risk of death[29]. The mechanism of HAART in PML is immunorestoration[20]. The presented patient received HAART and survived with slight improvement of the neurological deficits.

To the authors' knowledge, this is the first case report of definite PML confirmed by PCR for JCV of CSF in Thailand. This data emphasizes the use of CSF PCR for JCV to confirm the clinical diagnosis of PML. Brain biopsy, an invasive procedure, may be avoided in patients with a positive result of this test.

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การติดเชื้อของไวรัส JC ในผู้ป่วยเอดส์ที่เป็นโรค Progressive Multifocal Leuko-encephalopathy : รายงานผู้ป่วยรายแรกในประเทศไทย

ทวีเกียรติ ดุจหนึ่งคุณากร, พ.บ., สมนึก สังฆานุภาพ, พ.บ.*, อัษฎา วิภากุล, พ.บ.*, วันทนิช ไพโรจน์, วท.ม.**, วสันต์ จันทราทิตย์, ปร.ด.**, จุฑาทิพย์ ศรีจันทร์รัศมี, วท.บ.**, จิรพร เหล่าธรรมทัศน์, พ.บ.***, ธีรธร พูลเกษ, พ.บ.**

Progressive Multifocal Leukoencephalopathy (PML) เป็นโรคทางระบบประสาทที่เกิดจากการติดเชื้อไวรัส JC โรคนี้เป็นสาเหตุการเจ็บป่วยและการตายที่สำคัญของผู้ป่วยโรคเอดส์ การวินิจฉัยที่แน่นอนต้องอาศัยการตรวจชิ้นเนื้อสมอง การตรวจหาเชื้อไวรัสนี้โดยวิธี polymerase chain reaction (PCR) เป็นวิธีที่มีความแม่นยำสูงในผู้ป่วยที่มีอาการทางคลินิกและผลการตรวจทางรังสีที่ชี้นำว่าเป็นโรคนี้ คณะผู้ศึกษาได้รายงานผู้ป่วยหญิงอายุ 36 ปี ที่มาด้วยอาการไข้เรื้อรัง แขนขาอ่อนแรงและพูดช้ามา 2 เดือน อาการทางคลินิกและผลการตรวจทางรังสีที่ชี้นำว่าเป็นโรค PML ผลการตรวจหาเชื้อไวรัสนี้ในน้ำไขสันหลังโดยวิธี PCR พบว่าได้ผลบวก

คำสำคัญ : Progressive Multifocal Leukoencephalopathy, ไวรัส JC, Polymerase Chain Reaction

ทวีเกียรติ ดุจหนึ่งคุณากร, สมนึก สังฆานุภาพ, อัษฎา วิภากุล, และคณะ
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 1139-1144

* ภาควิชาอายุรศาสตร์,
** ภาควิชาพยาธิวิทยา,
*** ภาควิชารังสีวิทยา, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400