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Progressive Multifocal Leukoencephalopathy in a Patient with Acquired Immunodeficiency Syndrome (AIDS) Manifesting Gerstmann's Syndrome

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Saito, H., Sakai, H., Fujihara, K., Fujihara, K. and Itoyama, Y. —— *Progressive Multifocal Leukoencephalopathy in a Patient with Acquired Immunodeficiency Syndrome (AIDS) Manifesting Gerstmann's Syndrome.* Tohoku J. Exp. Med., 1998, **186** (3), 169-179 ———— We reported a case of acquired immunodeficiency syndrome (AIDS) via multiple blood transfusions, who manifested progressive multifocal leukoencephalopathy (PML) about 18 months after the development of AIDS. PML initiated with right hemiparesis, dysphasia, and Gerstmann's syndrome and resulted in death within 2 months after the onset. Neuroimaging examinations revealed white matter lesions mainly in the left posterior parietal lobe. The cortical gray matter also showed abnormal signal intensity. Peripheral $CD4^+$ lymphocyte count was $81/\mu l$. Routine cerebrospinal fluid (CSF) examinations were negative. CSF antibodies against herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus as well as serum antibody against *toxoplasma gondii* were negative. Though autopsy or biopsy of the brain was not performed, JC virus genomes were detected in the CSF sample by a polymerase chain reaction, and their sequencing showed unique alterations of the regulatory regions, characteristic to PML-type JC virus. ———— AIDS; Gerstmann's syndrome; progressive multifocal leukoencephalopathy; JC virus isolation from CSF; PML-type regulatory regions

Progressive multifocal leukoencephalopathy (PML) is a subacute progressive demyelinating disease of the brain caused by an ubiquitous JC virus (JCV) infection to oligodendrocytes with no proven therapy (Åström et al. 1958; Berger et al. 1997). While PML had been a rare disease almost exclusively occurring in subjects with suppressed immunity, its prevalence has been markedly increasing since the advent of acquired immunodeficiency syndrome (AIDS) pandemic (Berger et al. 1987; Gillespie et al. 1991; Holman et al. 1991).

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The presence of antibody against JCV in more than 70% of general population indicates that the primary asymptomatic JCV infection occurs widely before adulthood (Padgett and Walker 1973). Viruria without clinical symptoms has been observed in pregnant women or aged subjects who have no overt dysimmunity (Kitamura et al. 1990; Markowitz et al. 1991). JCV may be detected from monocytes in the bone-marrow and spleen, or from blood of PML patients, but not in non-PML subjects (Houff et al. 1988; Talenti et al. 1992; Tornatore et al. 1992). Thus, it is generally believed that JCV latent in organs like the kidney or lymphocytes may be reactivated under the suppressed immunity, and is hematogenically disseminated to the brain (Aksamit 1995; Berger et al. 1997).

Generally, the definite diagnosis of PML requires histological confirmation of characteristic demyelinating lesions and identification of JCV in the lesion site. However, recent molecular technology has enabled the detection of viral genomes in the cerebrospinal fluid (CSF) as well as in the brain (Berger et al. 1997).

In this communication, we report a case, clinically suspected of PML associated with hemophilia-A and AIDS, who presented abnormal integrative functions including Gerstmann's syndrome. The diagnosis of PML was supported by the characterization of the regulatory regions of the JCV genomes isolated from the CSF, the detail of which was reported elsewhere (Sugimoto et al. 1998).

Case Report

This 29 year-old hemophiliac patient had received multiple transfusions of nonheated blood-products. In June, 1994, he visited a local hospital because of fever, pharyngeal pain and diarrhoea. Serological studies revealed positive antibodies against human immunodeficiency virus (HIV) and hepatitis C virus. Peripheral lymphocyte count was $1204/\mu l$, and $CD4^+$ lymphocyte count was $81/\mu l$ (6.7%). Immunoglobulins were within normal ranges. He was referred to the National Nishitaga Hospital on April 30, 1994. *Pneumocystis carinii* pneumonia was treated with trimethoprim-sulfamethoxazole and pentamidine isetionate. Didanosine was used for a treatment of HIV-1 infection. During admission he developed gingivitis, swelling of the left parotid gland and cervical lymphnodes, and furuncles on the buttock. In September 1994, he complained head heaviness, but neurological examinations and computerized tomograms (CTs) of the brain revealed no abnormalities (Fig. 1A). In October 1994, he developed herpes zoster of the thorax. In spring 1995, he developed candidiasis of the tongue and esophagus, and *pneumocystis carinii* pneumonia. In October 1995, he was admitted again because of frequent bouts of fever, moderate pancytopenia, and further decrease in $CD4^+$ lymphocytes. He also had oral candidiasis, herpetic eruptions of the lips and perianal abscess. No behavioral or psychic symptoms were noted. Since the middle of February 1996, he complained of difficulties in speech and calculation. Neurological examinations revealed the right inferior quadrant anopsia, generalized hyperreflexia with positive Hoffmann reflex on the right side.

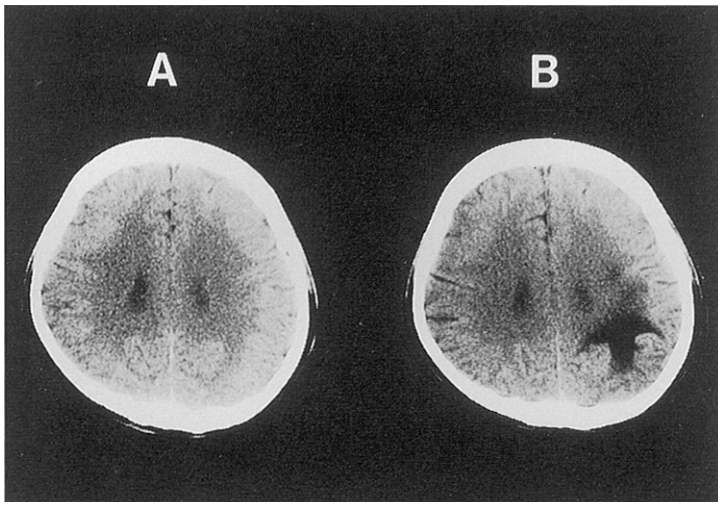

Fig. 1. Brain CTs of the patient, showing no abnormal images in September 1994 (A), but apparent low density areas in the white matter of the left posterior parietal lobe on February 16, 1996 (B).

He also presented dysphasia as well as Gerstmann's syndrome; severe aculculia, dysgraphia, right-left disorientation, and difficulty in finger-naming. Recognition of color, form, size and of line orientation as well as stereo-vision were preserved. On March 1, tests with Standard Japanese Aphasia Test Battery revealed that explanation of a comic strip, writing and dictation of words and sentenses either in *kanji* or *kana* were totally impossible. In contrast, oral repetition of words and short sentences as well as comprehension of words and short sentences written in *kanji* or *kana* were fully preserved. In other items, the rates of correct performance were 30 to 70%. On March 26, 1996, only limited numbers of tests were carried out because of his physical disability. Though the patient was cooperative throughout the examination, his responses were slow and instructions had to be often repeated due to his poor comprehension. The Western Aphasia Battery examination revealed atypical aphasia where his auditory comprehension was poor and his speech was non-fluent with reduced loudness and stuttering, but consisted of complete sentences. His intelligence was also impaired, being less than 60 in performance IQ of Wechsler Adult Intelligence Scale-Revised (WAIS-R). Because of aphasia, the verbal tasks was not performed. His visual memory was examined by the visual reproduction tasks from Wechsler Memory Scale-Revised. His immediate recall was slightly disturbed and delayed recall was severely disturbed. The result of Beck's depression test was within normal range.

CTs of the brain disclosed non-enhancing hypodense white matter lesions in the left parietal lobe without mass effect (Fig. 1B). On magnetic resonance images (MRI) of the brain, the irregular central part of the main lesion was hypointence in T1-weighted images, hyperintense on T2-weight images, and isointense in images by a fluid-attenuated inversion recovery (FLAIR) method. In T2-weighted and FLAIR images, the hyperintense peripheral part involved the

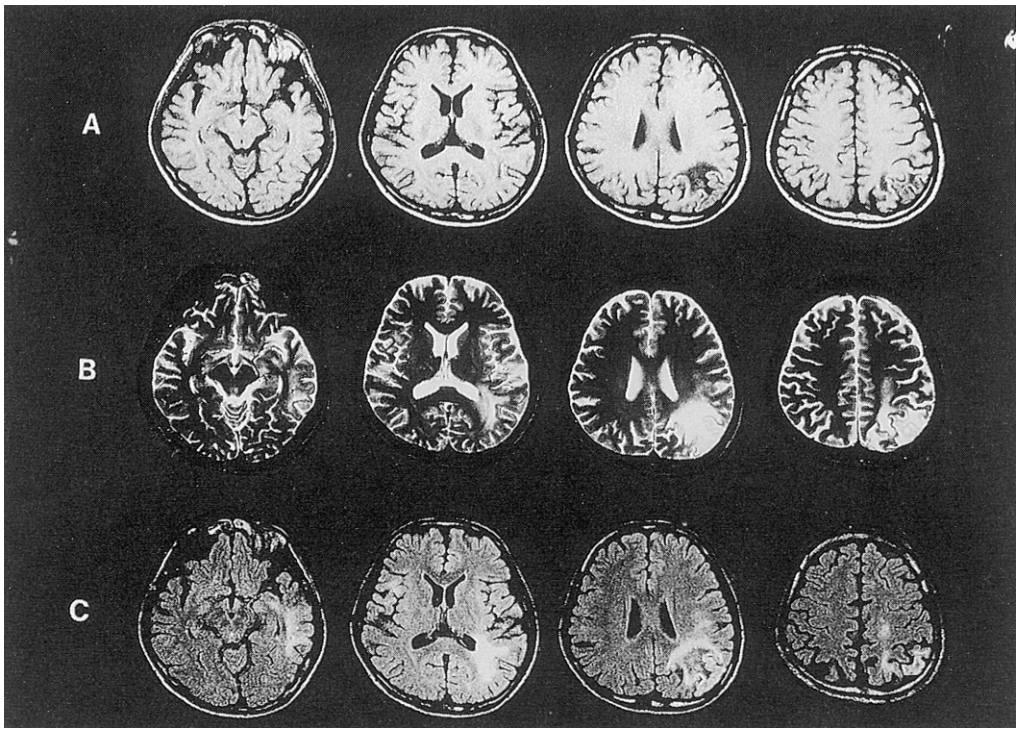

Fig. 2. MR images of the brain on March 4, 1996. The lesions involve mainly the subcortical structures in the parietal and temporal lobes, but also the gray matter of the parietal cortex. A small hyperintense area in the right fronto-parietal operculum is also visualized in B and C. A: T1-weighted images (TR: 600 milliseconds, TE: 16 milliseconds), B: T2-weighted images (TR: 4500 milliseconds, TE: 100 milliseconds), C: FLAIR images (TR: 6500 milliseconds, TI: 2000 milliseconds, TE: 100 milliseconds).

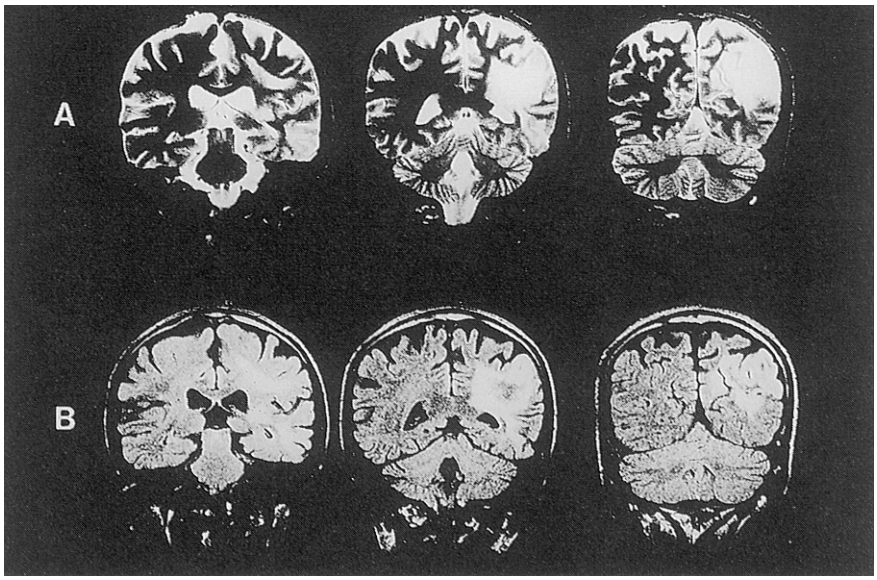

Fig. 3. Coronal MR images of the brain on March 4, 1996, showing parietal gray matter involvement. A: T2-weighted images (TR: 4500 milliseconds, TE: 100 milliseconds), B: FLAIR images (TR: 6500 milliseconds, TI: 2000 milliseconds, TE: 100 milliseconds).

gray matter of the posterior parietal cortex as well as the white matter of the temporal lobe. In addition, a small hyperintense area was visualized in the right fronto-parietal operculum (Figs. 2 and 3).

On March 5, 1996, CSF was under the opening pressure of 160 mmH_2O, and contained no cell, 0.29 mg/ml of protein, 0.35 mg/ml of glucose, and 126 mEq/liter of cloride. Stain and cultures were negative. Titers of serum antibodies were as follows; Epstein-Barr virus (EBV)-viral capsid antigen (VCA)IgG: $\times$320, herpes simplex-1 (HSV1) IgG: $\times$160, cytomegarovirus (CMV) IgG: $\times$39.8, toxoplasma IgG: less than $\times$3. Those in CSF against HSV1, VZV, CMV and EBV-VCA-IgM were negative. JCV regulatory region was successfully amplified by a nested polymerase chain reaction (PCR) from the CSF sample of the patient, but not from CSF samples from 80 non-PML patients. Furthermore, sequencing of the regulatory regions of the JCVs revealed unique deletions and/or duplications showing that the detected JCVs were of PML type (Sugimoto et al. 1998).

Since the end of March, right hemihypesthesia and hemiparesis became apparent, and dysphasia aggravated. The patient died on April 2. Permission for autopsy was denied.

Discussion

The present patient affected by HIV-1 had markedly decreased $CD4^+$ lymphocytes, recurrent *pneumocystis carinii* pneumonia and candidiasis. Thus, his condition was consistent with the diagnosis of AIDS. Two years after the recognition of AIDS, he developed focal cerebral dysfunctions which had initiated with mild right hemiparesis, dysphasia and Gerstmann's syndrome. His condition deteriorated rapidly and ended in death within six weeks after the onset of neurological deficits. Though the pathological confirmation was absent, the clinical diagnosis of PML was highly plausible because of focal cerebral manifestations and characteristic neuroimaging findings; hemispheric lesions involving predominantly white matter without mass sign or contrast enhancement (Whiteman et al. 1993; Giesen et al. 1997). Furthermore, the clinical diagnosis of PML was supported by the detection of JCV of PML type which will be discussed later.

Though there is no unique clinical picture of PML, a combination of hemiparesis, aphasia, visual dysfunction is common, while manifestation of cerebellar and brainstem lesions can be seen in about 10% of patients (Berger et al. 1997; Giesen et al. 1997). Gerstmann's syndrome (bilateral somatoagnosia) like in our patient has been also reported (Berger et al. 1987; Iranzo et al. 1992; Giesen et al. 1997). This syndrome consists of confusion of the right and left side of the body, inability to designate the different fingers of two hands, and inability to calculate and to write (Gerstmann 1924, 1957). There have been debates whether these four cardinal elements of Gerstmann's syndrome have a common base or only appear by chance association. Benton (1961) even regarded the syndrome as a

fiction or an artifacts of defective and biased observation. Isolated full syndrome is rare, and as our case, patients usually manifest, dysphasia, constructional apraxia, right homonymous hemianopsia. Hecaen (1972) stated that the sensory aphasia must be a necessary but not sufficient condition for the bilateral somatoagnosia. Still, Adams and Victor (1989) described that the syndrome has a special clinical significance in suggesting the lesions in the posterior parietal lobe of the dominant hemisphere, and that the essential feature of the syndrome may be an association of a defective body image; peripersonal spatial disorientation, and deficits in language and arithmetic functions centered in the dominant hemisphere.

In our patient, brain CT showed white matter lesions involving chiefly the posterior parietal lobe. Moreover, MRI revealed altered signal intensity of the overlying gray matter which we suspected to be the retrograde degeneration of the neurones due to axonal damage secondary to the severe loss of the myelin sheath. In cranial CT, only the late necrotic PML lesions are reportedly visualized and not the early foci of demyelination (Bosch et al. 1976). In AIDS-associated PML, the tissue destruction and cyst formation are more pronounced than in PML due to other causes of immunosuppression (Lang et al. 1989), and the gray matter is sometimes involved (Levy et al. 1986; Mark and Atlas 1989; von Einsiedel et al. 1993; Whiteman et al. 1993). These gray matter changes has been attributed to the followings; neuronal changes secondary to severe necrotic lesions in the white matter, JCV infection of oligodendrocytes distributed in the gray matter, concomitant HIV-1 or other viral encephalitis, or yet unknown process (Boudin et al. 1974; Levy et al. 1986; Rhodes et al. 1988; Vazeux et al. 1990; Sweeney et al. 1994).

PML had been a rare disease affecting immunocompromized hosts with lympho-proliferative diseases, other malignancy, autoimmune diseases or with dysmmunity of iatrogenic origins. Before 1984, its prevalence had been estimated approximately as 1.5 : 10 000 000 (Holman et al. 1991). However, the incidence has been markedly increasing since the spread of AIDS which is now a major single underlying disease of PML (Gillespie et al. 1991; Holman et al. 1991; Fong et al. 1995). Recent studies indicate that 55–85% of patients with PML have AIDS, and 4–7% of the AIDS patients develop PML (Berger et al. 1987, 1997; Lang et al. 1989). In addition, the patients with AIDS-associated PML are generally younger, the mean age being in the 3rd decade, while it occurs after the 6th decade among HIV-seronegative PML patients (Stoner et al. 1988; Giesen et al. 1997). Their course and pathological changes are more fulminant than those without AIDS (Rhodes et al. 1988; Stoner et al. 1988; Giesen et al. 1997), though exceptionally prolonged cases have been also reported (Berger and Mucke 1988). These observations suggest the possible interaction between HIV and JCV. The JCV T-protein transactivates the HIV long terminal repeat units (Gendelman et al. 1986). Conversely, Tada et al. (1990) suggested that the HIV-encoded *tat* protein may positively affect JCV gene expression.

Seroconversion to JCV occurs during childhood in the majority of the general population (Padgett and Walker 1973). Viruria without clinical symptoms has been observed in pregnant women or aged subjects who have no overt dysimmunity (Kitamura et al. 1990; Markowitz et al. 1991). Using PCR, Tornatore et al. (1992) demonstrated that approximately 40% of HIV infected subjects have JCV in peripheral blood lymphocytes in the absence of PML, whereas no immunologically competent subjects have JCV in peripheral blood lymphocytes. Therefore, PML is believed to result from either primary JCV infection (Gillespie et al. 1991), or more likely reactivation of JCV latent in such organs outside of the brain as the kidney or in B-lymphocytes (Houff et al. 1988; Aksamit 1995; Berger et al. 1997). Though the possible JCV latency in the CNS has been proposed (Talenti et al. 1990; Mori et al. 1992; White et al. 1992; Ferrante et al. 1995), this question still remains to be elucidated (Lipton 1991).

Two dominant regulatory regions configurations of JCV have been detected in human (Loeber and Dörries 1988). The first is archetypal JCV, which is excreted in the urine of normal and immunocompromized individuals (Yogo et al. 1990; Markowitz et al. 1991), and the second is PML type JCV found in PML brains. The latter group of variants appears to derived from archetypal JCV during their persistence by the deletions and duplications of sequences within the promotor-enhancer region; regulatory region. These mutations and rearrangements in the control elements of JCV may be responsible for their spread to and growth in the brain (Yogo et al. 1991; Ault and Stoner 1993; Aksamit 1995).

JCV-DNAs have been detected in the CSF samples from PML patients, HIV-infected patients without PML, and from individuals without PML or HIV-infection (Talenti et al. 1992; Tornatore et al. 1992; Gibson et al. 1993; Moret et al. 1993; Weber et al. 1994; Fong et al. 1995; McGuire et al. 1995; Antinori et al. 1997; Giesen et al. 1997; Sugimoto et al. 1998). Its diagnostic sensitivity varies from 62% to 100%, and specificity from 92% to 100% (Berger et al. 1997). Gibson et al. (1993) detected JCV genome in 10 of 13 CSF samples in patients with confirmed PML, while no amplification was obtained in 42 CSF samples from non-PML patients. Antinori et al. (1997) reported that in patients with AIDS-related focal brain lesions on CT or MRI without mass effect, the probability of PML increases up to 0.99, when positive JCV-DNA detection in CSF are combined with typical MRI pattern of PML.

Recently, Sugimoto et al. (1998) established a nested PCR for efficient amplification of the regulatory regions from most JCV subtypes, and amplified JCV regulatory regions from the CSF samples from the present case and other 3 morphologically proven cases of PML. In constrast, amplification was negative from 80 samples from patient without PML (Sugimoto et al. 1998). Furthermore, sequencing of the amplified fragments revealed that they had unique deletions and/or duplications. In 3 PML patients, the major regulatory sequences of the regulatory regions obtained from the brain tissue and CSF samples were identical

in each subjects. These findings indicate that JCV-DNA in brain lesions is excreted in the CSF, and that this method can rule out the possibility that amplification of JCV DNAs from CSF samples resulted from contamination with archetypal JCV DNAs from the same patients or with PML-type regulatory regions previously amplified from different patients. Thus, this method may be a useful diagnostic tool for PML, eliminating the need of invasive brain biopsy, though the morphological investigations remains crucial to elucidate disease process in each patient, especially the possibility of coexisting AIDS encephalitis or oppotunistic infections of the central nervous system.

The treatment of PML has not been established. Though there have been a vartiety of anecdotal reports on the efficacy of such medications as cytosine arabinoside and α-interferon, their benefits remain elusive (Hall et al. 1998). However, the patients with spontaneous remission or with an exceptionally long survival have been repeatedly reported indicating that PML is not always fatal (Kepes et al. 1975; Berger and Mucke 1988). The latter group includes the AIDS associated patients receiving anti-retroviral treatment (Conwey et al. 1990; Elliot et al. 1997; Domingo et al. 1997). According to Fong et al. (1995), AIDS-associated PML patients with $CD4^+$ lymphocytes less than $90/\mu l$ were of poorer prognosis than patients with $CD4^+$ lymphocytes more than that level. At present, the best strategy for HIV-1 associated PML might be the earlier diagnosis and reinforcement of the immune system by aggressive treatment with anti-retroviral drugs and adjunctive therapies, before the patients become intolerant of adverse effects of the medications.

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