Progressive Multifocal Leukoencephalopathy Complicating X-linked Hyper-IgM Syndrome in an Adult

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Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the central nervous system caused by reactivation of the human neurotropic polyomavirus, JC virus (JCV), in patients with impaired cell-mediated immunity. The incidence of PML is estimated to be about 3 per 1,000,000 in Japan. More than 85% of the patients with PML in recent years have had AIDS (1). PML in adulthood remains an exceedingly rare disease occurring with primary immune deficient disorders. The X-linked hyper-IgM syndrome (XHIM) is a primary immunodeficiency characterized by very low levels of or the absence of serum IgG, IgA and IgE with normal or increased serum IgM. XHIM is caused by mutations in the gene coding for CD40 ligand (CD40L), transmembrane protein expressed by activated T cells. Because patients with XHIM have deficits in both humoral and cell-mediated immunity, they experience recurrent bacterial and opportunistic infections from shortly after birth, and most patients with this disorder die before 20 years of age (2). Here, we present an adult patient with a novel mutation in the CD40L gene; unlike classic XHIM patients, the patient was almost asymptomatic until the age of 37, when he presented with PML.

A 37-year-old Japanese man complained of visual disturbance. He had left side hemianopia and slight hemiparesis in the left side. His parents had no symptoms. His younger brother died of pneumonia in childhood. Brain MRI showed respective hypointensity and hyperintensity areas on T1- and T2-weighted images in the deep white matter of the bilateral occipital, parietal, and temporal lobes (Fig. 1A). Those areas were not enhanced with gadolinium. Laboratory findings showed that the complete blood count was normal and abnormal serum immunoglobulins, IgG 539 mg/dl (reference range: 870-1700 mg/dl), IgA <5 mg/dl (reference range: 110-410 mg/dl), and IgM 448 mg/dl (reference range: 33-190 mg/dl). The human immunodeficiency virus antibody was negative. Cerebrospinal fluid showed 9μl (lymphocytes), glucose 50 mg/dl, and protein 41 mg/dl. After informed consent was obtained, brain biopsy was performed from the right occipital lobe; specimens revealed hyperchromatic enlarged oligodendrogial nuclei, enlarged bizarre astrocytes, and foamy macrophages. In situ hybridization and electrophoresis of the PCR products, performed by the method of Seyama et al (3), suggested JC virus infection in the brain (Fig. 1B&C). Peripheral blood mononuclear cell were stimulated with phorbol 12-myristate 13-acetate and inomycin. CD3 and CD40L expression was determined using two-color flow cytometry with CD3-APC-labeled mAb and CD40L-FITC-labeled mAb. He had a defective CD40L expression (Fig. 1D). A novel missense mutation (Leu225 Ser) of the CD40L gene was recognized. The diagnosis was made as PML complicating XHIM. Although he was treated with intravenous immunoglobulin twice a week for three months, he developed akinetic mutism.

PML in non-AIDS has rarely occurred as a consequence of organ transplantation, leukemia and lymphoma, and systemic lupus erythematosus over the last ten years (1). Until 1999 only 2 patients of the 156 PML were not AIDS related, Hodgkin’s disease or Wiskott-Aldrich syndrome (4). Redfearn et al reported a 6-year-old boy with PML complicating XHIM (5). CD40L molecules are required for B-cell activation and the production of IgG, IgA, and IgE in response to T cell-dependent antigens. Therefore, patients with XHIM have recurrent infections in childhood and develop chronic diarrhea and severe hepatobiliary disease associated with a poor prognosis. The survival rate is poor (about 20% at 25 years) (2). The present patient was almost asymptomatic until the age of 37 though XHIM is a rare and life threatening condition. Recently several adult men diagnosed as affected by common variable immunodeficiency, also called acquired hypogammaglobulinemia, adult-onset hypogammaglobulinemia, or dysgammaglobulinemia, have been found to have XHIM (6). PML is a complication of XHIM and could be the initial manifestation of the disease.

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Figure 1. A: MR images of the brain. T2-weighted MRI shows a hyperintensity area in the deep white matter. B: In situ hybridization for JC virus genome. C: Agarose gel electrophoresis of the PCR products for JC virus. Lane M, molecular size marker; NC, non-PML patient's brain PCR for JC; JC1 and JC2, the present patient's brain PCR for JC virus. D: Cell surface expression of the CD40L. T cells from the patient failed to express the CD40L.

References