X-linked Hyper-IgM Syndrome Associated With a Rapid Course of Multifocal Leukoencephalopathy

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Objective: To report an exceptional association between X-linked hyper-IgM syndrome and progressive multifocal leukoencephalopathy.

Design: Clinical, immunological, and histological analysis.

Patient: A 19-year-old male patient with X-linked hyper-IgM syndrome developed typical signs and symptoms of progressive multifocal leukoencephalopathy.

Results: The serum level of IgA was decreased; the serum level of IgM was slightly increased; and the serum level of IgG was normal as a result of monthly infusions of immunoglobulin. The expression of CD40 ligand on T cells was markedly reduced in the patient. Magnetic resonance imaging indicated confluent lesions involving the majority of the right hemisphere with a mass effect. The patient died after 6 weeks despite combined antiviral treatment.

Conclusion: Progressive multifocal leukoencephalopathy may follow a rapid course in patients with X-linked hyper-IgM syndrome because of global defects of cellular and B cell responses.

Arch Neurol. 2007;64:273-276

X-LINKED HYPER-IGM SYNDROME (X-HIGM) is a rare primary immunodeficiency disorder caused by a mutation in the gene encoding for CD40 ligand (CD40L) expressed on the surface of activated T cells. This molecule is necessary for T cells to induce isotype switching in B cells by binding to CD40. Because of the class switch recombination defect, patients with HIGM have decreased serum levels of IgG, IgA, and IgE, and elevated or normal levels of serum IgM. Signals generated by CD40L are also important in priming T cells and inducing IL-12 production by macrophages and dendritic cells. Thus, in addition to the defective production of antibodies, cellular immune responses that are critical for protection against intracellular pathogens are also impaired.

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system. The disease is caused by opportunistic infection by the JC virus (JCV). The primary infection is common and usually remains asymptomatic. The virus resides in the kidney in a latent form and can be reactivated when the immune system becomes compromised. B cells may transmit the virus to oligodendrocytes in the brain. Lysis of oligodendrocytes results in multiple and progressive central nervous system symptoms.

Progressive multifocal leukoencephalopathy affecting patients with congenital immunodeficiencies is exceptional. Herein, we report a unique association between X-HIGM and PML, which resulted in an unusually rapid progression that led to death within 6 weeks despite antiviral treatment.

CASE REPORT

A 19-year-old right-handed male patient was admitted to our neurology department because of progressive left faciobrachial paresis. He had been treated for X-HIGM since the age of 3 years. His brother died of pneumonia at 9 years of age after several recurrent episodes of aphthous stomatitis, upper and lower respiratory tract infections, purulent otitis media, mastoiditis, and bacterial pneumonia. Sequence analysis of the CD40L gene in the patient revealed a hemizygous C→A transversion at nucleotide position 216 in

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exon 2 and heterozygosity for this mutation in the genomic DNA from his mother. This mutation resulted in stop codon at amino acid 72 (p.C72X). Expression of CD40L was tested by flow cytometry as previously described. Heparinized whole blood samples were activated with 10 ng of phorbol myristate acetate per milliliter of blood (Sigma-Aldrich Corp, St Louis, Mo) and 250 ng of ionomycin per milliliter of blood (Calbiochem, San Diego, Calif) for 4 hours at 37°C in an atmosphere containing 5% carbon dioxide. Anti-CD69 staining was performed as a positive control to T cell activation. The expression of CD40L on CD4+CD69+ T cells of the patient was 4% in contrast to 100% of control cells. The patient was treated with regular monthly intravenous immunoglobulin infusions and occasionally with recombinant human granulocyte colony-stimulating factor because of recurrent neutropenia. He developed severe opportunistic infections, including Cryptococcus laurentii meningitis and esophageal candidiasis. One year before his admission, a hepatitis C virus infection was diagnosed, but no treatment had been initiated because of his neutropenia.

On admission, the patient complained of dizziness and an unsteady gait, followed by weakness of his left extremities and apathy after 4 days. Neurologic examination revealed left central facial and hypoglossus nerve palsy, visual neglect, left-sided hemiparesis with increased deep tendon reflexes, the Babinski sign, and spasticity. Decreased proprioceptive sensation was found on the left side of the body. His movements, speech, and attention were slowed, but memory and body perception were maintained; neither aphasia nor apraxia was detected. Electroencephalography showed a nonspecific diffuse slowing of background activity above the right frontotemporal regions. Cerebrospinal fluid examination revealed normal protein levels (0.25 g/L) and glucose content without cells. No intrathecal immunoglobulin synthesis or damage of blood-brain barrier were found (IgG index, 0.7) (no oligoclonal bands were detected by isoelectric focusing). Cultures were negative for bacteria and fungi. Antiviral antibodies for cytomegalovirus, varicella-zoster virus, herpes simplex virus 1, and herpes simplex virus 2 were not found; herpes simplex virus type 1 DNA could not be detected by polymerase chain reaction in the cerebrospinal fluid. Serology tests were negative for the human immunodeficiency virus (HIV). Immunoglobulin levels in the serum were measured twice. IgG levels were normal (6.9 g/L; normal range, 6-16 g/L), IgM levels were slightly increased (2.18 g/L; normal range, 0.5-2.0 g/L), and IgA levels were reduced 4 days after the patient's first symptoms (<0.2 g/L; normal range, 0.8-
against simian virus 40 (SV40) polyoma subgroup (diently stained by a cross-reactive, polyclonal antibody
godendrocytes loaded with nuclear inclusions (Figure,
lipid-laden macrophages with vacuoles, and scattered oli-
ventricle was slightly compressed.

Brain biopsy revealed hypertrophic giant astrocytes,
lipid-laden macrophages with vacuoles, and scattered oli-
godendrocytes loaded with nuclear inclusions (Figure, B and C). The oligodendrocytic inclusions were posi-
tively stained by a cross-reactive, polyclonal antibody
against simian virus 40 (SV40) polyoma subgroup (di-
lution, 1:200)10 (Figure, D). Based on the clinical, his-
tological, and immunohistochemistry findings, PML was
diagnosed, and thus polymerase chain reaction for JCV
in the cerebrospinal fluid or in situ hybridization was not
performed. The patient was treated with a combination
of interferon alpha (3 million IU, subcutaneously, 3 times
a week) and ribavirin (1200 mg daily), but he died with-
out improvement after 6 weeks.

Autopsy was performed and the formalin-fixed brain
was cut 4 weeks after death. Coronal brain slices con-
ﬁrmed asymmetrically conﬂuent areas of abnormal pa-
renchyma with cavitation of the white matter in the brain
and the brainstem (Figure, E and F).

The remarkably rapid progression of PML and the un-
usually large lesions involving the major part of the right
hemisphere suggested an unlimited propagation of JCV.
While absence of contrast enhancement was typical and
helpful in differentiation of PML from central nervous
system lymphoma, the involvement of the frontal lobe
and the mass effect were somewhat atypical.

Progressive multifocal leukoencephalopathy has been
increasingly detected in patients with AIDS and other sec-
ondary immunodeﬁciency conditions.11–13 However, the
disease is exceptional in primary immunodeﬁciencies, and
only a single case of PML associated with X-HIGM has
been reported.7 The central importance of T cells in con-
taining the replication of viruses is well established.14–16
Thus, a reduced number of CD4+ T cells and impaired
PML-speciﬁc CD8+ T cell responses may justify the high
frequency of PML in acquired immunodeﬁciencies.17–19
In contrast, the number of T cells is retained in X-HIGM,
which may explain the rarity of PML. However, im-
paired cellular immune responses should play a central
role in the evolution of PML in X-HIGM as well, be-
cause serum levels of IgG were normal and serum levels
of IgM were slightly increased while PML rapidly pro-
gressed in our patient. The markedly reduced CD4+LOL on
T cells certainly interferes with T cell activation because
of a deﬁcient costimulation in X-HIGM. The altered co-
stimulation may result in decreased priming of T cells
and production of interferon-γ as well as impaired func-
tions and IL-12 production of macrophages and den-

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