Atypical Progressive Multifocal Leukoencephalopathy Associated With an Unusual JC Polyomavirus Mutation

Emma C. Tallantyre, BMBS; Simon M. L. Paine, BMBS; Colin P. Sharp, PhD; James S. Lowe, DM; Bruno Gran, MD, PhD

**Objective:** To report the clinical and radiologic features in a patient with myelofibrosis who developed atypical progressive multifocal leukoencephalopathy.

**Design:** Case report.

**Setting:** Tertiary referral center.

**Patient:** A 72-year-old man with myelofibrosis and mild leukopenia experienced progressive limb weakness and dysarthria.

**Results:** Imaging revealed almost complete sparing of the white matter with isolated involvement of the brainstem and deep gray matter. Postmortem examination led to definitive diagnosis of progressive multifocal leukoencephalopathy and demonstrated an unusual miliary pattern of disease rather than the typical confluent involvement. Genetic analysis revealed a mutation in the transcription control region of the JC polyomavirus, prompting speculation about the pathogenesis of progressive multifocal leukoencephalopathy.

**Conclusions:** Leukopenia may render patients effectively immunosuppressed. The differential diagnosis should include progressive multifocal leukoencephalopathy even in patients with atypical clinical and radiologic features.

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**PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)** is a rare demyelinating condition caused by reactivated JC polyomavirus (JCV). The illness almost always occurs in the context of immunocompromise, usually from human immunodeficiency virus (HIV) or AIDS. We report atypical findings of PML in a patient with myelofibrosis that highlight the importance of recognizing functional immunosuppression in patients with mild leukopenia.

**PHYSICAL EXAMINATION**

At admission, respiratory and cardiovascular systems were functioning normally; however, there was palpable splenomegaly. Affect and cognition seemed normal. (The Mini-Mental State Examination score was 28 of 30.) There was mild dysarthria. Tongue movements were slow; however, the tongue showed no wasting or fasciculations. Jaw jerk was brisk; however, there were no primitive reflexes. Findings from an ophthalmic examination showed slightly slow horizontal saccades and jerky pursuits.

There was wasting of the limb girdle and torso musculature but no fasciculations. Power of shoulder abduction and fin-
Flexion was slightly reduced bilaterally, with increased tone in the right upper limb and mild bradykinesia. In the lower limbs, there was bilateral proximal weakness, more marked on the right side (a chronic feature attributed to previous poliomyelitis), and tone was normal. Reflexes were brisk and symmetric in the upper limbs, normal in the left lower limb, and absent in the right lower limb. Plantar reflexes were equivocal. There was slight intention tremor in the right upper limb but no gait ataxia. Sensation was normal. The patient could transfer from bed to chair independently and walked the length of the ward with unilateral assistance.

**CLINICAL EXAMINATION**

Results of a full blood cell count at admission yielded stable values since the diagnosis of myelofibrosis: hemoglobin, 9.5 g/dL (to convert to g/L, multiply by 10.0); leukocytes, 3600/µL (to convert to ×10⁹/L, multiply by 0.001); lymphocytes, 750/µL (to convert to ×10⁹/L, multiply by 0.001); and platelet count (thrombocytes), 26 × 10³/µL (to convert to ×10⁹/L, multiply by 1.0). A blood film showed no evidence of malignant transformation. Values for the levels of red cell folate, vitamin B12, creatine kinase, CA19-9, thyroid stimulating hormone, α-fetoprotein, urea and electrolytes, carcinoembryonic antigen, erythrocyte sedimentation rate and antibodies to nuclei, mitochondria, smooth muscle, thyroid peroxidase, glutamic acid decarboxylase, acetylcholine-receptor, and Hu, Yo, and Ri antigens were within normal limits. There was no serum paraprotein, and syphilis serology was negative.

Nerve conduction studies showed global reduction in sensory nerve action potential amplitude and a slight reduction in tibial and common peroneal compound muscle action potential with normal conduction velocity. Electromyography was not performed because of thrombocytopenia. A magnetic resonance (MR) image of the brain demonstrated mild atrophy and patchy T2-weighted hyperintensity in the left pons, thalami, medulla, striatal structures, and middle cerebellar peduncle (Figure 1 A). Spirometry, chest radiography, MR imaging of the spine, electroencephalography, and computed tomography of the thorax and abdomen yielded noncontributory findings.

Within 2 months of admission, the patient developed decreasing tone and bradykinesia in the limbs and required a wheelchair for mobility. There was mild symptomatic improvement after a trial of levodopa therapy. Repeat MR images obtained 3 weeks after admission revealed little change from previous findings. During the next 3 weeks, there was worsening of dysarthria and limb weakness and development of dysphagia and bilateral facial weakness. Power was Medical Research Council grade 2 in the left upper limb but grade 0 in all other limbs. There were some self-terminating episodes of shaking of the right arm and leg and some facial grimacing that seemed involuntary. Speech became incomprehensible. Palliative care was adopted, and the patient died on July 6, 2006, 8 months after development of the initial symptoms.

**RESULTS**

**POSTMORTEM EXAMINATION**

At necropsy, the cause of death was determined to be severe pneumonia. Extramedullary hemopoiesis had re-
sulted in massive splenomegaly; however, there was no malignant transformation of the underlying myelofibrosis. The external appearance of the brain was normal. However, multitudinous recessed lesions smaller than 1 mm in greatest diameter were distributed in a striking military pattern throughout the cerebral hemispheres, predominantly at the gray-white matter interface. Microscopically, these areas occurred throughout the brain and consisted of focal myelin loss and gliosis with gemistocytic astrocytes and oligodendroglia with large basophilic nuclear inclusions and eccentric clumped chromatin (Figure 1B). Electron microscopy showed that the inclusions contained abundant virions that were confirmed to be JCV at immunohistochemistry (Figure 1C-E). There was no evidence of any other underlying pathologic process such as caused by HIV infection.

**POLYOMAVIRUS DETECTION AND GENETIC ANALYSIS**

The DNA extracted from affected brain tissue was positive for JCV sequences but not for other known human polyomaviruses (BK, WU, and KIPy) at polymerase chain reaction. The transcriptional control region (TCR) of JCV spans the origin of replication through to the first ATG start codon for late gene transcription. To look for TCR rearrangements in this patient, the TCR was amplified from brain tissue DNA using the polymerase chain reaction and cloned into the pCR-Blunt II-TOPO vector for sequencing. Analysis of 7 cloned sequences relative to archetypal JCV revealed a 75-base pair deletion and insertion of motifs C through E (clone 6) or motifs B through E (clone 7). Arrows indicate first nucleotide positions of these elements; mRNA indicates messenger RNA; NF-1, nuclear factor-1 binding site; Sp1, Sp-1 transcription factor binding site; TATA, complete TATA box; and TAR, Tat-responsive DNA homologous element.

**COMMENT**

The clinical manifestations of PML vary widely; however, typical features of monoparesis or hemiparesis, homonymous hemianopia, cognitive decline, dysarthria, and ataxia seem common to both HIV-positive and HIV-negative patients. In our patient, the unusual features of muscle wasting and extrapyramidal signs, the absence of cognitive deficits, and atypical findings at MR imaging led us to consider a diagnosis of motor neuron disease (amyotrophic lateral sclerosis) or multiple system atrophy. Neuroimaging usually reveals extensive areas of patchy or confluent, often asymmetric (subcortical), white matter abnormality with relative sparing of the spinal cord, cortical gray matter, and posterior fossa structures. In contrast, our patient had cerebral atrophy and scarce white matter involvement confined to the posterior fossa. Postmortem examination revealed extensive cortical demyelination that was undetected at MR imaging.

Serologic studies for HIV were not performed in this patient; however, at postmortem examination, no features of HIV infection were identified. Chronic lymphocytic leukemia and non-Hodgkin lymphoma are also increasingly reported in association with PML, possibly because of the high dosages of immunosuppressive agents used in treatment of these conditions. Our patient had myelofibrosis, a myeloproliferative disorder that can cause cellular immunodeficiency as a result of underprodu-
tion and dysfunction of white blood cells, and also received thalidomide, which has been associated with leukopenia. The lowest leukocyte count (2800/µL; lymphocytes, 600/µL) was reached in mid-February 2006, 2 months before admission because of neurologic symptoms. Although PML has not been described in the context of myelofibrosis, it was recently reported in a patient with polycythemia vera treated with thalidomide. Polycythemia vera carries a considerable risk of transformation to secondary myelofibrosis. In our patient, it is conceivable that myelofibrosis and thalidomide may have contributed to reactivation of JCV.

At postmortem examination, we used the polymerase chain reaction to characterize mutations within the viral TCR, which contains promoter and enhancer sequences associated with control of early and late gene expression and is important for virus survival and replication. Duplications of the TAR element, a late JCV promoter located within the TCR, are often noted in patients with HIV-associated PML. The TCR analysis in our patient revealed absence of the TAR element (Figure 2), which suggests a nonessential role of the TAR sequence in the development of PML. We also found an additional nuclear factor–I binding site, which supports the hypothesis that the nuclear factor–I motif has a role in HIV-independent PML.

In recent years, PML has been diagnosed more commonly in association with new causes of immunosuppression. This case illustrates that leukopenia may render a patient effectively immunosuppressed and that PML should be included in the differential diagnosis even in patients with atypical clinical and radiologic features.

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Correspondence: Bruno Gran, MD, PhD, Division of Clinical Neurology, University of Nottingham, Room B31 Medical School, Queen’s Medical Centre, Nottingham NG7 2UH, England (bruno.gran@nottingham.ac.uk).

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