Prolonged Progressive Multifocal Leukoencephalopathy Without Immunosuppression

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**ABSTRACT:** Atypical forms of progressive multifocal leukoencephalopathy (PML) may simulate other disorders. A previously healthy 70-year-old female developed unsteadiness of gait, dysarthria, dementia and weakness leading to inanition and death from bronchopneumonia over a 43 month period. The diagnosis of PML was not suspected prior to death.

Neuropathologic examination of the brain disclosed characteristic findings of PML—deep bilateral cerebral demyelinating foci with enlarged gemistocytic astrocytes and swollen oligodendrocytes containing intranuclear inclusions. Electron microscopy identified papova virus particles within these inclusions. An underlying source of immunosuppression was not identified either premortem or at the time of autopsy.

The prolonged clinical course, simulating that of a primary degenerative disease, and the lack of apparent immunocompromise are unusual features of PML and lend credence to the suggestions that variations in its expression and course are to be expected.

**RESUME:** Leuco-encéphalopathie multifocale progressive de longue durée sans immunosuppression. Des formes atypiques de leuco-encephalopathie multifocale progressive (LMP) peuvent simuler d'autres affections. Une femme âgée de 70 ans, jusque là en bonne santé, a développé une démarche instable, de la dysarthrie, de la démence et de la faiblesse conduisant à l'inanition et au décès par bronchopneumonie dans un délai de 43 mois. Le diagnostic de LMP n'avait pas été soupçonné avant le décès.

L'examen neuropathologique du cerveau a révélé des manifestations caractéristiques de LMP — des foyers de démyélinisation bilatéraux situés profondément dans le cerveau contenant des astrocytes gemistocytaires augmentés de volume et des oligodendrocytes oedématisés contenant des inclusions intranucléaires. Des particules de papova-virus à l'intérieur de ces inclusions ont été identifiées à la microscopie électronique. Aucune cause d'immunosuppression sous-jacente n'a été identifiée avant la décès ou à l'autopsie.

L'évolution prolongée de la maladie, simulant celle d'une maladie dégénérative et l'absence de déficit immunitaire apparent sont des manifestations inhabituelles de LMP et sont en faveur de l'hypothèse selon laquelle on peut s'attendre à observer des variations dans l'expression et dans l'évolution de cette maladie.
progressive weakness and unsteadiness of her lower limbs, in spite of
which she managed her affairs appropriately while living alone. Past
medical history was uneventful and she took no regular medications.
Functional review and family history were non-contributory.

General physical examination disclosed pallor, a blowing systolic
aortic murmur, osteoarthritic finger deformities and a blood pressure of
120/70. Neurological examination was limited by her difficulty follow­
ing commands. She was alert and oriented but slow to answer questions.
Speech was dysarthric. Extracranial movements were full but she had
impaired smooth pursuit. She appeared to have generalized weakness,
especially in distal muscle groups, most marked on the right. Deep
tendon reflexes were present and symmetric with the exception of
absent ankle jerks. Both toes were upgoing on plantar stimulation.
Sensory examination disclosed mild loss of vibration and position
sense distally in the feet. She ambulated with a walker, leaning forward
and dragging her feet, particularly on the right.

The following investigations were normal: hemoglobin, white blood
count, platelet count and peripheral blood smear; serum glucose, urea,
creatinine, uric acid, creatine kinase, lactic dehydrogenase, gluta­
mic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline
phosphatase, B12 and folate; RBC folate; thyroid studies; electro­
cardiogram; skull x-ray; isotope brain scan; electromyography and
nerve conduction studies. Erythrocyte sedimentation rate was 18 mm/hr.
Chest x-ray showed possible segmental atelectasis at the left base but
was otherwise normal. Urinalysis revealed a few white cells and bacte­
ria but culture yielded no growth. An EEG showed excessive slow
activity from both cerebral hemispheres, at times more prominently
from the right posterior head region. A CT scan (EMI) of the head with
and without intravenous contrast revealed only generalized cerebral
atrophy.

Over the next two years her condition advanced. She became extremely
confused, choked on her food, and developed joint contractures in her
lower limbs such that she had to be lifted from bed to chair. Death
resulted from bronchopneumonia 43 months following the onset of
symptoms.

PATHOLOGY

The immediate cause of death was bronchopneumonia particu­
larly involving the basilar and dependent portions of the right
lung. There was evidence of foreign body reaction from chronic
aspiration. A sodium level of 188 mmol/l in vitreous humor
indicated severe premortem dehydration. Other findings included
a calcific nodule of the mitral valve, mild arteriosclerosis and
two villous adenomas of the rectum. An extensive search for
occult malignancy included analysis of vertebral marrow and
sections of lymph nodes, spleen and liver. Evidence of malig­
nancy or a systemic disease associated with immunocompromise
was not discovered. There was no evidence that she had suf­
f fered multiple or sequential opportunistic infections.

The brain was transferred in formalin to University Hospital
for neuropathological examination. Brain weight was 1180 grams
prior to fixation. Coronal sections of the brain of 10 mm thick­
ness disclosed moderate cortical atrophy and dilatation of the
ventricular system. Small areas of soft grey discoloration were
identified in the centrum semiovale especially in the superior
and medial aspects of the frontal, parietal and occipital lobes.
The corpus callosum was thin. The cerebellum and brainstem
appeared normal to gross examination.

Myelin staining of microscopic sections of white matter iden­
tified numerous patches of demyelination (Figure 1). When
confluent, these areas corresponded to areas of discoloration
noted grossly. Lesions were found on sections of the centrum
semiovale but were not noted in white matter tracts of the
cerebellum and brainstem. The areas were patchy, asymmetric
and variable in size. Stains for axon cylinders demonstrated
relative axon preservation. Under higher power, the lesions
were occupied by enlarged gemistocytic astrocytes, frequently
containing one or more bizarre pleomorphic nuclei (Figure 2).
There was no consistent relationship between areas of demye­
lination and the presence of vessels. Collections of mononu­
clear cells were observed, however, cuffed small blood vessels
in non-demyelinated portions of the white matter (Figure 3). At
the edges of the demyelinated zones, there were oligodendrocytes
with swollen discoloured nuclei identified under oil immersion
as containing inclusion bodies (Figure 4). Thin sections of the
formalin fixed lesions were stained with lead citrate and uranyl
acetate for electron microscopy. Arrays of rounded viral parti­
cles occupied nuclei of oligodendrocytes (Figure 5); the parti­
cles measured 36.5 nm in diameter and were morphologically
consistent with papova virus. Other than an occasional neurofi­
 brillary tangle without associated plaques in the left parahippocampal
 gyrus and changes of arteriosclerosis in blood vessels,
further findings were not encountered-examination of both
hippocampi was normal; multiple infarcts were not observed.
Specific degeneration of descending motor tracts (in view of the
history of upgoing plantar responses) was not identified but the
spinal cord was unavailable for review.

DISCUSSION

The neuropathologic findings in this patient are characteris­
tic of PML. The clinical features, however, are unusual. No

Figure 1 — Section of occipital lobe stained for myelin (Solochrome R x 1.8).
Note numerous punctate areas of white matter demyelination.
evidence of systemic immunosuppressive disease was encountered during her two years in hospital or at autopsy. Her course, extraordinarily prolonged, simulated that of a primary degenerative disorder.

PML without immunosuppression, termed ‘primary PML’, is reported in a small number of previous publications. Had the diagnosis been suspected premortem, provocative skin testing or other tests may have demonstrated an immune defect. Anergy has been observed in normal elderly patients rendering its potential usefulness in our patient uncertain. Our patient had lymphocytic cuffing of small vessels, a finding linked to intact immunity in other cases of ‘primary PML’.

The diagnosis of PML was not made before death because her slowly progressive motor and intellectual decline misled the attending physicians into believing she had a degenerative disorder such as multisystem atrophy or Alzheimer’s disease. In 80% of cases PML leads to death in 9 months. Rare cases lasting up to several years have been reported and are often examples of primary PML. Some prolonged cases have also been observed in association with immunosuppressive or other conditions. Previously reported atypical cases of PML with a prolonged course or without immunosuppression are listed in Table 1. We did not identify under any other disease process which could account for our patient’s slow neurologic demise. At autopsy her lesions were widespread and bilateral involving white matter correlating with the clinical findings of dementia, dysarthria, dysphagia and quadriparesis. The lesions were likely too small to be identified on the CT scan. Death was due to aspiration, dehydration and inanition complicating her neurologic state.

Our case provides a further illustration of the variable clinical features of PML and suggests that it be included in the differential diagnosis of degenerative neurologic disease. Variations in the course of PML with apparent remissions shed doubt on reports of beneficial treatment in single patients and underline the need for a controlled trial of treatment.

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Table 1: Reported Cases of Prolonged PML or PML Without Immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>Age/Sex*</th>
<th>Duration</th>
<th>Presentation</th>
<th>Associated Disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman and Rubinstein</td>
<td>64F</td>
<td>7 months</td>
<td>dementia</td>
<td>none</td>
</tr>
<tr>
<td>Stain</td>
<td>7M</td>
<td>20 years</td>
<td>tremor, poor handwriting</td>
<td>?</td>
</tr>
<tr>
<td>Fermaglich et al</td>
<td>44M</td>
<td>3 years</td>
<td>seizures</td>
<td>none</td>
</tr>
<tr>
<td>Bolton and Rozdilsky</td>
<td>40M</td>
<td>18 months</td>
<td>nervousness, clumsiness, dysarthria</td>
<td>none</td>
</tr>
<tr>
<td>Arseni and Nereantu</td>
<td>26M</td>
<td>1 month</td>
<td>hemiparesis</td>
<td>none</td>
</tr>
<tr>
<td>Faris and Martinez</td>
<td>55F</td>
<td>22 months</td>
<td>blindness</td>
<td>none</td>
</tr>
<tr>
<td>Rockwell et al</td>
<td>43F</td>
<td>3.5 +years</td>
<td>paraesthesia, dysarthria, weakness</td>
<td>none</td>
</tr>
<tr>
<td>Brun et al</td>
<td>33F</td>
<td>33 years</td>
<td>vertigo, poor balance, poor vision</td>
<td>anemia</td>
</tr>
<tr>
<td>Kepes et al</td>
<td>47M</td>
<td>10 years</td>
<td>clumsiness, numbness</td>
<td>sprue</td>
</tr>
<tr>
<td>Hedley-Wyby et al</td>
<td>63M</td>
<td>5 years</td>
<td>dementia</td>
<td>lympho-sarcoma</td>
</tr>
<tr>
<td>Schlitt et al</td>
<td>55M</td>
<td>5 + years</td>
<td>dementia, headaches, blurred vision</td>
<td>lymphoma</td>
</tr>
<tr>
<td>Present case</td>
<td>70F</td>
<td>43 months</td>
<td>weakness, tremor</td>
<td>renal transplant</td>
</tr>
</tbody>
</table>

*+ alive at publication
*age at onset of PML
REFERENCES


