Prolonged Progressive Multifocal Leukoencephalopathy Without Immunosuppression

Douglas W. Zochodne and John C.E. Kaufmann

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 demyelinative 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 nor 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.

RÉSUMÉ: Leuco-encéphalopathie multifocale progressive de longue durée sans immunosuppression. Des formes atypiques de leuco-encéphalopathie 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 gémistocytaires augmentés de volume et des oligodendrocytes oedèmatiés contenant des inclusions intranucléaires. Des particules de papovavirus 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.

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Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of brain white matter. Papova virus, usually JC type, has been cultured from the brain of PML patients.[1] Viral particles may be identified in oligodendroglial nuclei[2] and virus specific DNA has been reported in both oligodendroglial nuclei and transformed astrocytic nuclei observed in the lesions.[3]

Although the papova virus is ubiquitous,[4] brain infection occurs when host defences fail. The first reported cases of PML complicated leukemia and Hodgkin's disease.[5] Subsequent reports have linked PML with malignancy, autoimmune disease, inflammatory diseases, granulomatosis and immunosuppression.[4,6,7,8] More recently, it has been observed in patients with AIDS.[9] The disease is usually rapidly and relentlessly progressive, leading to death within months. There is no definitive therapy.

This report describes a patient in whom PML advanced slowly, simulating a degenerative disorder. Following the onset of symptoms she survived for 43 months and autopsy failed to identify a source or other manifestations of immunocompromise.

Case Report

This 71-year-old female patient was examined at her local hospital because of frequent falling. Over the previous year, she had noted

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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 following commands. She was alert and oriented but slow to answer questions. Speech was dysathric. Extraocular 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, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, B^{12} and folate; RBC folate; thyroid studies; electrocardiogram; 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 bacteria 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 particularly 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 malignancy or a systemic disease associated with immunocompromise was not discovered. There was no evidence that she had suffered 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 thickness 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 identified 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 demyelination and the presence of vessels. Collections of mononuclear cells were observed, however, cuffing 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 particles occupied nuclei of oligodendrocytes (Figure 5); the particles measured 36.5 nm in diameter and were morphologically consistent with papova virus. Other than an occasional neurofibrillary 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 characteristic of PML. The clinical features, however, are unusual. No

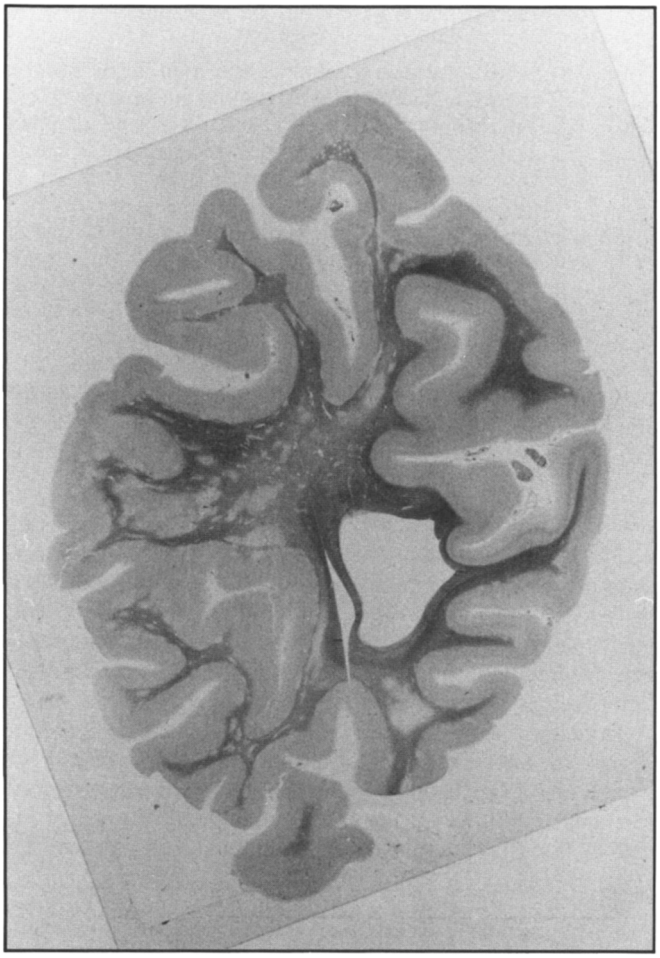

Figure 1 — Section of occipital lobe stained for myelin (Solochrome R x 1.8). Note numerous punctate areas of white matter demyelination.

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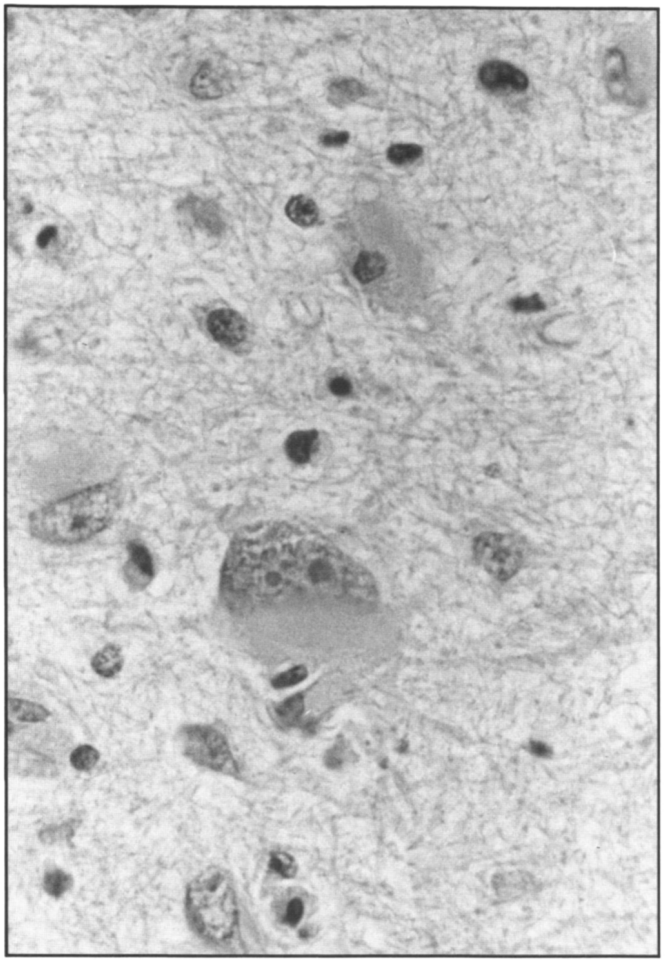

Figure 2 — Enlarged bizarre gemistocytic astrocyte in demyelinated zone. (H & E x 864).

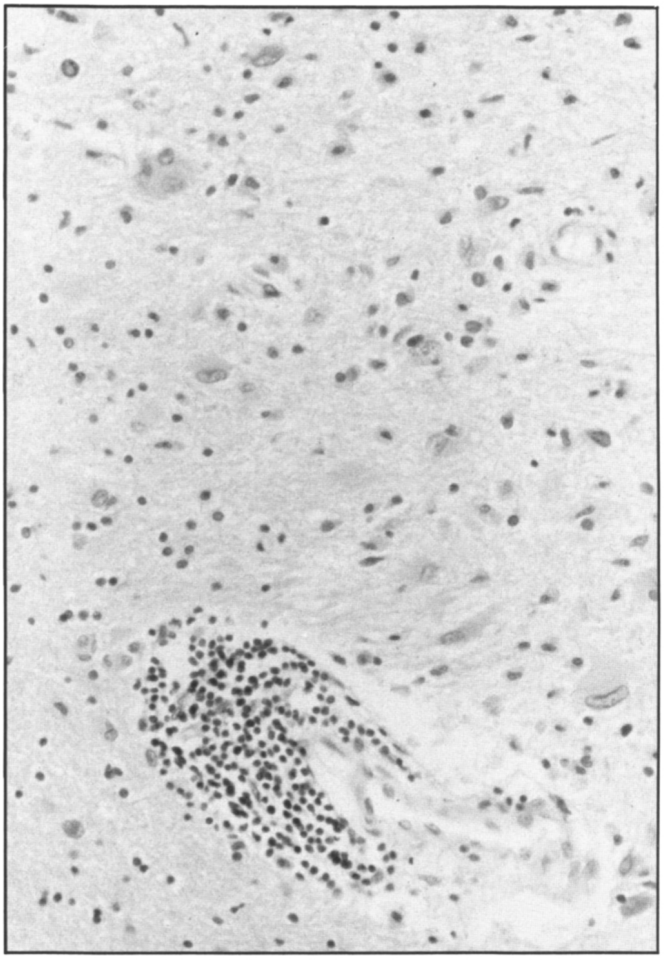

Figure 3 — Mononuclear cuffing around white matter blood vessel (H & E x 510).

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.[10-16] Had the diagnosis been suspected premortem, provocative skin testing or other tests may have demonstrated an immune defect.[17-19] 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'.[8]

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.[4] Rare cases lasting up to several years have been reported and are often examples of primary PML.[12,15,16] Some prolonged cases have also been observed in association with immunosuppressive or other conditions.[20-23] 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[22,24,25] shed doubt on reports of beneficial treatment[26] in single patients and underline the need for a controlled trial of treatment.

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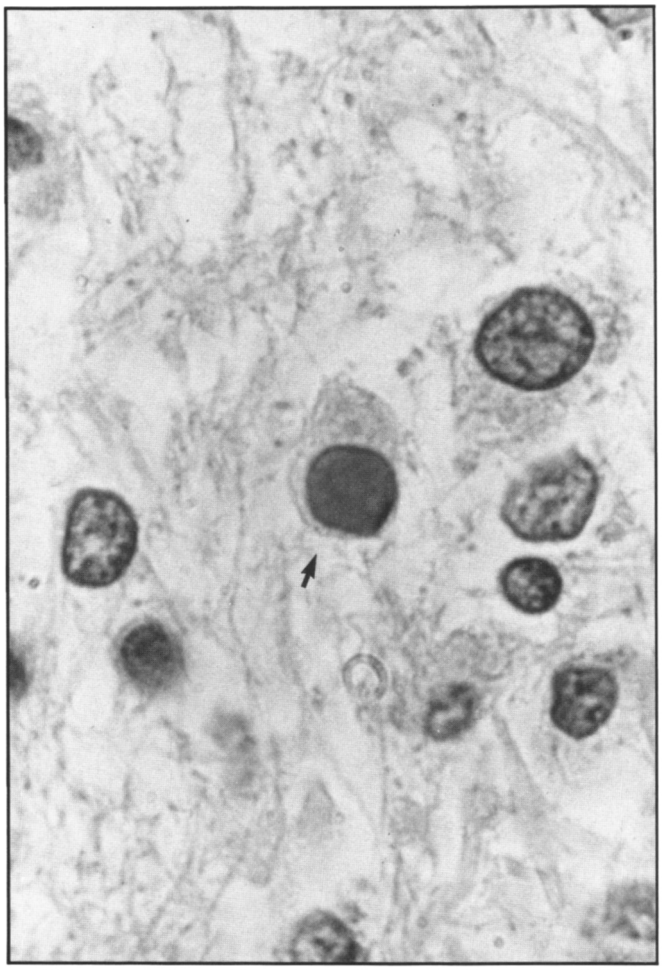

Figure 4 — Oligodendrocyte adjacent to demyelinated zone with swollen nucleus and intranuclear inclusion filling the nucleus (arrow). (H & E x 2120 Oil Immersion).

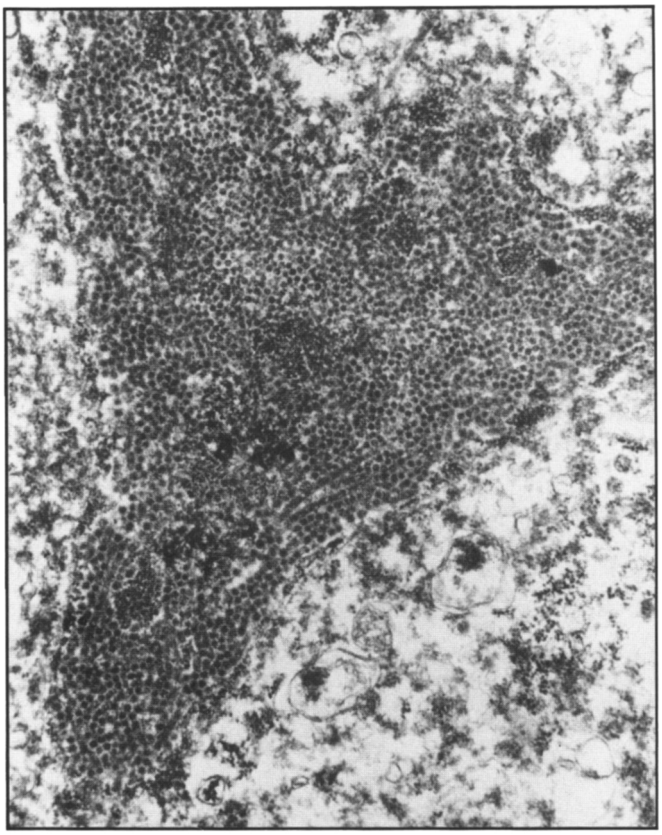

Figure 5 — Electron micrograph of oligodendrocytic intranuclear inclusion material. Note arrays of viral particles which measure approximately 36.5 nm in diameter.

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

	Age/Sex*	Duration	Presentation	Associated Disorder(s)
Silverman and Rubinstein[10]	64F	7 months	dementia	none
Stam[11]	?M	20 years	tremor, poor handwriting	?
Fermaglich et al[12]	44M	3 years	seizures	none
Bolton and Rozdilsky[13]	40M	18 months	nervousness, clumsiness, dysarthria	none
Arseni and Nereantiu[14]	26M	1 month	hemiparesis	none
Faris and Martinez[15]	55F	22 months	blindness	none
Rockwell et al[16]	43F	3.5+ years	paraesthesias, dysarthria, weakness	none
Brun et al[21]	33F	33 years	vertigo, poor balance, poor vision	anemia
Kepes et al[20]	47M	10 years	clumsiness, numbness	sprue
Hedley-Whyte et al[22]	63M	5 years	dementia	lympho-sarcoma
Schlitt et al[23]	55M	5+ years	dementia, headaches, blurred vision	lymphoma
	28M	2+ years	weakness, tremor	renal transplant
Present case	70F	43 months	falling	none

+alive at publication
*age at onset of PML

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