# Ophthalmologic Manifestations of Acquired Immune Deficiency Syndrome-associated Progressive Multifocal Leukoencephalopathy

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**Purpose:** Progressive multifocal leukoencephalopathy (PML) is increasingly described as a late complication of the acquired immune deficiency syndrome (AIDS). The purpose of this study is to evaluate retrospectively the ophthalmologic, clinical, and investigational aspects of AIDS-associated PML.

**Methods:** The authors evaluated ten patients in whom ophthalmologic manifestations developed in the course of AIDS-associated PML. Findings at clinical examination and their progression over time, neuroimaging correlates, the results of pathologic investigation, and visual outcomes were reviewed.

**Results:** Progressive multifocal leukoencephalopathy was the AIDS-defining illness in six of ten patients. Homonymous visual field defects were the presenting symptom in three patients and detected in six patients overall. Occipital blindness developed in one patient. Cerebellar signs and brain stem nuclear and supranuclear palsies also were common. Confluent white matter lesions with increased intensity on T2-weighted magnetic resonance imaging were supratentorial in seven patients and infratentorial in three patients. With incomplete data, the median survival time was 3 months from PML onset. Histopathologic confirmation of PML diagnosis was available for nine of the ten patients.

**Conclusions:** The development of progressive retrochiasmal visual field defects, supranuclear and nuclear cranial nerve palsies, or nystagmus ataxia in the relatively young patient should alert the ophthalmologist to the possibility of PML, particularly in the presence of long-tract central nervous system signs or dementia. Progressive multifocal leukoencephalopathy will often be human immunodeficiency virus associated. Human immunodeficiency virus encephalopathy, cerebral toxoplasmosis, lymphoma, and infarction need to be discriminated. Effective therapy is required urgently for this devastating disease. *Ophthalmology* 1996;103:899–906

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Described for the first time in 1958,<sup>1</sup> progressive multifocal leukoencephalopathy (PML) was defined as a rare but devastating demyelinating brain disorder that complicated the late stages of a variety of diseases with impaired cellmediated immunity, notably the lymphoproliferative dis-

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orders.<sup>2,3</sup> Progressive multifocal leukoencephalopathy proved to be an opportunistic infection caused by JC virus, a papovavirus (named by the initials of the patient from whose brain the virus was first cultivated). The papova-viruses consist of two DNA virus groups that differ in size but have similar morphologies: the PAPilloma viruses and the POlyoma-VAcuolating viruses.<sup>4</sup> The JC virus is one of only two known polyomaviruses that are pathogenic in humans, and PML is the only known JC virus-associated disease.

Recently, PML has been described in human immunodeficiency virus (HIV)-infected individuals. United States PML annual death rates rose fourfold between 1979 and 1987,<sup>5</sup> reflecting not only the expanding HIV epidemic, but also an increased PML predilection in acquired immune deficiency syndrome (AIDS) compared with other immunosuppressed diseases.<sup>6,7</sup> Most clinical AIDS series report a PML prevalence of 1% to 2%, but several autopsy and brain biopsy-derived series describe prevalence rates of 4% to 8% in patients with AIDS,<sup>7-11</sup> and PML comprises 10% of cerebral radiologic lesions occurring in patients with AIDS.<sup>12</sup> Moreover, rates of HIVassociated PML appear similar among the various AIDS risk groups and across the United States.<sup>13</sup> Ophthalmic symptoms and signs are common manifestations of PML but have received limited attention in the ophthalmologic and neurologic literature.14-17

## **Patients and Methods**

The medical records of patients diagnosed with PML and an HIV infection were reviewed retrospectively from three institutions: the Los Angeles County-University of Southern California Medical Center, Los Angeles, CA; Riverside General Hospital, Riverside, CA; and the Detroit Medical Center Hospitals, Detroit, MI. Patients were derived from different time periods at each institution, and a true population denominator could not be determined. The diagnosis of HIV infection in all patients was based on the presence of HIV seropositivity as determined by enzyme-linked immunosorbent assay, and confirmed by Western blot analysis of the HIV viral protein bands p24, gp 160/120, and gp41. Clinical records, including available pathologic slides and radiographic studies, were reviewed in detail in tandem with autopsy findings, if available. Ten patients were included in the study if ophthalmic PML manifestations were present, based on appropriate clinical and magnetic resonance imaging (MRI) findings. Three of the ten patients (cases 1, 4, and 5) have been reported briefly elsewhere.<sup>17-19</sup> The pathologic diagnosis of PML<sup>7,18,20,21</sup> was confirmed in nine of the ten patients, by examination of biopsy material in seven patients, and at autopsy in four patients.

## Results

Ten patients with AIDS who had PML involvement of the visual sensory or visual motor system are presented.

The mean age ( $\pm$  standard error) was 42 ( $\pm$ 9) years. Nine of the patients were men. Six of the patients were homosexual (two also used intravenous drugs), and there were individual patients with other HIV risk factors intravenous drug abuse, blood transfusion, and heterosexual transmission. One patient had an HIV infection in which no known risk factor could be determined. Progressive multifocal leukoencephalopathy was the AIDSdefining illness (Centers for Disease Control criteria<sup>22</sup>) in six of the ten patients.

The clinical and radiologic features of these patients are listed in Table 1, and their PML ophthalmologic complications are summarized in Table 2.

A homonymous hemianopia or homonymous quadrantanopia was a prominent feature of the symptom complex in six patients, and in three cases (2, 7, and 9) visual field loss was the presenting symptom of PML. In one patient (case 2), PML involvement of both occipital lobes led to legal blindness (without Anton syndrome).

Progressive multifocal leukoencephalopathy involvement was principally supratentorial in seven patients, with the main areas of demyelination found in the occipital lobes (four patients), temporal lobes (three patients), and the parietal or frontal lobes (two patients each). The three patients whose PML was primarily infratentorial (cases 1, 5, and 8) presented with cerebellar signs as well as brain stem nuclear and supranuclear motor palsies. Patients with infratentorial PML had a very poor prognosis, with survival of only 4, 6, and 12 weeks from the onset of PML symptoms. Overall, in four patients a horizontal nystagmus developed, three patients had a trigeminal or an abducent cranial nerve palsy, or both, and one patient had a vertical gaze palsy. A nuclear/fascicular facial palsy was observed in one patient. The brain pathology of PML is illustrated from two of the cases in Figures 1 and 2.

Progressive multifocal leukoencephalopathy occurred in severely immunosuppressed individuals. The CD4 lymphocyte levels at the time of diagnosis of the PML were available from six patients; the median CD4 level was 48/ml, with a range from 2 to 276/ml. Two other patients were noted to have severe lymphocyte depletion of lymph node and spleen at autopsy.

Survival data were incomplete. The median time from the development of PML-related symptoms to death was 3 months in the five patients with complete data, with a range of 1 to 13 months. The almost inexorably progressive nature of PML is emphasized in Table 1 by the increasing clinical complexity observed in the five patients who were observed until their death. The PML lesions continued to enlarge and develop throughout the natural history of the disease. In these cases, PML was believed to be the primary cause of inanition that led to death from bronchopneumonia or septicemia. No specific antiviral therapy for PML was attempted in any patient other than anti-HIV retroviral treatment.

#### **Case Reports**

**Case 1.** A 60-year-old man had received 12 U whole blood as treatment for a bleeding gastric ulcer 3 years before diagnosis;

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Case No.	Age (yrs)/ Sex	HIV Risk Factors	Ophthalmologic Features	Other CNS Features	MRI CNS Involvement	Tissue Diagnosis	Other AIDS Features
1	W/09	Transfusion	L V palsy L VI palsy L VII palsy	R hemiparesis R hemianesthesia Neurogenic bladder	Extended from L posterior capsule and thalamus to lower medulla	Biopsy Autopsy	Oral Candida CD4 44/ml t 3 mos
7	30/M	Homosexuality IV drugs	Legal blindness (HM) R homonymous hemianopia L loss of macular field	Dementia R hemiparesis	L and R occipital lobes L optic radiation and splenium L frontal lobe L external capsule	None	Oral Candida Deltopectoral abscess CD4 70/ml t 13 mos
ŝ	41/M	Homosexuality	Horizontal nystagmus R hemianopia	L hemiparesis	L occipital lobe Small lesion R occipital lobe Thalamus and basal ganglia	Biopsy	Oral Candida
4	42/M	Homosexuality IV drugs	Horizontal nystagmus L homonymous hemianopia	Seizures Dementia L hemiparesis Cerebellar ataxia Dysarthria	R frontal lobe R and L parietal lobes	Biopsy Autopsy	Oral Candida Cerebral toxoplasmosis Molluscum contagiosum E. histolyticum t 5 mos Nodal lymphocyte depletion
ŝ	37/M	Homosexuality	Horizontal nystagmus R and L V palsy R VI palsy Upgaze palsy	L hemiparesis Cerebellar ataxia Dysarthria	R lateral lobe of cerebellum Basis pontis Central medulla	Autopsy	PCP Oral Candida Disseminated herpes zoster t 1 mo Nodal lymphocyte depletion
Q	40/M	IV drugs	Upper R quadrantanopia	Mixed dysphasia	L temporal lobe L parietal lobe	Biopsy	Oral Candida
2	30/M	Homosexuality	R homonymous hemianopia Reduced R saccades	Dementia	L occipital lobe	Biopsy	Oral Candida
ø	51/M	Homosexuality	Horizontal nystagmus L V palsy L VI palsy	Cerebellar ataxia Dysarthria	Pons Cerebellum	Autopsy	Oral Candida Klebsiella pneumonia CD4 2/ml t 6 wks
6	47/F	Heterosexual transmission	R hemianopia		L occipital lobe	Biopsy	Oral Candida CD4 276/ml
10	44/M	Unknown	R hemianopia	Ataxia	L temporal lobe L insular gyrus	Biopsy	PCP CD4 5 ml
HIV = h <sub>i</sub> lymphocy (where no	uman immunodefic tes/ml blood at dia, t stated, patient su	:iency virus; CNS = cent gnosis of progressive mul rvival is not known).	ral nervous system; MRI = mag tifocal leukoencephalopathy; IV	netic resonance imaging; AI = intravenous; HM = hanc	DS = acquired immune deficiency I motions; t = time from progressiv	syndrome; L = left; /e multifocal leukoer	R = right; CD4 = CD4.positive neephalopathy symptoms to death

Table 1. Demographic and Clinical Features of Ten Patients with Acquired Immune Deficiency Syndrome-associated Progressive Multifocal Leukoencephalopathy with Ophthalmologic Features

Table 2. Ophthalmologic Signs in Ten Patients
with Acquired Immune Deficiency Syndrome-
associated Progressive Multifocal
Leukoencephalopathy

Ophthalmologic Signs	No. of Patients
Visual field defects	
Homonymous hemianopia or	
quadrantanopia	6
Bilateral cortical blindness	1
Isolated unilateral quadrantanopia	1
Horizontal nystagmus	4
Nuclear cranial nerve palsies	
V	3
VI	2
VII	1
Supranuclear gaze palsy	1
Other findings	
Pontine pupils	1
Reduced saccades	1

there were no other known HIV risk factors. Progressive right hemiparesis and rapid weight loss developed over a 2-month period. Horizontal diplopia and dysarthria developed shortly before admission. The CD4 lymphocyte count was 44/ml, and an HIV infection was confirmed. The neurologic and radiologic findings are summarized in Table 1. A sagittal T2-weighted brain MRI is illustrated in Figure 3, showing a high-intensity axial lesion that extended from the left thalamus, through the pons, and ending in the lower medulla. The results of a stereotactic brain biopsy were equivocal. Rapid physical deterioration ensued, and the patient died 1 month after diagnosis. The extensive brain stem PML lesions were confirmed at autopsy.

**Case 2.** A 30-year-old homosexual man with a history of intravenous drug use was diagnosed with an HIV infection in March 1990. He suffered intermittently with fevers, a nonproductive cough, and diarrhea until April 1990, when rapid visual loss developed to 20/100 visual acuity in both eyes. His CD4 level was 70/ml. A right homonymous hemianopia and left central homonymous hemianopia were shown. The patient soon had signs of dementia and of a slowly progressive right hemiparesis. The neurologic and radiologic findings are listed in Table 1. An axial T2-weighted brain MRI is illustrated in Figure 4. The principle lesions were a diffuse increase in white matter signal involving both occipital lobes that failed to enhance with intravenous contrast. Symptoms were uninfluenced by a trial of pyrimethamine (Daraprim, Burroughs Wellcome, Research Triangle Park, NC) and clindamycin (Cleocin, Upjohn, Kalamazoo, MI). Over a period of 4 months, the visual acuity in both eyes diminished progressively to hand movements. The visual field defects became denser, but unchanged in extent. Visual-evoked potentials to pattern stimulation suggested mildly delayed conduction in the left visual pathway only, with grossly normal waveform and amplitude in both eyes. There was a slowly progressive decline in the patient's mental and physical function. He became bedridden and died in July 1992.

**Case 3.** A 41-year-old homosexual man had been diagnosed and treated for an asymptomatic HIV infection for 5 years. Table 1 summarizes the neurologic and radiologic findings. In January 1993, he was discovered to have a right homonymous hemianopia during an ophthalmic evaluation of floaters. Visual acuity was 20/40 in both eyes. An intention tremor of the left hand with end-point dysmetria and impaired fine hand movements were detected. The T2-weighted brain MRI showed increased signal in the white matter of both occipital lobes and left temporal lobe (Fig 5), and several smaller lesions involved the basal ganglia and thalamus bilaterally. A 3-week course of sulfamethoxazoletrimethoprim (Bactrim, Roche, Nutley, NJ), sulfadiazine, pyrimethamine, and leucovorin calcium failed to produce clinical or MRI improvement. An open left occipital brain biopsy showed characteristic features of PML. Over the next 6 months, the right homonymous hemianopia was unchanged, but there was progressive left hemiparesis and left cerebellar signs, nystagmus on right gaze, and increasing fevers and confusion. He was lost eventually to follow-up.

#### Discussion

The natural history and pathogenesis of JC virus infection is incompletely understood. In most individuals, JC virus latency appears to become established after almost ubiquitous subclinical infection in childhood and early adulthood, with reactivation during immunosuppression.<sup>3,20,23</sup> The balance of evidence suggests that JC virus reaches the brain by hematogenous spread after this reactivation. A specific virus tropism for brain oligodendroglia is probably a major factor in the pathogenesis, with lesions generally confined to brain white matter.<sup>20,23</sup>

Progressive multifocal leukoencephalopathy can cause a variety of cerebral and brain stem manifestations depending on the pattern of focal or multifocal demvelinated plaques in the deep myelinated fiber tracts of the brain. Neurologic dysfunction usually begins insidiously, and early focal signs and rapid, relentless deterioration are the norm. Certain syndromes are more commonly found in PML, notably hemiparesis/monoparesis, mental deterioration. homonymous hemianopia/quadrantanopia, dysarthria/dysphasia, ataxia, or central cranial nerve palsies. An important feature is that disease involvement is usually markedly asymmetric. Table 3 compares the distribution of the most common PML presentations in four large series with the present ophthalmologically derived series.24,25

The retrochiasmal visual pathways commonly are disrupted, causing hemianoptic field defects. Overall, there is a predilection for involvement (in descending order) of the parietal, occipital, frontal, and temporal lobes, and with less frequent infratentorial involvement.<sup>2,7–10,19,21,26</sup> Bilateral occipital lobe PML may lead to cortical blindness, which appears to be a relatively common event,<sup>1,2,7,15,25</sup> as in case 2, but has received inadequate recognition. In one patient (case 9), visual symptoms were the sole manifestation at diagnosis. Nystagmus, cranial nerve lesions, and supranuclear gaze palsies also are common findings.

Less frequent presentations include headaches, internuclear ophthalmoplegia,<sup>10,25</sup> visual inattention,<sup>27</sup> seizures,<sup>28</sup> and other focal neurologic deficits. Involvement of the thalamus or basal ganglia was seen in cases 1 and 3; although previously considered uncommon, such involvement recently was reported in 20% of patients in a



large series of HIV-associated PML.<sup>11</sup> Despite the myelinated nature of the optic nerve fibers, there is no evidence that the optic nerve or chiasm is involved in PML. Autopsy studies of the optic nerves from such patients are needed to inform the question of possible PML involvement. There appear to be no significant clinical and pathologic differences between AIDS-associated PML and that complicating other immunodeficiency states,<sup>26,29</sup> with the exception of a possibly increased severity in the former.<sup>6,18</sup>

Progressive multifocal leukoencephalopathy commonly is the presenting AIDS-defining illness.<sup>10,11,20,24,25,30</sup> This occurred in six of the ten patients in this series. Several large studies of PML occurring in patients with AIDS record a 20% to 38% prevalence of ocular signs at the time of PML diagnosis. There also is evidence to suggest that ophthalmic involvement increases with the duration of survival.<sup>7,10,19,24,25,31,32</sup>

The diagnosis of PML is suggested by the insidious onset of neurologic signs in a setting of immunosuppression, usually as a complication of AIDS. Other neurologic illnesses need to be considered in a differential diagnosis, <sup>7–9,12,13,17,19,26,31,32</sup> particularly HIV encephalopathy, cerebral toxoplasmosis, cerebral lymphoma, and cerebral infarction, all of which are common complications of AIDS.<sup>33,34</sup> Many of the clinical features of these diseases

overlap, but their neuroimaging characteristics are helpful in aiding the diagnostic algorithm.<sup>10,11,20,35-38</sup> The MRI is the neuroimaging procedure of choice because it shows changes that are characteristic for PML. The computed tomographic findings in PML grossly underrepresent the disease process.

Scattered or confluent areas of increased signal in proton density and T2-weighted MRI images are found confined to the white matter and are usually coextensive with clinical findings. The lesions do not show intravenous contrast enhancement, which usually is a feature of toxoplasmic encephalitis, central nervous system lymphoma, and cerebral infarct. The increased signal intensity on T2-weighted images, the lack of contrast enhancement, and the lack of mass effect have been used to establish neuroimaging diagnostic criteria for PML.<sup>38</sup> Progressive multifocal leukoencephalopathy lesions often have scalloped edges, defining the anatomy of the subcortical arcuate fiber tracts. Human immunodeficiency virus-associated demyelination<sup>34</sup> is more difficult to differentiate radiologically, but tends to have a more diffuse, bilateral increased signal intensity on T2-weighted images and is often hypointense on T1weighted images.<sup>11</sup> Human immunodeficiency virus encephalopathy also tends to be associated with distinct clinical features.



**Figure 3.** Case 1. Brain stem progressive multifocal leukoencephalopathy. T2-weighted sagittal magnetic resonance image showing high-intensity signal consistent with a large area of intrinsic left brain stem demyelination (asterisk) that extended contiguously from the left thalamus to lower medulla. The water density signal of the progressive multifocal leukoencephalopathy lesion is equal to the cerebrospinal fluid. The study was undertaken on an early low-field strength magnetic resonance imaging system that accounts for the poor image quality. (Reproduced with permission from *Neurol Clin 1991;9:55–72*, copyright 1988, WB Saunders Co, and with the courtesy of JR Keane, MD, Los Angeles.)

A definitive diagnosis always requires pathologic confirmation. It is the routine practice in many centers to consider stereotactic or open brain biopsy after a failed 2- to 3-week trial of antitoxoplasmosis therapy (usually with combined clindamycin and pyrimethamine).<sup>39</sup> Other indications for brain biopsy include atypical imaging characteristics and neurologic instability.<sup>39</sup> Certainly, the individual's anticipated quality and quantity of life is an important consideration, and brain biopsy should be pursued rarely in very ill patients with AIDS.<sup>39</sup>

The pathologic features of PML are usually sufficiently distinctive to establish the diagnosis.<sup>1,2,11,18,21,25</sup> Focal demyelinating lesions are associated with relative sparing of the axon cylinders, often with an absence of inflammation. The demyelinated areas contain variable numbers of enlarged oligodendrocytes with deeply purple intranuclear inclusions on hematoxylin and eosin staining, often with bizarre astrocytes. In older lesions, infected oligodendrocytes tend to disappear, and only a few of the bizarre astrocytes may remain among the demyelinated axons. Tissues surrounding the demyelinated areas generally are normal. The oligodendrocytes with nuclei enlarged by viral inclusions show positive staining with antiserum to polyomal antigens, and electron microscopy can show the polyomaviral particles in their nuclei.<sup>18</sup> DNA and RNA in situ hybridization and polymerase chain reaction assays are being developed for diagnostic use in PML.<sup>29,40-42</sup>

Progressive multifocal leukoencephalopathy remains one of the most devastating complications of AIDS, for which no useful therapy has yet been identified. Although most individuals show progressive neurologic involvement, often over just a few weeks, there are cases with a



Figure 4. Case 2. Bilateral occipital progressive multifocal leukoencephalopathy causing occipital blindness. Axial T2-weighted 1.5-T field strength brain magnetic resonance imaging shows asymmetric progressive multifocal leukoencephalopathy lesions with increased signal intensity involving the white matter of both occipital lobes that did not enhance with contrast (not shown). The involvement of the splenium is not illustrated on this image.



Figure 5. Case 3. Axial T2-weighted 1.5-T field strength brain magnetic resonance imaging shows large, contiguous, confluent areas of increased signal intensity involving left temporal and occipital white matter and right occipital lobe white matter that did not enhance with contrast. There was no substantial mass effect. The involvement of thalamus and basal ganglia is not shown on this image.

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	References					
	Gillespie et al, 1991 <sup>24</sup>	Berger et al, 1987 <sup>7</sup>	Karahalios et al, 1992 <sup>10</sup>	von Einsiedel et al, 1993 <sup>25</sup>	Current Study	
Dementia	66%	39%	46%	34%	30%	
Hemiparesis/monoparesis	67%	86%	15%	40%	50%	
Hemianopia and other retrochiasmal visual field defects	30%	36%	15%	20%	70%	
Cranial nerve palsies	38%+	N/A	38%	N/A	30%	
Dysarthria/dysphasia	31%	25%	38%	34%	40%	
Ataxia	26%	18%	46%	20%	40%	
Headache	23%	18%	N/A	<b>7</b> %	10%	
Hemisensory loss	18%	18%	15%	7%	10%	
Seizures	11%	7%	N/A	20%	10%	
No. of patients	79	28	13	15	10	

#### Table 3. Percentage Distribution<sup>\*</sup> of Symptoms and Signs in Four Acquired Immune Deficiency Syndrome-related Progressive Multifocal Leukoencephalopathy Series Compared to Present Ophthalmologically Derived Series

N/A = not available.

\* Percentages are approximate because precise data comparisons are impossible.

relapsing and remitting course, and a few longer term survivals occur.<sup>27</sup> In general, however, death occurs within 9 months from the onset of PML symptoms, an interval characterized by progressive and multiple neurologic deficits. We are increasingly likely to see patients with the ophthalmologic complications of PML.

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