Progressive Multifocal Leukoencephalopathy in Persons Infected with Human Immunodeficiency Virus, San Francisco, 1981–1989

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Progressive multifocal leukoencephalopathy (PML), a rare neurological disease, has been sporadically reported in persons infected with human immunodeficiency virus (HIV), the causative agent of acquired immune deficiency syndrome (AIDS). From January 1981 through February 1989, in San Francisco, we identified 94 HIV-infected persons with PML, of whom 48 (51%) were pathologically confirmed (as required for AIDS case reporting). These 48 patients were significantly older when diagnosed with AIDS (20% older than 50 years) than patients with AIDS without PML. The remaining 46 (49%) patients, diagnosed clinically and by neuroimaging, did not differ significantly from definitive patients in demographic or survival characteristics after PML diagnosis. We detected antibodies to JC virus, the causative agent of PML, in 9 of 14 (64%) AIDS-related patients with PML, and in 9 of 14 (64%) matched control subjects, suggesting that determination of JC virus antibody status before AIDS diagnosis does not reliably indicate which patients will contract PML. Our study shows that the proportion of patients with AIDS who contracted PML remained stable between 1981 and 1988, but increased in the first 2 months of 1989. Our findings further indicate that PML in HIV-infected patients may be underestimated by as much as 50%.

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Progressive multifocal leukoencephalopathy (PML), a rare neurological illness caused by infection of the central nervous system (CNS) with JC virus (JCV), a papovavirus [1–4], was first described in 1958 [5] and has been sporadically reported in persons with various immunodeficiencies [6]. In 1982, Miller and colleagues [7] reported the first case of PML in a patient with acquired immunodeficiency syndrome (AIDS), and other investigators have subsequently reported more than 50 persons with PML who were infected with human immunodeficiency virus (HIV) [8–20]. National AIDS surveillance conducted by the Centers for Disease Control (CDC) indicates that since 1981 approximately 0.5% of all patients with AIDS present with pathologically confirmed PML [21]. The actual incidence of HIV-related PML is not known because surveillance data do not reflect patients with PML who are diagnosed clinically, without pathological confirmation, or PML that develops in persons who already have AIDS.

Our investigations reported here include (1) an epidemiological study to determine the incidence of PML in people in San Francisco and to identify the demographic and clinical characteristics of HIV-infected patients with PML, and (2) studies related to the pathological and causal characteristics of PML in which neuropathological specimens were examined to validate definitive PML diagnoses, and a seroprevalence study conducted to see if the presence of JCV antibodies predicts who will develop HIV-related PML.

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Methods

Patient Definitions

For this study, HIV infection was defined as written documentation in a medical record of either (1) gay-related immune deficiency, (2) AIDS, (3) AIDS-related complex, (4) HIV seropositivity, or (5) evidence of immunodeficiency without another cause and with behavioral risk factors (i.e., homosexual/bisexual behavior or intravenous drug use [IVDU]) for HIV infection. In this study, AIDS or AIDS-related refers to the subgroup of patients who meet the CDC diagnostic criteria for AIDS.

PML was defined as either definitive, which required a brain biopsy or autopsy specimen with the presence of multifocal areas of demyelination with axonal sparing, abnormal oligodendrocytes with enlarged nuclei containing eosinophilic intranuclear inclusions, and abnormal reactive astrocytes [1, 5, 22–25], or presumptive (clinical), which required a physician's diagnosis of PML and neuroimaging studies with white matter lesions without mass effect, consistent with PML, without another cause.

Patient Ascertainment

For this study, we ascertained patients from the following three sources (1) patients detected between January 1981 and February 1989 through the AIDS surveillance program of the San Francisco Department of Public Health (SFDPH) [26], (2) computerized hospital discharge data from January 1981 to June 1988 at six San Francisco hospitals that comprise 74% of hospital-reported patients with AIDS in San Francisco, and (3) neurosurgical or autopsy logs and neuroimaging (computerized tomography or magnetic resonance imaging) log books from July 1988 through February 1989 at four hospitals. All patients with multifocal white matter lesions consistent with PML were identified from the last source and verified by reviewing hospital discharge records. All patients with a documented discharge diagnosis of PML (ICD-9 code 043.6) were included.

Once a patient with PML was identified, we reviewed all available medical records and abstracted data on demographics, medical history, risk factors for HIV infection, initial symptoms, method of diagnosis, and duration of PML.

Validation of Definitive Diagnoses

HISTOPATHOLOGY. To confirm the definitive PML diagnoses, we examined brain tissue specimens from 23 of the 48 patients with definitive PML and brain tissue specimens from 4 patients with presumptive PML. Brain specimens were obtained by brain biopsy (n = 22) or autopsy (n = 5) and fixed in 10% (brain biopsy) or 20% (whole brain from autopsy) buffered formalin, and embedded in paraffin for examination by light microscopy. Sections were stained with hematoxylin and eosin (H & E) and examined by three neuropathologists.

ELECTRON MICROSCOPY. Twenty-three specimens were prepared for examination by electron microscopy (EM) from fresh tissue (n = 16) or from paraffin blocks (n = 7). Fresh tissue was placed in a 1% phosphate-buffered glutaraldehyde, postfixed with 2% osmium tetroxide, and embedded in resin. Paraffin-embedded tissues were deparaffinized in xylene, rehydrated through a series of ethanols, and fixed in glutaraldehyde overnight. One-micrometer-thick sections were stained with toluidine blue, recut, and stained with uranyl acetate and lead citrate. These tissues were then examined by EM for the presence of papovavirus particles, which are characteristically round, averaging 40 nm in diameter, and sometimes appear in crystalline arrays or with filamentous profiles.

Prevalence Study of JCV Antibodies in Sera and CSF

To determine the seroprevalence of JCV antibodies in patients with AIDS with and without PML, the following were examined for the presence of antibodies to JCV: (1) acute-phase sera from 3 patients definitively diagnosed with PML from November 1988 through January 1989, and (2) sera from 14 men before PML diagnosis and 14 control men matched for age, date of blood sample, and HIV antibody status who participated in the San Francisco City Clinic Cohort Study from 1978 to 1983. Information about the control patients was variable; however, none had neurological diagnoses and all died of AIDS without contracting PML before October 1988.

JCV-specific antibody titers were determined by an enzyme-linked immunosorbent assay that has been described previously [27]. Briefly, JCV antigen was harvested from infected primary human amnion cell cultures and purified by density gradient centrifugation in cesium chloride. The resulting bands were dialyzed against phosphate-buffered saline and the retentate stored at −70°C until use. Sera were tested at dilutions of 1:100 and 1:1,000. Optical densities (OD) for each sample were corrected by subtracting the OD of duplicate control wells containing no antigen from the OD of duplicate antigen-containing wells. JCV-specific antibody titers of serum specimens were determined by extrapolation from a standard curve generated by plotting the dilutions of a high-titered standard serum versus OD. Results were calculated according to the dilution of the sample that was on the linear part of the standard curve and titers were rounded to the nearest 100th dilution. Titers derived by this method are comparable with endpoint titers.

Statistical Analysis

Descriptive statistics were used to calculate means, medians, and standard deviations. χ^2 and relative risks, and rank sums were calculated using computerized epidemiological/statistical software packages that use confidence limits from the formula of Greenland and Robins [28] and the probability value, p, from a formula by Poole and Borchers [29].

Results

Patient Finding

From January 1981 through February 1989, 94 patients with HIV-related PML were identified in San Francisco (85 were residents at the time of diagnosis). Of the 94, PML was diagnosed definitively in 48 (reported to AIDS surveillance, SFDPH) and presumptively in 46 patients. PML was the first opportunistic infection in 57 patients and a subsequent diagnosis in 37 individuals.

The first patient was identified in 1981 (Fig 1). No

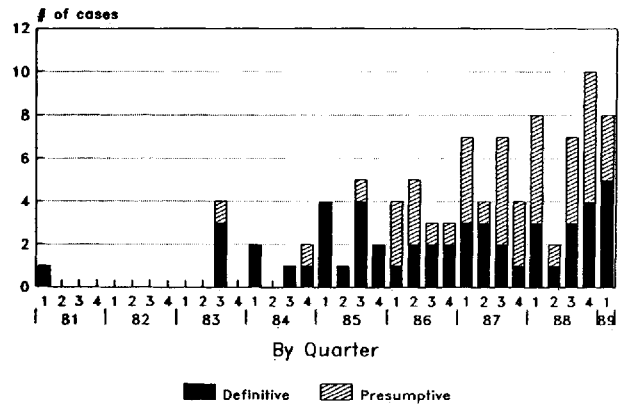

Fig 1. Progressive multifocal leukoencephalopathy in human immunodeficiency virus–infected individuals in San Francisco, by date of diagnosis, January 1981 through February 1989.

patients were identified for 1982, but the number of patients gradually increased over the next 7 years, with 10 patients diagnosed during the last quarter of 1988 and 8 patients diagnosed in January and February 1989. Because many were diagnosed at autopsy (17 of 94), we also examined patients by date of onset of PML symptoms (n = 84) to determine any clustering of disease. The same trend was observed, with no more than 4 patients having onset of PML symptoms in a single month. No evidence of seasonality was found.

PML as an Initial Diagnosis of AIDS

To help assess the apparent increasing incidence of PML in San Francisco, we examined the annual proportions of incident patients with AIDS who resided in San Francisco and presented with definitively diagnosed PML from 1981 through the first 2 months of 1989 (Table 1). Overall, of 6,370 incident patients with AIDS, 29 (0.5%) presented with definitively diagnosed PML. The proportion of patients with AIDS in San Francisco who presented with definitively diagnosed PML appeared to decline slightly over the initial 8-year period before the unexplained increase in the first 2 months of 1989.

Although patients with presumptively diagnosed PML do not meet the CDC AIDS diagnostic criteria unless other diagnoses fulfilling AIDS criteria are also present, data on these patients is included in Table 1 to provide a better approximation of the frequency of clinically diagnosed PML. Overall, 23 HIV-infected San Francisco residents presented with presumptively diagnosed PML. If presumptively diagnosed PML patients were regarded as fulfilling AIDS criteria, then approximately 0.8% of patients with AIDS in San Francisco presented with PML, a proportion that remained remarkably stable over an 8-year period, 1981 through 1988.

PML as a Subsequent AIDS-related Diagnosis

PML that develops in patients with previously diagnosed AIDS is not reflected in AIDS surveillance data. To determine whether the proportion of AIDS-related PML in such patients has changed over time, we estimated the prevalence of patients with AIDS each year among San Francisco residents by using annual incidence and mortality AIDS data reported to the SFDPH. We then determined the proportion of patients with AIDS who subsequently contracted PML (Table 2) (patients with PML as an initial diagnosis of AIDS were excluded). The number of prevalent patients with AIDS grew from a low of 22 patients in 1981 to a high of 2,356 in the first 2 months of 1989. Overall, during this period, the mean estimated annual proportion of definitively and presumptively diagnosed PML among patients with AIDS was 0.3% (range, 0–0.8%).

Table 1. Proportion of Incident Patients with AIDS Residing in San Francisco Who Presented with PML as Initial Diagnosis

Year	Incident Patients with AIDS	Patients with PML (n, %)					
		Definitive		Presumptive		Totals	
1981	31	1	3.2	0	0	1	3.2
1982	103	0	0	0	0	0	0
1983	295	2	0.7	0	0	2	0.7
1984	578	3	0.5	1	0.2	4	0.7
1985	876	6	0.7	1	0.1	7	0.8
1986	1,296	3	0.2	6	0.5	9	0.7
1987	1,491	4	0.3	9	0.6	13	0.9
1988	1,430	5	0.4	6	0.4	11	0.8
1989[a]	278	5	1.8	0	0	5	1.8
Total	6,370	29	0.5	23	0.4	52	0.8

[a]Includes January through February only.

AIDS = acquired immunodeficiency syndrome; PML = progressive multifocal leukoencephalopathy.

Table 2. Estimated Proportion of Prevalent Patients with AIDS Residing in San Francisco Diagnosed with PML (Subsequent Presentation of PML Only)

Year	Prevalent Patients with AIDS	Patients with PML (n, %)					
		Definitive		Presumptive		Totals	
1981	22	0	0	0	0	0	0
1982	93	0	0	0	0	0	0
1983	265	1	0.4	1	0.4	2	0.8
1984	545	1	0.2	0	0	1	0.2
1985	878	4	0.5	0	0	4	0.5
1986	1,337	0	0	2	0.2	2	0.2
1987	1,929	3	0.1	5	0.3	8	0.4
1988	2,309	5	0.2	10	0.4	15	0.6
1989[a]	2,356	0	0	1	0.04	1	0.04
Totals		14		19		33	

[a]Includes January through February only.

AIDS = acquired immunodeficiency syndrome; PML = progressive multifocal leukoencephalopathy.

Before 1986, 6 of the 7 (86%) patients with AIDS who contracted PML were definitively diagnosed; subsequently 8 of the 26 (31%) patients with PML were definitively diagnosed, and 18 (69%) were presumptively diagnosed. Only 1 patient with PML among patients with prevalent AIDS was reported as being diagnosed during the first 2 months of 1989.

Demographics/Risk Factors

Of the total 94 patients with PML identified from January 1981 through February 1989, most were homosexual or bisexual (91%), white (88%), males (98%), and aged 23 to 66 years (median, 38 years) (Table 3). Most were employed in white-collar jobs (60%), but 12% were disabled or unemployed at the time of PML diagnosis.

PML VERSUS NON-PML. The demographics of the 94 patients with PML identified in our study were compared with those of the following two subgroups reported through SFDPH AIDS surveillance: (1) Fifty (including 2 with presumptively diagnosed PML) patients with AIDS with definitive PML, and (2) 6,053 patients with AIDS without PML (see Table 3). Patients with AIDS with PML were significantly older (20% were older than 50 years) at the time of AIDS diagnosis than patients with AIDS without PML (10% older than 50 years, χ^2 test for trends = 4.0; $p = 0.04$). The geographical distribution (not shown) and other demographic and behavioral risk factors of patients with PML, residing in San Francisco, was remarkably similar to that of patients with AIDS without PML.

Clinical Findings/Survival Patterns

At the time of diagnosis, 79 of the 94 (84%) patients with PML had documented neurological examinations, with motor function problems (hemiplegia, gait disturbances) and mental status changes (confusion, dementia, and obtundation) as the most common abnormalities (Table 4).

By March 1989, 85 of the patients with PML had died, 5 were documented as alive, and 4 were lost to follow-up. The survival curve for patients with PML in San Francisco is shown in Figure 2. The median time from onset of symptoms to death was 3.5 months. Survival curves for patients with AIDS in San Francisco with Kaposi's sarcoma and *Pneumocystis carinii* pneumonia are included for comparison (median time from diagnosis to death, 16 and 10 months, respectively) (unpublished data, SFDPH) [30]. No specific factors could be associated with length of survival, including age and other demographics, neurological findings, or medications (including zidovudine).

Presumptive Versus Definitive PML

The 46 patients with presumptively diagnosed PML did not differ significantly from the 48 patients with definitively diagnosed PML in their demographics, medical history, and course of illness. Patients with PML diagnosed by brain biopsy or autopsy did, however, have significantly more motor function abnormalities (relative risk [RR] = 2.62; 95% confidence intervals [CI] = 1.3, 5.5), hemiplegias (RR = 2.65; 95% CI = 1.6, 4.3), cranial nerve VII palsies (RR = 3.14; 95% CI = 1.9, 5.1), and speech abnormalities (RR = 1.6; 95% CI = 1.1, 2.5) before PML diagnosis. These patients were also significantly less likely to have taken zidovudine (RR = 0.55; 95% CI = 0.3, 0.9).

Initial Versus Subsequent PML

Patients who presented with PML (n = 57) were significantly older at diagnosis than patients with AIDS

Table 3. Demographics of 94 Patients with PML Compared with Reported Patients with AIDS, with and without PML, San Francisco, 1981 to February 28, 1989

Characteristic	Present Study (Patients with PML, n = 94)	AIDS (SFDPH)	
		Patients with PML (n = 50)	Patients without PML (n = 6,053)
Race (%)			
White	88	88	83
Black	3	2	7
Latin American	3	10	8
Asian	0	0	2
American Indian	0	0	0.1
Sex (%)			
Male	98	98	99
Female	2	2	1
Age (yr) (%)			
0–29	6	8	13
30–39	50	46	49
40–49	31	26	28
50+	13	20[a]	10
Risk factors (%)			
Homosexual/bisexual (no IVDU)	78	88	84
Homosexual/bisexual (IVDU)	13	8	11
IVDU	1	2	2
Hemophilia	0	0	0.2
Heterosexual	1	0	0.5
Transfusion	1	0	1.2
None apparent	5	2	0.4

[a]Patients with PML vs patients without PML; χ^2 test for trends, $\chi^2 = 4$; $p = 0.04$.

PML = progressive multifocal leukoencephalopathy; AIDS = acquired immunodeficiency syndrome; SFDPH = San Francisco Department of Public Health; IVDU = intravenous drug use.

Table 4. Clinical Signs and Symptoms of Patients with PML with Documented Physical Exams Prior to Diagnosis (n = 79), San Francisco

Sign/Symptom	%
Motor function abnormalities	67
Mental status changes	66
Hemiparesis	39
Seventh cranial nerve palsy	38
Fine motor coordination problem	34
Speech difficulties (i.e., aphasia)	31
Visual problems (i.e., peripheral loss, hemianopsia)	30
Cranial nerve palsies (other than VII)	27
Ataxia	26
Headache	23
Sensory loss	18
Seizures	11

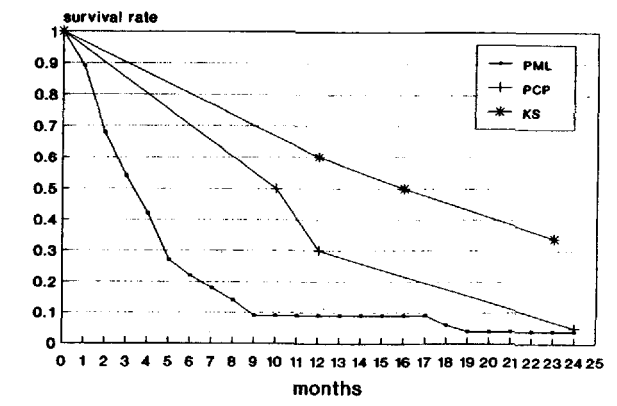

Fig 2. Survival curves of patients with progressive multifocal leukoencephalopathy in San Francisco compared with patients with Pneumocystis carinii *pneumonia and Kaposi's sarcoma from primary opportunistic infection to death.*

with PML diagnosed subsequently (n = 37) (median, 41 versus 37 years; $\chi^2 = 4.6$; $p = 0.03$). Patients presenting with PML were significantly more likely to have behavioral risk factors for HIV infection other than being homosexual or bisexual (RR = 1.83; 95% CI = 1.5, 2.2); the only 2 women were in this group (RR = 1.8; 95% CI = 1.5, 2.1). Patients presenting with PML had more documented speech abnormalities (RR = 1.5; 95% CI = 1.1, 2.2) at the time of PML diagnosis. In patients with AIDS who subsequently contracted PML, the time from initial AIDS diagnosis to PML ranged from 1 to 52 months (median, 7 months).

Validation of Definitive Diagnoses

HISTOPATHOLOGY. Twenty of the 27 H & E–stained brain tissue specimens had findings characteristic of PML. Three patients originally reported as definitive PML to the SFDPH could not be confirmed as PML during this review because oligodendrocytes and intranuclear inclusions were not seen. Four specimens originally reported as "probable" or "possible" PML could not be confirmed as PML on reexamination. These patients were classified as presumptive in our study because they had a physician diagnosis of PML and neuroimaging studies consistent with PML; their brain tissue specimens were inadequate for a PML diagnosis (i.e., no white matter), and no other cause was documented.

ELECTRON MICROSCOPY. No additional patients with PML were identified by EM. Of the 20 patients identified as PML by histopathological examination, 11 were positive for papova-like virus particles, 6 (3 from paraffin-embedded blocks) were negative, and 3 were not submitted for examination by EM.

JCV Seroprevalence Study

JCV reciprocal antibody titers ranged from less than 100 to 11,600, with titers of 100 or greater considered positive. Acute-phase serum specimens collected from 3 patients with PML in February 1989 were all positive for JCV antibodies (titers = 400, 800, and 1,500). We detected JCV antibodies in 9 of 14 (64%) initial serum specimens collected from patients who 1 to 9 years later contracted PML and in 9 of 14 (64%) matched control subjects. One patient with an additional sample seroconverted from HIV/JCV-negative in August 1978 to HIV/JCV-positive in August 1980. No significant differences were found between JCV antibody titers in patients with PML (range, <100 to 10,500; median, 400) and control subjects (range, <100 to 4,900; median, 200; signed rank sum, $p > 0.5$).

Discussion

This is the first systematic analysis of PML in a defined geographical area that includes patients diagnosed presumptively as well as patients diagnosed definitively. PML is being diagnosed clinically in HIV-infected persons without pathological confirmation with increasing frequency. Therefore, the following HIV-associated CNS manifestations need to be ruled out when considering a clinical diagnosis of PML: toxoplasmosis, CNS lymphoma, and HIV encephalopathy (AIDS dementia complex), all of which have different clinical and neuroimaging findings than PML. CNS lymphoma and toxoplasmosis are usually characterized by focal neurological abnormalities, but on neuroimaging reveal ring-enhancing lesions not characteristic of PML. In addition, many patients with presumptive PML in our study received a therapeutic trial of pyrimethamine and sulfadiazine, the treatment for *Toxoplasma gondii,* without improvement, indicating they probably did not have toxoplasmosis. Patients with HIV encephalopathy, unlike patients with PML, generally do not have focal neurological abnormalities and on neuroimaging show cortical atrophy and occasionally nonspecific white matter changes. The patients identified with presumptive PML in San Francisco did not differ from definitively diagnosed patients in demographic, neuroimaging, or survival patterns, suggesting that they indeed had PML.

Our data indicate that, in San Francisco, the proportion of patients with AIDS with PML as either an initial or subsequent diagnosis of AIDS has remained remarkably stable between 1981 and 1988. A pronounced increase in the number of patients with definitively diagnosed PML, however, was seen in the first 2 months of 1989. The absence of apparent risk factors for HIV infection in 3 of these patients and the on-service physicians' research interest in HIV-related CNS manifestations may help explain the high proportion (100%) with definitive diagnoses.

Patients with AIDS with PML in San Francisco had demographic characteristics similar to patients with AIDS without PML. Although those with PML were significantly older when their AIDS was diagnosed, the significance of this association is not clear.

PML is believed to result from either primary infection or, more likely, reactivation of latent JCV infection [2, 13, 17, 20, 31]. Little is known, however, about transmission and progression from JCV infection to signs and symptoms of CNS involvement. Knowledge of JCV antibody titers in HIV-infected patients did not help us identify persons who were at higher risk for contracting PML. Sixty-four percent of our patients had antibodies to JCV 1 to 9 years before diagnosis of PML, a proportion similar to that of our control subjects and to the reported JCV seroprevalence rate of approximately 65% for adults with nor-

mal immune systems [32, 33]. Our data suggest that PML in most of our patients was caused by reactivation of JCV because many patients had antibodies years before becoming ill. Primary infection may also play a role because 40% of our patients were JCV antibody negative at the time of initial testing.

Our study had several limitations. Patient ascertainment was incomplete because we had access to discharge data from only 6 of 10 hospitals reporting patients with PML to SFDPH; computerized discharge data were not available at all sites, and neuroimaging results were not systematically documented or reported, making this form of patient identification cumbersome and open to error. Another limitation was the omission of essential data from many medical records because of California law prohibiting unauthorized disclosure of HIV status, a restriction requirement that discouraged entry of HIV antibody results. In addition, the seroprevalence study was limited by the small number of patients with sera available for testing. A prospective study using serial serum and CSF samples obtained both before and at the time of PML diagnosis is needed.

Although PML is rare, even in patients with AIDS, our review suggests that, through February 1989 in San Francisco, this disease was diagnosed more than 1.5-fold as often as is reflected in AIDS surveillance data. This difference is largely due to the many presumptively diagnosed patients with PML and to PML that develops in patients with previously diagnosed AIDS. The CDC criteria for patients with definitive PML are useful for examining trends in disease; however, these criteria may result in the underestimation of the incidence of PML among HIV-infected patients. If presumptively diagnosed patients with PML were reflected in surveillance data, the incidence of AIDS-related PML would increase. Further, the annual ratio of patients with definitive PML to patients with presumptive PML has varied over time. Given the difficulties in diagnosing PML, use of the CDC criteria for patients with definitive PML assures that the majority of reported patients are indeed correctly diagnosed. Despite some differences in the clinical signs and symptoms, patients with PML diagnosed presumptively did not differ significantly from patients diagnosed definitively. This study indicates that between 1981 and 1988 the total increase in patients with PML in San Francisco paralleled the increase in reported patients with AIDS. As the AIDS epidemic continues, the importance of further research and education regarding diagnosis and treatment of PML will undoubtedly increase.

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