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Progressive multifocal leukoencephalopathy in patients with HIV infection

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Progressive multifocal leukoencephalopathy (PML), a formerly rare disease, is estimated to occur in up to 5% of all patients with AIDS. The high prevalence of PML in AIDS patients currently enables a comprehensive evaluation of this disorder. We evaluated the clinical and radiographic features of PML in a large cohort of AIDS patients identified by retrospective chart review from 1981 to 1994. Two hundred and five patients were diagnosed with PML of which 154 met the inclusion criteria. Seventy-two (47%) were pathologically confirmed and the remaining 82 (53%) met clinical and radiographic criteria. There was a 12-fold increase in the frequency of PML between 1981–1984 and 1991–1994. PML affected 136 men and 18 women with AIDS. Eighty-four percent of cases were 20–50 years old (range 5 to 68 years). The most common AIDS risk factors were homosexuality (57%) among men and heterosexual transmission (28%) and intravenous drug abuse (28%) among women. In 27% of patients, PML heralded AIDS. Common manifestations included weakness, gait abnormalities, speech disturbance, cognitive disorders, headache, and visual impairment. The CD4 lymphocyte counts exceeded 200 cells in 11% at the time of presentation. Involvement of posterior fossa structures was evident in 48% of cranial magnetic resonance imaging (MRI) studies, but in only 11% of computed tomographies (CT) of the brain. Contrast enhancement, typically faint and peripheral, was seen in 10% of CT scans and 15% of MRIs. The median survival was 6 months and survival exceeded 1 year in 9%. PML is no longer a rare disease. It often heralds AIDS and may occur in the absence of significant decline in CD4 lymphocytes. Survival is generally poor, although prolonged survival beyond 1 year is not unusual.

Keywords: progressive mutlifocal leukocencephalopathy; JC virus; AIDS; Human immunodeficiency virus; type 1

Introduction

Progressive multifocal leukoencephalopathy (PML) was first crystallized as a syndrome by Åstrom, Mancall, and Richardson in 1958 on the basis of characteristic histopathological features (Åstrom, 1958). A viral etiology was proposed due to recognition of inclusion bodies in the nuclei of damaged oligodendrocytes (Cavanaugh *et al*, 1959). Electron microscopic criteria suggested a polyoma virus (ZuRhein, 1967; 1969), later confirmed by isolation of a papovavirus in human fetal brain cultures (Padgett *et al*, 1971). In almost, if not all instances, the papova virus responsible for PML is the JC virus (Major *et al*, 1992). Seroepidemiologic studies have revealed that the majority of the world's population develops antibody to this virus at an early age (Rhiza, 1978; Walker and Padgett, 1983). By middle adulthood, 80–90% of the population have IgG antibodies against JC virus and seroconversion rates have exceeded 90% in some urban areas (Walker and Padgett, 1983).

PML is typically observed in the setting of cellular immunodeficiency. The initial report was in individuals with chronic lymphocytic leukemia and Hodgkin's disease (Åstrom *et al*, 1958). In 1984, a review of 230 previously published cases of PML revealed that lymphoproliferative disease were the most common underlying disorders accounting for 62.2% of the cases. Other predisposing illnesses

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included myeloproliferative diseases in 6.5%, carcinoma in 2.2%, granulomatous and inflammatory diseases, such as, tuberculosis and sarcoidosis, in 7.4% and other immune deficiency states in 16.1%. AIDS was included in the latter category and was observed in only 3.0% of the total cases (Brooks and Walker, 1984).

The first description of PML complicating AIDS was reported in 1982 (Miller *et al*, 1982), 1 year after the initial description of AIDS. By the late 1980s, AIDS was reported to be the most common underlying disorder predisposing to the development of PML at insitutions in New York (Krupp *et al*, 1985) and Miami (Berger *et al*, 1987). AIDS has been estimated to be the underlying disease for PML in 55% to more than 85% of all current cases (Major *et al*, 1992).

The subsequent evolution of the AIDS epidemic has resulted in a significant change in the epidemiology of PML. This formerly rare disease has become remarkably common. Gillespie and colleagues (Gillespie *et al*, 1991) found that patients with AIDS in the San Francisco Bay area have an estimated prevalence of PML of 0.3%, although the investigators acknowledged that this may be a significant underestimate. Based on reporting of AIDS to the Centers for Disease Control (CDC) between 1981 and June 1990, 971 (0.72%) of 135 644 individuals with AIDS were reported to have PML (Holman *et al*, 1991); this is also likely a significant underestimate of the true prevalence due to the notorious inaccuracies in death certificate reporting (Messite and Stellman, 1996) and the requirement of pathologic confirmation for inclusion in this study. Other studies have suggested that the prevalence of PML in AIDS cases is substantially higher than that reported by the CDC with most estimates ranging between 1–5% in clinical studies and as high as 10% in pathological series (Krupp *et al*, 1985; Berger *et al*, 1987; Stoner *et al*, 1986; Lang *et al*, 1989; Kure *et al*, 1991; Kuchelmeister *et al*, 1993; Whiteman *et al*, 1993). In 1987, a large, retrospective, hospital-based, clinical study (Berger *et al*, 1987) found PML in approximately 4% of patients hospitalized with AIDS. In a combined series of seven separate neuropathological studies comprising a total of 926 patients with AIDS (Kure *et al*, 1991), 4% had PML. Two other large neuropathologic series found PML in 7% (Lang *et al*, 1989) and 9.8% (Kuchelmeister *et al*, 1993) of autopsied AIDS patients. The authors of the latter study acknowledged that an unusually high estimate may have resulted from numerous referral cases from outside the study center (Kichelmeister, 1993). However, a study of 548 consecutive, unselected autopsies between 1983 and 1991, performed on patients with AIDS by the Broward County (Florida) Medical Examiner revealed that 29 (5.3%) had PML confirmed at autopsy (Whiteman *et al*, 1993). Although these estimates may be susceptible to selection bias, there does appear to be a marked increase in the frequency with which PML has been observed since the inception of the AIDS epidemic.

The remarkable increase in frequency of PML associated with HIV infection has allowed us to study the largest series of PML patients reported to date.

Results

During the time period of this study, 205 patients were diagnosed with PML, however, 51 patients did not meet the inclusion criteria. The remaining 154 patients were included in this study: 72 were pathologically-proven by brain biopsy (31), autopsy (38), or both (3); 82 met the clinical and radiographic criteria for inclusion, but did not have pathologic confirmation.

Of the 51 excluded cases, 11 without pathological confirmation of PML had alterations in mental state, but no focal findings on neurological examination; because of the concern of misinterpreting the white matter changes of HIV dementia seen on CT scan or MRI for those of PML (Whiteman *et al*, 1993; Olesen *et al*, 1988; Post *et al*, 1988), these patients were excluded from the study. In three of these 11, seizures prompted medical evaluation. Nine patients were excluded because concomitant established illnesses may have explained their neurological findings. The spectrum of these illnesses included CNS toxoplasmosis (3), primary central nervous system lymphoma (1), neurosyphilis (1), meningitis (3 – cryptococcal, tuberculous, and unidentified pathogen), and cocaine overdose (1). Six patients without pathologically proven PML failed to meet the CT or MRI inclusion criteria; mass effect was observed in four of these six. Seven patients failed to meet both the clinical and the radiographic inclusion criteria. Histopathology failed to establish the diagnosis in two patients: biopsy in one patient was interpreted as shown 'alcoholic cerebellar degeneration' and autopsy in another revealed multiple cerebral infarctions and the pathological hallmarks of HIV dementia (Katz *et al*, 1994). Two patients with pathologically-proven PML were excluded as they were not HIV infected: one was a 15-year-old boy with Wiskott-Aldrich syndrome who has been previously reported (Katz *et al*, 1994) and the other was a 58-year-old woman with Hodgkin's disease. In 14, insufficient data precluded proper assessment.

All but nine of the 154 patients with PML lived in a four county region (Dade, Broward, Palm Beach and Monroe) of south Florida. As shown in Figure 1, a dramatic increase in the annual frequency of PML among the 145 HIV-infected persons from south Florida was observed during the study period. During the first 4 years of the study (1981–1984)

only six confirmed cases were identified. In contrast, during the last 4 years (1991–1994), 69 cases were identified. This represents nearly a 12-fold increase in the number of identified PML cases among HIV-infected persons over this 14-year period.

The age distribution of the study population is depicted in Figure 2. This mean age was 39 years (s.d.=10.3) with a range of 5–68 years. Four patients were under 20 years old: the three pathologically-confirmed cases were 10, 13, and 19 years old, respectively, and the single clinically-diagnosed case was 5 years old. Two of the children with pathologically-confirmed PML had been reported previously (Berger *et al*, 1992), the youngest of whom had been infected by HIV during liver transplantation for congenital biliary atresia. The 5-year-old child had acquired HIV by maternal-fetal transmission as had the 13-year-old child, who had been the subject of a report on prolonged latency to the development of symptomatic HIV disease following vertical transmission (Burger *et al*, 1990). The 19-year-old girl had acquired HIV by heterosexual transmission.

There were a total of 136 males and 18 females in the study. Among the males, the most common identified risk factor (Table 1) for HIV infection was homosexuality/bisexuality. As an isolated risk factor for HIV infection, it accounted for 57% of the total group and was identified as a potential risk factor in another 4% in whom multiple risk factors were present, such as, gay men who were also parenteral drug users. Among females, the most commonly identified risk factors were heterosexual transmission (28%) and parenteral drug use (28%), although the numbers were small and no risk factor was identified in 33% of this group. Many of the women without identified risk factors were suspected to have acquired HIV through heterosexual transmission.

Historical data regarding the existence and nature of other AIDS-related were available in 135 cases at the time of presentation. PML was the initial AIDS-defining illness in 36 (27%) of these cases.

CD4 lymphocyte counts were obtained either at the time of diagnosis or within 6 months of diagnosis in 94 patients. The mean CD4 count was 104 cells/mm^3 (s.d.=143.0) and the median CD4 count was 54 cells/mm^3 with a range of 0 to 793 cells/mm^3. Eleven percent of the study population (10 cases) had CD4 lymphocyte counts in excess of 200 cells/mm^3 within 6 months of diagnosis of PML.

Symptoms and signs were evaluable in 139 and 144 cases, respectively. The initial symptoms of PML are summarized in Table 2. The most common

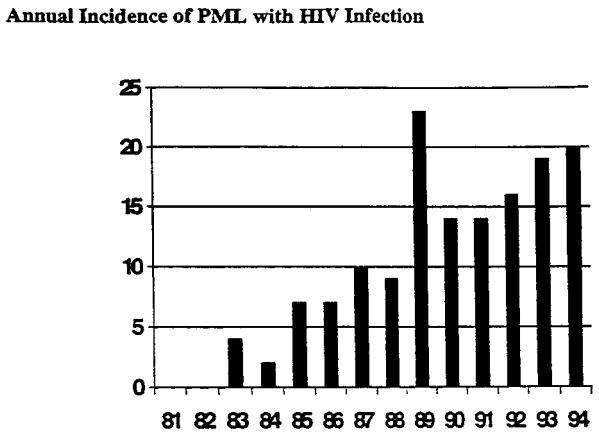

Figure 1 Annual incidence of PML with HIV infection.

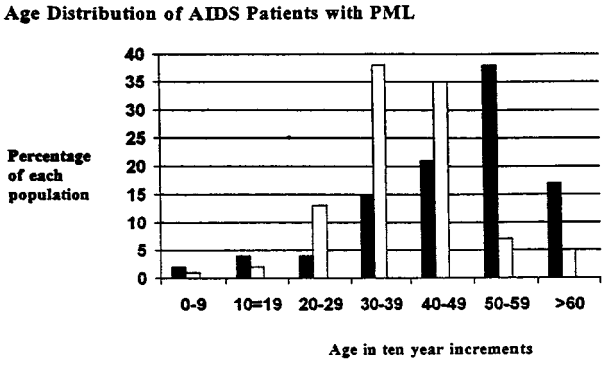

Figure 2 Age distribution of AIDS patients with PML. The change in the pattern of age distribution of PML since the AIDS era is highlighted in this figure. The clear bars display the age distribution of AIDS patients with PML from this study and the solid bars represent the age distribution of 53 pathologically and virologically proven cases of PML published in 1983. None of the patients in the latter study were identified as having AIDS.

Table 1 Risk factors for HIV infection.

Risk factor	*Men* n=*136*	*Women* n=*18*	*Combined* n=*154*
Gay/bisexual	78 (57%)	0 (0)	78 (51%)
Heterosexual	16 (12%)	5 (28%)	21 (14%)
IVDA	13 (10%)	5 (28%)	18 (12%)
Blood products	5 (4%)	1 (6%)	6 (4%)
Multiple	10 (7%)	1 (6%)	11 (7%)
Unknown	14 (10%)	6 (33%)	20 (13%)

Table 2 Initial symptoms of PML.

Symptom	n=*139*
Weakness	59 (42%)
Speech abnormalities	56 (40%)
Cognitive abnormalities	50 (36%)
Headache	45 (32%)
Gait abnormalities	40 (29%)
Sensory loss	27 (19%)
Visual impairment	26 (19%)
Seizures	13 (9%)
Diplopia	13 (9%)
Limb incoordination	9 (6%)

initial symptoms included weakness, speech abnormalities, cognitive abnormalities, headache, and gait abnormalities. The initial signs of PML are summarized in Table 3. The most common initial signs included weakness, cognitive abnormalities, gait abnormalities, and dysarthria.

No strict neuroimaging protocol was followed in these patients. CT scans of the head were available for analysis in 99 patients at the time of initial presentation, and in 117 patients at some point in their illness. The CT scan at presentation was interpreted as normal in 13 patients. In ten of these patients, an MRI obtained 1 day to 2 months later was abnormal. In the other three, repeat CT scans obtained 13 days to 22 months later demonstrated abnormalities consistent with PML. Cranial MRI scans were available for analysis in 109 patients at the time of initial presentation, and in 111 patients at some point in their illness. No cranial MRIs were interpreted as normal. The distribution of lesions on MRI at the time of initial clinical presentation is illustrated in Table 4. Posterior fossa lesions were observed in only 11% of the initial CT scans in comparison to 48% of the MRIs. Contrast enhancement was observed in 10% of the CT scans obtained and in 15% of the MRIs. The contrast enhancement was typically faint and present at the edges of the lesion. When there were multiple lesions, contrast enhancement was generally evident in at least one of these lesions. Mild mass effect was evident radiographically in two (3%) of the 72 patients with pathologically proven disease. Any patients with mass effect on radiographic imaging who did not have pathological confirmation by brain biopsy or at autopsy were excluded from the study.

Cerebrospinal fluid studies were obtained on 67 patients. The mean cell count was 7.7 cells/mm^3 (s.d.=36.7) with a median of 2 cells/mm^3 and a range of 0 to 301 cells/mm^3. Fifty-six (83.6%) had normal cell counts (0 to 5 cells/mm^3), 10 (14.9%) had mild CSF pleocytosis (6 to 50 cells/mm^3), and only one (1.5%) had a marked CSF pleocytosis (greater than 200 cells/mm^3). The mean CSF protein was 66.5 ng/dl (s.d.=37.7) (0.664 gm/L; s.d.=0.377 gm/L) with a median of 58 mg/dl (0.58 gm/L) and a range of 17 to 180 mg/dl (0.17 to 1.8 gm/L). Thirty (44.8%) had normal CSF protein levels of 15 to 50 mg/dl (0.15 gm/L to 0.5 gm/L), 20 (30%) had levels of 51 to 100 mg/dl (0.51 to 1.0 gm/L), and 17 (25.4%) had levels greater than 100 mg/dl (>1.0 gm/L). The mean CSF glucose was 54.2 mg/dl (s.d.=11.4) (3.01 mmol/L; s.d.=0.63 mmol/L) with a median of 52 mg/dl (2.88 mmol/L) and range of 31 to 87 mg/dl (1.72 to 4.83 mmol/L). Nine (13.4%) had hypoglycorhachia defined as glucose values less than 45 mg/dl (2.5 mmol/L) and two did not have CSF glucose determinations. Of those with hypoglycorrhachia, four had values between 40 to 45 mg/dl (2.2 to 2.5 mmol/L), five had values between 30 to 39 mg/dl (1.67 to 2.16 nmol/L), and none had values below 30 mg/dl (<1.67 mmol/L).

The median survival was 183 days (95% confidence interval 155 to 303 days) (Figure 3). Six (8.3%) of the 72 pathologically proven cases had survivals in excess of 12 months (range 18 to 92 months). Eight (9.4%) of the 82 non-pathologically confirmed cases had survivals exceeding 12 months with the longest length of survivorship exceeding 37 months in this group. All but one of the six patients in the pathologically confirmed

Table 3 Initial signs of PML.

Sign	n=*144*
Weakness	78 (54%)
Gait abnormalities	41 (28%)
Cognitive abnormalities	40 (28%)
Dysarthria	34 (24%)
Aphasia	28 (19%)
Sensory loss	27 (19%)
Visual impairment	25 (17%)
Oculomotor palsy	8 (6%)
None	8 (6%)

Table 4 Location and nature of lesions on MRI (*n*=111).

Hemisphere	*89 (80%)*
Frontal	30 (27%)
Temporal	17 (15%)
Parietal	39 (35%)
Occipital	23 (21%)
Corpus callosum/centrum semiovale	21 (19%)
Internal capsule/basal ganglia	13 (12%)
Thalamus	16 (14%)
Posterior fossa	*53 (48%)*
Cerebellum	38 (34%)
Brainstem	39 (35%)
Contrast enhancement	*17 (15%)*

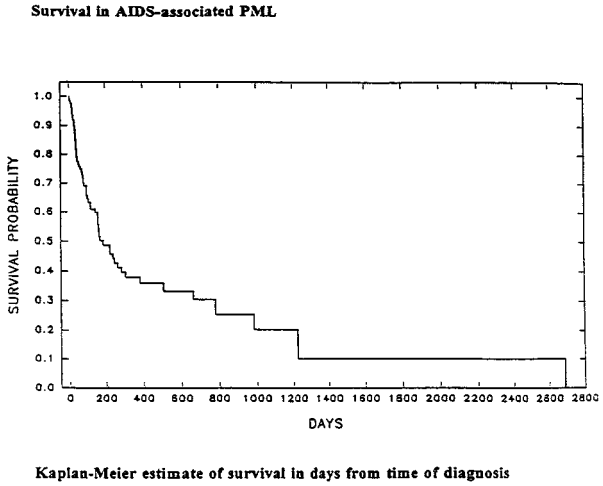

Figure 3 Survival in AIDS-associated PML.

group who had survived greater than 1 year demonstrated both clinical and radiographic improvement after the diagnosis was established. The patient who continued to deteriorate was also the only one in this group to have received therapy directed at JC virus, namely, intravenous cytosine arabinoside.

Discussion

During the 14 year study period, the frequency of PML in the study population increased dramatically. In the first 2 years of the study, 1981 and 1982, no cases of PML were observed, whereas in the last 4 years of the study there were an average of 18 cases per year. The Multicenter AIDS Cohort Study also identified a dramatic rise in the incidence of PML over a similar time period. Specifically, the Multicenter AIDS Cohort Study identified 22 cases of PML among the cohort of AIDS cases studied from 1985 to 1992: the average annual incidence of PML was 0.15 per 100 person-years with a yearly rate of increase of 24% between 1985 and 1992 (Bacellar *et al*, 1994).

In this study, only two patients (both pathologically proven) from among the 156 cases meeting our criteria for the diagnosis of PML did not have AIDS as the underlying etiology of their immunosuppression. The reasons for the high rate of PML in HIV infection in comparison to other predisposing causes, such as lymphoproliferative disorders and organ and bone marrow transplantation, are unknown. Possible explanations include differences in the degree and duration of the cellular immunosuppression in HIV infection, facilitation of the entry into the brain of JC virus infected B-lymphoctyes (Houff *et al*, 1988) by alterations in the blood-brain-barrier due to HIV (Power *et al*, 1993) or the upregulation of adhesion molecules on the brain vascular endothelium due to HIV infection (Hofman *et al*, 1994; Sasseville *et al*, 1992) and the potential for the HIV *tat* protein to transactivate JC virus (Tada *et al*, 1990).

The population with PML is vastly different than it was just a decade ago. In their review of 230 patients with PML in 1984, Brooks and Walker found that males and females were affected in a ratio of 3 : 2 and the incidence of the condition increased steadily from middle age (Brooks and Walker, 1984). More than 50% of individuals with PML had lymphoproliferative disease as the underlying etiology (Brooks and Walker, 1984). In contrast, in our population currently, AIDS is the overwhelming predisposing cause for PML. Consequently, the disorder chiefly affects homosexual/bisexual men between the ages of 25 and 50 years, with a correspondingly high male-female ratio of 7.6 to 1.0. PML continues to be rare in children, but it has been reported in this age group (Brooks and Walker, 1984; Berger *et al*, 1992; Wrozlek *et al*, 1995) and it was identified in four cases from the current series.

PML was the initial AIDS-defining illness in more than one quarter of those with PML associated with HIV infection, although figures as high as 57% (16 of 28 patients) have been reported from some smaller series (Fong and Toma, 1995). In patients who are not suspected to be at risk from AIDS, the initial presentation with PML can be a dignostic enigma. Therefore, a high level of suspicion for HIV is required in anyone presenting with focal neurological deficits and abnormal radiographic studies consistent with PML. The importance of a thorough sexual and social history cannot be overemphasized. In those individuals in whom PML occurred subsequent to other AIDS-defining illnesses, there did not appear to be any particular opportunistic disorder that was predictive of its subsequent development.

As anticipated, severe cellular immunosuppression, as defined by CD4 lymphocyte counts below 200 cells/mm^3, was seen in the overwhelming majority of patients. The mean CD4 count in the present study was 104 cells/mm^3, which is similar to that seen in other studies of PML in AIDS patients. The mean CD4 lymphocyte value was 85 cells/mm^3 in one study (Fong and Toma, 1995) and 84 cells/mm^3 in another (von Einsiedel *et al*, 1993). Nevertheless, 11% of patients in the present study had CD4 lymphocyte counts in excess of 200 cells/mm^3.

With few exceptions, the spectrum of symptoms and signs observed in this series is similar to that seen in earlier series of non-HIV related PML (Brooks and Walker, 1984). The symptoms most commonly reported by patients or their caregivers in HIV-associated PML were weakness and disturbances of speech. Other common symptoms included cognitive abnormalities, headache, gait disorders, visual impairment, and sensory loss. Each of these symptoms was seen in more than 15% of patients. Except for headache, the symptoms reported in the present study are similar to those among series of non-HIV-associated PML cases. Indeed, headache was recorded in only 7.2% of PML patients in one large, previous review (Brooks and Walker, 1984). However, headache may be observed with a significant frequency in HIV infection in the absence of underlying neurological disease. In a prospective study in a large cohort of HIV infected patients, headache was reported by 50% of patients at study entry and 2 years later (Berger *et al*, 1996); these headaches were neither associated with the degree of immunosuppression nor with underlying intracranial disease (Berger *et al*, 1996). Therefore, it is quike likely that some of the headaches reported by the patients in this series were unrelated to PML.

Seizures were seen in 9% of patients; this figure approximates that reported by Brooks and Walker (1984), but is less than the 20% reported in a French study of 49 AIDS patients with PML (Moulignier *et al.*, 1995). Seizures in AIDS-associated PML may reflect involvement of the cortex by the JC virus (Sweeney *et al.*, 1994) or may be secondary to some other process of HIV infection of the brain itself (Wong *et al*, 1990). Wong and colleagues (Wong *et al*, 1990) reported no identifiable etiology in 32 (46%) of 70 AIDS patients with seizures and attributed their occurrence to HIV infection.

The most common sign observed with HIV-associated PML was limb weakness occurring in over 50%. Brooks and Walker (1984) noted weakness in 33% of patients with PML at onset of their disease and found it to be present in more than 80% by the time of diagnosis. Cognitive disturbances and gait disorders were observed in 28% each. Diplopia, noted by 9% of patients, was usually the consequence of involvement of the third, fourth or sixth cranial nerves and was typically observed in association with other brain stem findings. As has been observed by others (Brooks and Walker, 1984; Omerud *et al*, 1996), visual field loss due to involvement of the retrochiasmal pathways was significantly more common than diplopia. No patients in this series were observed to have optic nerve disease as a consequence of PML.

From this study alone it is not possible to adequately compare the performance of CT and MRI in the diagnosis of PML, since both radiologic studies were not obtained on every patient, since the studies when obtained were often obtained at different stages of the illness, and since the studies were not reviewed in a blinded fashion. Previous reports (20) suggest that MRI is more sensitive than CT to the presence of lesions. Indeed, in some instances in the present study, lesions that were not observed on the CT scan were conspicuously present on MRI.

The distribution and character of changes on imaging studies can be very helpful in the diagnosis of PML. The absence of intense contrast enhancement and mass effect (except in very rare instances) help to distinguish the lesions of PML from toxoplasmosis and central nervous system lymphoma. Unlike the white matter changes observed radiographically in association with HIV dementia, the lesions of PML are more likely subcortical, often hypintense on T1-weighted MRI, and occasionally show faint, peripheral enhancement (Whiteman *et al*, 1993). In this study, the subcortical white matter of the frontal and parieto-occipital lobes was most commonly affected. In 12% of patients, deep nuclear structures were involved. In one pathologically proven case, both basal ganglia were exclusively affected, resulting in diagnostic confusion. Isolated involvement of the basal ganglia has been previously reported with PML (Kuchelmeister *et al*, 1993; Sarrazin *et al*, 1995). Forty-eight percent of all patients had lesions in the brain stem or cerebellum and in 20% lesions were located solely infratentorially. Because of the association of mass effect with other opportunistic intracranial processes with HIV infection, its presence was an exclusion criteria for the non-pathologically proven group. However, two (3%) patients with pathologically-proven PML demonstrated mild mass effect on radiographic imaging. Therefore, the presence of mass effect cannot be used as an absolute criteria to exclude PML, but it is very rare and typically quite mild. Contrast enhancement was seen in 10% of CT scans and 15% of MRIs. Contrast enhancement of the lesions of PML has been previously noted (Whiteman *et al*, 1993; Sarrazin *et al*, 1995; Wheeler *et al.*, 1993). In some patients with contrast-enhancing lesions that had undergone brain biopsy, inflammation was noted, suggesting that this may be a cause of the blood-brain-barrier breakdown responsible for the contrast enhancement. However, contrast enhancement was also seen in the absence of inflammation (Whiteman, 1993). The rare occurrence of focal hemorrahge in PML lesions detected radiographically (Sarrazin *et al*, 1995; Ng *et al*, 1995) was not observed in this series.

CSF examination was most helpful in excluding other diagnoses. Three patients labelled with PML were not included in this study because of meningitis. *Cryptococcus neoformans* and *Mycobacteria tuberculosis*, respectively, were identified in the CSF of two of these patients. The median CSF cell count was 2 cells/mm^3 and the mean was 7.7 cells/mm^3. Sixteen percent of patients had CSF cell counts $\geqslant 6$ cells/mm^3 and, with the sole exception of one patient with a cell count of 301 cells/mm^3, no counts exceeded 50 cells/mm^3. Fifty-five percent of our patients had an abnormally elevated CSF protein. The highest recorded value was 208 mg/dl (2.08 gm/L). Hypoglycorrhachia was observed in 13.4% of our patients with the lowest recorded value being 31 mg/dl (1.72 mmol/L). These abnormalities are not inconsistent with that previously reported to occur with HIV infection alone (Marshall *et al*, 1988; Katz *et al*, 1989; Elovaara *et al.*, 1987). No trend was observed in this study with respect to other CSF parameters, but these tests were obtained infrequently and inconsistently precluding meaningful analysis. Similarly, polymerase chain reaction (PCR) for JC virus in the CSF was obtained on too few patients for meaningful comment. Several recent studies (Weber *et al*, 1994; Fong *et al*, 1995; McGuire *et al*, 1995) demonstrate a high sensitivity and specificity of CSF PCR for JC virus in PML. Validation of these results and standardization of the methods for CSF PCR for JC virus may eventually obviate the need for brain biopsy to establish the diagnosis.

The prognosis of HIV-associated PML was dismal and not very different from that described in the

pre-AIDS era (Brooks and Walker, 1984). The median survival was 6 months. The length of survival was similar to that observed in the pre-AIDS era (Brooks and Walker, 1984) and in two different cohorts of AIDS patients with PML (Fong and Toma, 1995; Moor and Chaisson, 1996). Survival greater than one year was seen in six (8.3%) pathologically-proven patients with the longest survival being 92 months from the time of onset. Two of these patients have been previously reported (Berger and Mucke, 1988). Subsequent to that initial report, one experienced almost complete clinical and radiographic recovery with a survival of 92 months and the other, surviving 37 months from the time of brain biopsy, experienced significant clinical improvement, but less dramatic radiograhic resolution of her lesions. Eight (9.7%) of the 82 non-pathologically confirmed cases had survival exceeding 12 months. The remarkable clinical and radiographic recovery in some of these patients suggests that remyelination of the lesions of PML is possible. The lack of recurrence of PML in some of the patients exhibiting long term survival and recovery also suggests that the JC virus may be cleared or rendered nonpathogenic.

Although antiretroviral therapy has been anecdotally reported to result in improvement in PML (von Einsiedel *et al*, 1993; Bauer *et al*, 1973; Singer *et al*, 1994; Conway *et al* 1990; Martin-Suarez *et al*, 1994; Fiala *et al*, 1988), in none of the patients in this series did survival appear to be associated with a specific treatment. In general, we failed to notice any significant clinial or radiologic improvement despite the administration of antiretroviral therapy, but incomplete data regarding the type and durations of antiretroviral therapies precluded detailed analysis. Furthermore, we cannot comment on the value of highly active antiretroviral therapy (HAART), particularly, the use of protease inhibitors, nor the prognostic significance of HIV viral load in patients with PML, as this study predated their introduction into the clinical arena.

Cytosine arabinoside has also been associated with improvement in PML with or without underlying HIV infection in anecdotal reports (Bauer *et al*, 1973; Conomy *et al*, 1974; Buckman and Wiltshaw, 1976; Peters *et al*, 1980; O'Riordan *et al*, 1990; Portegies *et al*, 1991) and has been shown to inhibit JC virus replication *in vitro* (EO Major, personal communication). However, intravenous and/or intrathecal cytosine arabinoside administered to eight patients in this series demonstrated no detectable benefit. This lack of benefit of cytosine arabinoside is concords with the results of the AIDS Clinical Trials Group Study #243 in which cytosine arabinoside administered either intravenously or intrathecally showed no benefit in the prognosis of HIV-infected persons with PML in comparison to patients treated with antiretroviral therapy alone (Hall *et al*, submitted). Despite anecdotal reports of improvements in PML following treatment with alpha-interferon either alone (Colosimo *et al*, 1992) or in combination with cytosine arabinoside (Steiger *et al*, 1993), none of the 13 patients treated with alpha interferon and antiretroviral therpy in this series demonstrated a significant clinical or radiograpahic improvement.

PML has ceased to be a rare disease. It will be confronted by phsicians caring for AIDS patients in ever increasing numbers due to the spread of HIV infection and the worsening immunosuppression in HIV-infected persons who are currently asymptomatic.

Methods

This study was a retrospective chart review for the years 1981 through 1994 inclusive. The sources of the records included the outpatient records of the Department of Neurology at the University of Miami School of Medicine, Miami, Florida, the hospital discharge records of Jackson Memorial Hospital/University of Miami Medical Center, and the records of the Broward County Medical Examiner's Office, Fort Lauderdale, Florida, USA. The Broward County Medical Examiner's Office was included because individuals dying with AIDS or serological evidence of HIV infection were routinely autopsied there during the years of this study and many of the patients treated for AIDS at the Univerity of Miami School of Medicine resided in Broward County.

To be considered as a pathologically-confirmed case of PML, the classic histopathological triad of (1) demyelination; (2) hyperchromatic, enlarged oligodendroglial nuclei, and (3) enlarged bizarre astrocytes needed to be demonstrated on biopsy or autopsy specimens of the affected brain. If only two of the above histopathological features were evident, JC virus needed to be demonstrated by *in situ* hybridization techniques or electron microscopy.

In the absence of pathological confirmation, the following criteria were required to be considered as a case of PML: (1) PML was diagnosed clinically; (2) focal neurological findings were evident on neurological examination; (3) focal white matter lesions were present on magnetic resonance imaging (MRI) or computed tomographic scanning (CT); (4) no mass effect was observed on MRI or CT and (5) no other diagnosis to explain the observed abnormalities was established at the time of the initial hospitalization or during follow-up.

Cases of PML included in this study were those with documented HIV infection. Cases were analyzed by age, sex, risk factors for HIV infection. CD4 lymphocyte counts at the time of presentation or the most proximate CD4 lymphocyte count within six

months of diagnosis, whether PML was the heralding illness for AIDS, symptoms and signs of PML, radiographic findings, cerebrospinal fluid (CSF) findings, and survival. Estimates of survival from diagnosis (in days) were determined in SAS using the product-limit (Kaplan-Meier) method. For purposes of this study, the date of the initial radiographic study demonstrating lesions consistent with PML was considered to be the date of diagnosis.

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References

Åstrom KE, Mancall EL, Richardson Jr EP (1958). Progressive multifocal leukoencephalopathy. *Brain* **81;** 92–127.

Bacellar H, Munoz A, Miller EN, *et al* (1994). Temporal trends in the incidence of HIV-1-related neurologic disease: Multicenter AIDS Cohort Study, 1985–1992. *Neurology* **44:** 1892–1900.

Bauer WR, Turel Jr AP, Johnson KP (1973). Progressive multifocal leukoencephalopathy and cytarabine: remission with treatment. *JAMA* **226:** 174–176.

Berger JR, Kaszovitz B, Post JD, Dickinson G (1987). Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection: a review of the literature and report of 16 cases. *Ann Intern Med* **107:** 78–87.

Berger JR, Mucke L (1988). Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology* **38:** 1060–1064.

Berger JR, Scott G, Albrecht J, Belman A, Tornatore C, Major EO (1992). Progressive multifocal leukoencephalopathy in HIV-1-infected children. *AIDS* **6:** 837–841.

Berger JR, Stein N, Pall L (1996). Headache and HIV infection: a case control study. *European Neurol* **36:** 229–233.

Brooks BR, Walker DL (1984). Progressive multifocal leukoencephalopathy. *Neurol Clin* **2:** 299–313.

Buckman R, Wiltshaw E (1976). Progressive multifocal leukoencephalopathy successfully treated with cytosine arabinoside. *Br J Haematol* **34:** 153–158.

Burger H, Belman AL, Grimson R *et al.* (1990). Long HIV-1 incubation periods and dynamics of transmission within a family. *Lancet* **336:** 1234–1236.

Cavanaugh JB, Greenbaum D, Marshall A, Rubinstein L (1959). Cerebral demyelination associated with disorders of reticuloendothelial system. *Lancet* **ii:** 524–529.

Colosimo C, Lebon P, Martelli M, Tumminelli F, Mandelli F (1992). Alpha-interferon therapy in a case of probable progressive multifocal leukoencephalopathy. *Acta Neurol Belg* **92:** 24–29.

Conomy JP, Beard NS, Matsumoto H, Roessmann U (1974). Cytarabine treatment of progressive multifocal leukoencephalopathy. *JAMA* **229:** 1313–1316.

Conway B, Halliday WC, Brunham RE (1990). Human immunodeficiency virus-associated progressive multifocal leukoencephalopathy: apparent response to 3′-azido-3′-deoxythymidine. *Rev Infect Dis* **12:** 479–482.

Elovaara I, Iivanainen M, Valle S-L, Suni J, Tervo T, Lähdevirta J (1987). CSF protein and cellular profiles in various stages of HIV infection related to neurological manifestations. *J Neurol Sci* **78:** 331–342.

Fiala M, Cone LA, Cohen N, *et al.* (1988). Responses of neurologic complications of AIDS to 3′-azido-3′-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl) luanine. I. Clinical features. *Rev Infect Dis* **10:** 250–256.

Fong IW, Toma E (1995). The natural history of progressive multifocal leukoencephalopathy in patients with AIDS Canadian PML Study Group. *Clin Infect Dis* **20:** 1305–1310.

Fong IW, Britton CV, Luinstra KK, Toma E, Mahony JB (1995). Diagonstic value of detecting virus DNA in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *J Clin Microbiol* **33:** 484–486.

Gillespie SM, Chang Y, Lemp G, *et al.* (1991). Progressive multifocal leukoencephalopathy in persons infected with human immunodeficiency virus, San Franciso, 1981–1989. *Ann Neurol* **30:** 597–604.

Hall CD, Dafni U, Simpson D, *et al* (1998). Failure of cytosine arabinoside therapy for human immunodeficiency virus-1 associated progressive multifocal leukoencephalopathy. *N Eng J Med* (in press).

Hofman FM, Dohadwala MM, Wright AD, Hinton DR, Walker SM. (1994). Exogenous tat protein activates central nervous system-derived endothelial cells. *J Neuroimmunol* **54:** 19–28.

Holman RC, Janssen RS, Buehler JW, Zelasky MT, Hooper WC (1991). Epidemiology of progressive multifocal leukoencephalopathy in the United States: analysis of national mortality and AIDS surveillance data. *Neurology* **41:** 1733–1736.

Houff SA, Major EO, Katz D, *et al* (1988). Involvement of JC virus-infected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy. *N Engl J Med* **318:** 301–305.

Katz RL, Alappattu C, Glass JP, Bruner JM (1989). Cerebrospinal fluid manifestsations of the neurologic complications of human immunodeficiency virus infection. *Acta Cytologica* **33:** 233–244.

Katz DA, Berger JR, Hamilton B, Major EO, Post MJD (1994). Progressive multifocal leukoencephalopathy complicating Wiskott-Aldrich syndrome. *Arch Neurol* **51:** 422–426.

Krupp LB, Lipton RB, Swerdlow ML, Leedes NE, Llena J (1985). Progressive multifocal leukoencephalopathy: clinical and radiographic features. *Ann Neurol* **17:** 344–349.

Kuchelmeister K, Gullotta F, Bergmann M, Angeli F, Masini T. (1993). Progressive multifocal leukoencephalopathy (PML) in the acquired immunodeficiency syndrome (AIDS). A neuropathological autopsy study of 21 cases. *Path Res Pract* **189:** 163–173.

Kure K, Llena JF, Lyman WD, *et al* (1991). Human immunodeficiency virus-1 infection of the nervous system: an autopsy study of 268 adults, pediatric and fetal brains. *Hum Pathol* **22:** 700–710.

Lang W, Miklossy J, Deruaz JP, *et al* (1989). Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. *Acta Neuropathol* **77:** 379–390.

Major EO, Amemiya EE, Tornatore CS, Houff SA, Berger JR (1992). Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JV virus-induced demyelinating disease of the human brain. *Clin Microbiol* **5:** 49–73.

Marshall DW, Brey RL, Cahill WT, Houk RW, Zajac RA, Boswell RN (1988). Spectrum of cerebrospinal fluid findings in various stages of human immunodeficiency virus infection. *Arch Neurol* **45:** 954–958.

Martin-Suarez I, Aguayo Canela M, Merino Munoz D, Pujol de la Llave E (1994). Prolonged surival in patients with progressive multifocal leukoencephalopathy associated with AIDS treated with high doses of zidovudine (letter). *Rev Clin Esp* **194:** 136–138.

McGuire D, Barhite S, Hollander H, Miles M (1995). JC virus DNA in cerebrospinal fluid of human immunodeficiency virus-infected patients: predictive value for progressive multifocal leukoencephalopathy. *Ann Neurol* **37:** 395–399.

Messite J, Stellman SD (1996). Accuracy of death certificate completion. *JAMA* **275:** 794–796.

Miller J, Barrett R, Britton C (1982). Progressive multifocal leukoencephalopathy in a male homosexual with T-cell immune deficiency. *New Engl J Med* **307:** 1436–1438.

Moore RD, Chaisson RE (1996). Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med* **124:** 633–642.

Moulignier A, Mikol J, Pialoux G, Fenelon G, Gray F, Thiebaut F (1995). AIDS-associated progressive multifocal leukoencephalopathy revealed by new onset seizures. *Am J Med* **99:** 64–68.

Ng S, Tse VC, Rubinstein J, Bradford E, Enzmann DR, Conley FK (1995). Progressive multifocal leukoencephalopathy: unusual MR findings. *J Comput Asst Tomogr* **19:** 302–304.

O'Riordan T, Daly PA, Hutchinson M, Shattuck AG, Gardner SD (1990). Progressive multifocal leukoencephalopathy – remission with cytarabine. *J Infect Dis* **20:** 51–54.

Olesen WI, Longo FM, Mills CM, Normal D (1988). White matter disease in AIDS: findings at MRI imaging. *Radiology* **169:** 445–448.

Omerud LD, Rhodes RH, Gross SA, Crane LR, Houchin KW (1996). Opthalmologic manifestations of acquired immune deficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ophthalmology* **103:** 899–906.

Padgett BL, Walker D L (1983). Viorlogic and serologic studies of progressive multifocal leukoencephalopathy. In: Sever JL, Madden DL. *Polyomaviruses and human neurological diseases*. Alan R Liss, Inc, New York, pp. 107–117.

Padgett BL, ZuRhein G, Walker D, Echroade R, Dessel B. (1971). Cultivation of papova-like virus from human brain with progressive multifocal leukoencephalopathy. *Lancet* **i:** 1257–1260.

Peters ACB, Versteeg J, Bots GTA, *et al*. (1980). Progressive multifocal leukoencephalopathy: immunofluorescent demonstration of SV40 antigen in CSF cells and response to cytarabine therapy. *Arch Neurol* **37:** 497–501.

Portegies P, Algra PR, Hollar CEM, Prins JM, Reiss P, Valk J, Lange JMA (1991). Response to cytarabine in progressive multifocal leukoencephalopathy in AIDS. *Lancet* **337:** 680–681.

Post MJD, Tate LG, Quencer RM, *et al* (1988) CT, MR and pathology in HIV encephalitis and meningitis. *AJNR* **9:** 469–476.

Power C, Kong PA, Crawford TO, *et al* (1993). Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alteration of the blood-brain-barrier. *Ann Neurol* **34:** 339–350.

Rhiza HJ, Bornkamm G, ZurHausen H (1978). Seroepidemiological studies and serologic response to viral infection. *Med Microbiol Immunol* **165:** 73–92.

Sarrazin JL, Soulie D, Derosier C, Sescop J, Schill H, Cordoliani YS (1995). MRI apsects of progressive multifocal leukoencephalopathy. *J Neuroradiol* **22:** 172–179.

Sasseville VG, Newman WA, Lackner AA, *et al* (1992) Elevated vascular cell adhesion molecule-1 in AIDS encephalitis induced by simiam immunodeficiency virus. *Am J Pathol* **141:** 1021–1030.

Singer EJ, Stoner GL, Singer P, Tomiyasu U, Licht E, Gahy-Chandon B, Tourtellotte WW (1994). AIDS presented as progressive multifocal leukoencephalopathy with clinical respone to zidovudine. *Acta Neurol Scan* **90:** 443–447.

Steiger MJ, Tarnesby G, Gabe S, McLaughlin J, Schapira AH (1993). Successful outcome of progressive multifocal leukoencephalopathy with cytarabine and interferon. *Ann Neurol* **33:** 407–411.

Stoner GL, Ryschkewitsch CF, Walker DL, Webster HD (1986). JC papovavirus large tumor (T)-antigen expression in brain tissue of acquired immune deficiency syndrome (AIDS) and non-AIDS patients with progressive multifocal leukoencephalopathy. *Proc Natl Acad Sci USA* **23:** 2271–2275.

Sweeney BJ, Manji H, Miller RF, Harrison MJ, Gray F, Scaravilli F (1994). Cortical and subcortical JC virus infection: two unusual cases of AIDs associated progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry* **57:** 994–997.

Tada H, Rappaport J, Lashgari M, *et al* (1990). Transactivation of the JC virus late promoter by the tat protein of the type 1 human immunodeficiency virus in glial cells. *Proc Natl Acad Sci USA* **87:** 3479–3483.

von Einsiedel RW, Fife TD, Aksamit AJ, *et al*. (1993). Progressive multifocal leukoencephalopathy in AIDS: a clinicopathological study and review of the literature. *J Neurol* **240:** 391–406.

Walker DL, Padgett BL (1983). The epidemiology of human polyomavirus. In: Sever JL, Madden D (eds) *Polyomaviruses and human neurological disease.* Alan R. Liss, Inc., New York, pp. 99–106.

Weber T, Turner RW, Frye S, Kretzschmer HA, Luer W, Hunsmann G. (1994). Progressive multifocal leukoencephalopathy diagnosed by amplification of JC virus-specific DNA from cerebrospinal fluid. *AIDS* **8:** 49–57.

Wheeler L, Truwit CL, Kleinschmidt-DeMasters BK, Byrne WR, Hannon RN (1993). Progressive multifocal leukoencephalopathy: contrast enhancement on CT scans and MR images. *AJR Am J Roentgenol* **161:** 1049–1051.

Whiteman M, Post MJD, Berger JR, Limonte L, Tate LG, Bell M (1993). PML in 47 HIV+patients. *Radiology* **187:** 233–240.

Wong MC, Suite ND, Labar DR (1990). Seizures in human immunodeficiency virus infection. *Arch Neurol* **47:** 670–642.

Wrozlek MA, Brudkowska J, Kozlowski PB, *et al* (1995). Opportunistic infections of the central nervous system in children with HIV infection: repot of 9 cases and review of the literature. *Clin Neuropathol* **14:** 187–194.

ZuRhein GM (1969). Association of papovirions with a human demyelinating disease (progressive multifocal leukoencephalopathy). *Prog Med Virol* **11:** 185–247.

ZuRhein GM (1967). Polyoma-like virions in a human demyelinating disease. *Acta Neuropathol* **8:** 57–68.