J. Neurovirol. (2013) 19:198–208
DOI 10.1007/s13365-013-0168-8

CLINICAL REVIEW

Progressive multifocal leukoencephalopathy (PML) associated with HIV Clade C—is not uncommon

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Received: 4 March 2013 / Revised: 12 April 2013 / Accepted: 17 April 2013 / Published online: 23 May 2013

Abstract Progressive multifocal leukoencephalopathy (PML) is a rare, subacute, demyelinating disease of the central nervous system caused by JC virus. Studies of PML from HIV Clade C prevalent countries are scarce. We sought to study the clinical, neuroimaging, and pathological features of PML in HIV Clade C patients from India. This is a prospective cum retrospective study, conducted in a tertiary care Neurological referral center in India from Jan 2001 to May 2012. Diagnosis was considered "definite" (confirmed by histopathology or JCV PCR in CSF) or "probable" (confirmed by MRI brain). Fifty-five patients of PML were diagnosed between January 2001 and May 2012. Complete data was available in 38 patients [mean age 39±8.9 years; duration of illness—82.1±74.7 days). PML was prevalent in 2.8 % of the HIV cohort seen in our Institute. Hemiparesis was the commonest symptom (44.7 %), followed by ataxia (36.8 %). Definitive diagnosis was possible in 20 cases. Eighteen remained "probable" wherein MRI revealed multifocal, symmetric lesions, hypointense on T1, and hyperintense on T2/FLAIR. Stereotactic biopsy (n=11) revealed demyelination, enlarged oligodendrocytes with intranuclear inclusions and astrocytosis. Immunohistochemistry revelaed the presence of JC viral antigen within oligodendroglial nuclei and astrocytic cytoplasm. No differences in clinical, radiological, or pathological features were evident from PML associated with HIV Clade B. Clinical suspicion of PML was entertained in only half of the patients. Hence, a high index of suspicion is essential for diagnosis. There are no significant differences between clinical, radiological, and pathological picture of PML between Indian and Western countries.

Keywords Progressive multifocal leukoencephalopathy · JC virus · Stereotactic biopsy

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Introduction

Progressive multifocal leukoencephalopathy (PML), is a rare, subacute, demyelinating disease of the central nervous system caused by infection of the oligodendrocytes and astrocytes by an opportunistic polyoma virus—JC virus (JCV). There are seven different genotypes of JCV occurring in different geographical regions (Dubois et al. 2001); the circulating genotypes in India being type 2 and 7 (Agostini et al. 2001).

Being an opportunistic pathogen, it causes disease predominantly in the immunocompromised host, including those with lymphoproliferative disorders, Hodgkin's lymphoma, HIV, patients on antineoplastic therapy, and more recently, increasing incidence is noted in patients with autoimmune disorders (multiple sclerosis, Crohn's disease) receiving therapy with monoclonal antibodies like natalizumab, efalizumab, and rituximab (Saribas et al. 2010). Progressive multifocal leukoencephalopathy (PML) occurs in 1–4 % of patients with advanced HIV infection (Berger et al. 1987; Adcock et al. 1997).

Prior to the AIDS epidemic, the incidence of PML was very low (0.07 %) and the incidence increased to nearly 3–5 % in the West in the HIV positive subjects (Saribas et al. 2010). The incidence of PML was believed to be low in

India and Africa and was attributed to the differences in host susceptibility and pathogenetic potential differences in HIV-1 subtypes; subtype C being predominant in Asia and Africa unlike Clade B in the West (Shankar et al. 2003). We reviewed our cohort of HIV positive patients with neurological complications to determine the prevalence of PML in a tertiary care university hospital and compare the clinical, neuroimaging, and neuropathological findings with that reported in the Western literature.

Materials and methods

All HIV seropositive positive patients presenting with neurological complications between Jan 2001 to May 2012 (11.5 years) in a tertiary care hospital in South India catering to neurological, neurosurgical, and psychiatric diseases were reviewed. The demographic profile, age at onset, clinical presentation, neurological findings, evidence of co-existent or past opportunistic infections, and systemic features were reviewed. Treatment history including the details of highly active antiretroviral therapy (HAART)/opportunistic infection prophylaxis were noted. Patients were investigated with complete hemogram, renal, liver function tests, and VDRL test for syphilis. Depending on available resources; the CD4 count, HIV viral loads, and PCR test to detect the presence of JCV in CSF were performed. CSF analysis following a lumbar puncture was performed in all, except in cases where the procedure was contraindicated, to rule out other neuroinfections. Radiological tests included chest skiagram to look for evidence of pulmonary tuberculosis, pneumocystis carinii infection, etc., and neuroimaging [contrast enhanced computed tomography (CT) scan/MRI brain with T1, T2, FLAIR, or both]. Diagnostic brain biopsy was performed in eleven cases, following informed consent. A clinical autopsy limited to the examination of brain was carried out in those who expired following written, informed consent from the next of kin.

The patients were classified as cases of "definite" or "probable" PML based on the following criteria (Cinque et al. 2003):

a) Probable PML (Clinical and Imaging criteria):
   i. Clinical history suggestive of PML (gradually progressive focal neurological deficit without evidence of raised intracranial tension)
   ii. Presence of focal neurological deficits
   iii. MRI or CT brain showing multifocal non-enhancing, white matter lesions, without perilesional edema.
   iv. Exclusion of other diagnoses to explain the observed radiological abnormalities at the time of initial visit or follow-up.

b) Definite PML: In addition to the clinical and imaging criteria;
   i. ***Histology confirmed*** - by stereotactic brain biopsy or autopsy examination
   ii. ***Laboratory confirmed*** – Presence of JCV in CSF as confirmed by JCV PCR whenever feasible.

Histopathological diagnosis of PML was considered in the presence of classic triad of (a) zones of demyelination, (b) enlarged oligodendroglia with intranuclear basophilic inclusions, and (c) enlarged, bizarre astrocytes in lesions examined at autopsy/biopsy and immunohistochemical localization of JC virus antigen in the glial cells.

Statistical Analysis

The data was analysed using SPSS-16 statistical software package for descriptive and analytical statistics. The results were expressed as mean with standard deviation and range for continuous variables and as percentages for discrete variables. Logistic regression analysis was used to identify prognostic factors.

Results

During the 11.5-year-study period (January 2001–May 2012), 1,965 HIV patients with neurological manifestations were evaluated in our neurological institute. Among these, 55 patients were suspected to have PML (2.8 %). Thirty-eight patients were included in the current study cohort and others were excluded due to various reasons as enumerated in Fig. 1. The mean age of the cohort was 39±8.9 years

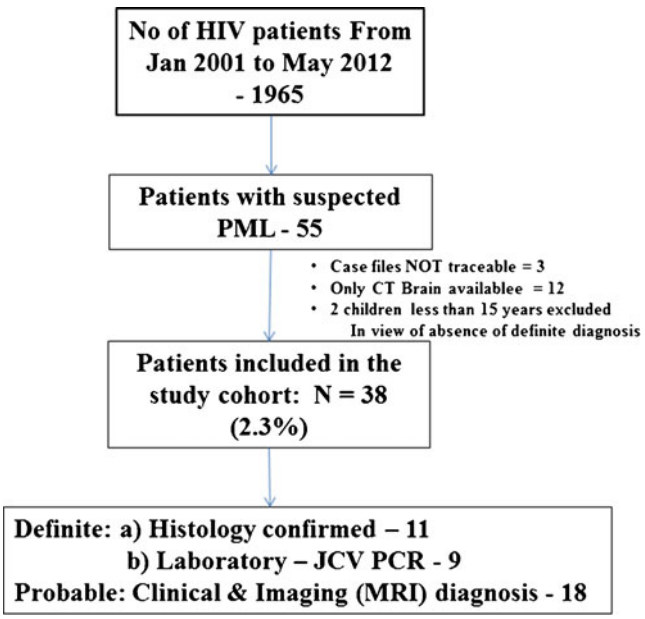

Fig. 1 Causes for case exclusion

(range 25 to 68 years, M:F=29:9). The duration of illness at the time of initial presentation ranged from 1 to 360 days (mean ± SD=82.1±74.7 days) and 81 % of the patients presented within three months of the onset of illness. Twenty patients were definite cases of PML (histology confirmed, 11; JCV PCR confirmed, 9), while 18 patients were probable cases as per the inclusion criteria.

Clinical features The various clinical manifestations are listed in Table 1. Hemiparesis was most frequent (44.7 %) followed by ataxia (36.8 %), speech and cognitive disturbances (26.3 % each). Cognitive disturbances were in the form of memory impairment, behavioral abnormalities, and altered sensorium. Speech disturbances were either spastic, cerebellar, or a combination of both. Headache was diffuse, non-localizing in a few (13.2 %) and was unassociated with other symptoms of raised intracranial tension. Five (13.2 %) patients presented with seizures; three with focal seizures and two had generalized seizures. Visual dysfunction in the form of decreased visual acuity was found in 4 (10.5 %) patients. Involuntary movements in the form of tremors were noted in two (5.3 %) patients. Both these patients had gradually progressive hemiplegia along with cerebellar disturbances which is one of the classical presentation of PML. One of the patient had mild intentional tremor whilst the other had titubation, voice tremor and wing-beating tremor of proximal upper limb. Systemic findings were frequent that included—weight loss (56.8 %), malnutrition (51.4 %), fever (32.4 %), anemia (29.7 %), skin and hair changes in the form of hyperpigmentation, dermatitis, alopecia (24.3 %), oral candidiasis (13.5 %), cough (10.8 %), diarrhea (8.1 %), and chronic suppurative otitis media (CSOM—2.7 %).

Prior history of CNS opportunistic infections was recorded in nine (24.3 %) patients; four had tubercular meningitis, three had Varicella zoster radiculopathy (one patient had 2 episodes of herpes zoster in the thoracic dermatomes), and one case each had toxoplasma meningoencephalitis and cryptococcal meningitis. Non-infectious CNS complications were noted in nine (24.3 %) patients in the form of: seizures (4), psychosis (1), HAART-induced neuropathy (1), and subdural hematoma (1). Nearly half (~54 %) of the study cohort had other non-neurological systemic opportunistic infections. Pulmonary tuberculosis was the most common (24.3 %), followed by tuberculous lymphadenitis (5.4 %), hepatitis (5.4 %), tuberculous knee effusion (2.7 %), oesophageal candidiasis (2.7 %), CSOM (2.7 %), cytomegalovirus (CMV) retinitis (2.7 %), and pneumocystis carinii pneumonia in 2.7 %.

Table 1 Various clinical presentation in the study cohort

Clinical features	*N*	Percentage
Hemiparesis	17	45.9
Ataxia	14	37.8
Cognition	10	27
Speech	10	27
Cranial nerve	6	16.2
Seizures	5	13.5
Headache	5	13.5
Vision	4	10.8
Quadriparesis	3	8.1
Monoparesis	3	8.1
Hemisensory	3	8.1
Movement disorders (tremor)	2	5.4
Paraparesis	1	2.7

PML was the AIDS defining illness in 29 (76.3 %) patients. Nearly half (56.8 %) of the patients were detected to have immunocompromised state after admission to our hospital and evaluation. Sixteen (43.2 %) patients were already detected to be immunocompromised at admission, and 13 (35.1 %) patients were on HAART prior to presentation to the neurological services. PML was suspected clinically in only 50 % of the patients during initial evaluation. Other clinical diagnosis entertained during initial presentation to the hospital is depicted in Fig. 2.

Investigations CD4 count was available in 23 (60.5 %) patients and it ranged from 50–289 cells/μL (mean ± SD= 153.8±60.0 cells/μL). Lumbar puncture was performed in 35 patients (Table 2). CSF pleocytosis of more than 5 cells/cu mm was noted in 13 (38.2 %) and elevated protein in 25 (73.5 %) patients. Among these, two patients had coexistent CNS opportunistic infections (cryptococcal meningitis—1, toxoplasma meningoencephalitis—1). HIV-1 viral load could be tested in only nine patients due to financial constraints. Haematological and biochemical parameters are depicted in Table 2. Renal parameters were abnormal in five (13.5 %), liver enzymes were deranged in two (5.4 %), and electrolyte abnormality was detected in one (2.7 %). Chest X-ray was abnormal in 13 (26.7 %) patients and revealed features of pulmonary tuberculosis in 9 (69.2 %), pneumocystis pneumonia in 2 (15.4 %), and hilar adenopathy in 2(15.4 %) patients.

Imaging The neuroimaging features are depicted in Table 3. Cranial CT scan was available in 6 (15.8 %) patients, all of whom were confirmed to have PML by PCR positivity in CSF for JCV or by tissue diagnosis (biopsy/autopsy). MRI was performed in 32 (84.2 %) patients. Lesions were predominantly multifocal in 29 (76.3 %) and unifocal in 9 (23.7 %) patients, involving supratentorial compartment in 77.4 % patients, and infratentorial, involving the cerebellum (11.3 %) and brainstem (11.3 %) in 22.6 % patients. Fronto-parietal white matter (44.3 %) was the most frequent site of predilection. Lesions appeared hypodense on CT brain and on MRI; they were hypointense on T1-weighted images and hyperintense on T2-

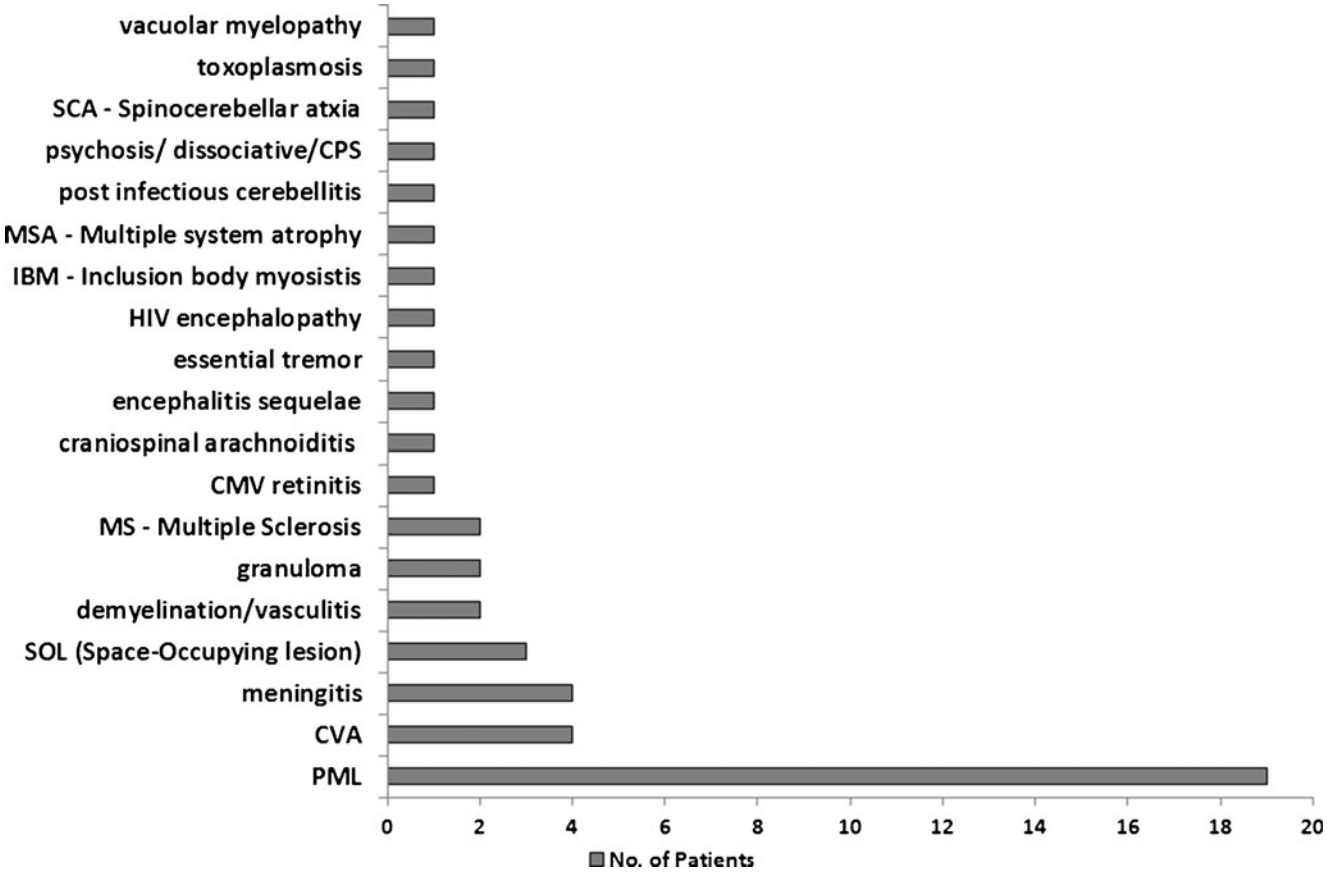

Fig. 2 Probable clinical diagnosis at initial visit

weighted/FLAIR sequence, without mass effect. Contrast enhancement was observed in 8 (21 %) patients. There was no correlation with the CD4 count or survival pattern in patients with contrast enhancement. Grey matter involvement was detected in very few patients restricted to the deep grey matter (thalamus and basal ganglia; Fig. 3, Table 5).

Eight (21 %) patients however revealed faint contrast enhancement at the periphery of the lesions. Four of them were on HAART prior to presentation. CD4 count available in four patients was below 200 mg/dl. Two of them had systemic opportunistic infections in the form of pulmonary tuberculosis and Varicella zoster prior to

Table 2 Haematological, biochemical, and CSF parameters of the cohort

Parameter	Mean	SD	Range	Median
Haemoglobin	12.3	1.7	9–16.2	12.2
TC—total count	6,012	2,497.5	2,500–12,000	5,450
ESR	53.6	26.6	10–130	57.5
Platelets	184,785.7	87,959.6	38,000–435,000	170,500
RBS—random blood sugar	99.4	34.9	42–226	92
Creatinine	1.02	0.5	0.4–3.3	0.9
Total bilirubin	0.6	0.3	0.3–1.7	0.5
SGOT	56.3	105.5	19–637	31
SGPT	36.6	30	7–163	24.5
Sodium	137.7	6.8	119–155	138
Potassium	4	0.4	3–4.8	4.1
CSF cell count	16.7	38.1	0–200	3
CSF protein	99.2	144.9	24–744	55
CSF sugar	56.5	16.2	19–119	56

Table 3 Neuroimaging features

Patient	No. of lesions	Imaging	Site of involvement	Contrast enhancement	Mass effect	Edema	MRS
1	4	CT	B/L cerebellum, parieto-occipital	No	No	No	
2	1	CT	RT frontal	Yes	yes	yes	
3	3	MRI	B/L parieto-occipital, cerebellum	No	No	No	
4	7	MRI	B/L fronto-parietal, B/L thalamus, B/L basal ganglia, brain stem	No	No	No	CH/CR ratio=1.2
5	9	MRI	B/L fronto-parietal and occipital WM				
6	2	MRI	Brain stem, left basal ganglia	No	No	No	CH/CR ratio=2.3
7	2	MRI	LT parieto-temporal	Yes			
8	7	MRI	B/L frontal, B/L thalamus, brain stem, left MCP, left cerebellar W.M.	No	No	No	
9	9	MRI	Brainstem, B/L MCP, cerebellar W.M., I.C. P/L, left caudate		No	No	CH/CR ratio=1.7
10	1	CT	RT frontal	Yes	Yes	Yes	
11	2	MRI	LT fronto-parietal				
12		MRI	RT half midbrain, LT BG	Yes			
13	5	MRI	B/L temporoparietal, right ext. capsule, P/L I.C., splenium	Nodular marginal	No	No	CH/CR ratio=1.8
14	3	MRI	B/L temporal lobes				
15	5	MRI	Brainstem, B/L MCP, cerebellar W.M.	No	No	No	CH/CR ratio=1.9
16	4	MRI	Right parietal, left frontoparieto-occipital, left ext. cap, P/L IC. CC	MARGINAL	No	No	
17	4	MRI	B/L parieto-occipitial	Yes			
18	2	CT	Cerebellum				
19	6	MRI	Right P/L I/C., brainstem, B/L MCP, cerebellar W.M.	No	No	No	CH/CR ratio=1.2
20	2	MRI	B/L frontal WM				
21	3	CT	B/L frontal, RT fronto-parietal				
22	5	CT	LT frontal., B/L parieto-occipital				
23	4	MRI	B/L diffuse cerebral W.M.	No	No	No	CH/CR ratio=1.3
24	2	MRI	Right frontotemporoparietal, right thalamus	No	No	No	CH/CR ratio=1.2
25	2	MRI	B/L anterior temporal	No	No	No	
26	3	MRI	Right temporal, B/L fronto-parietal	No	No	No	
27	1	MRI	RT parietal	No	No	No	
28	7	MRI	B/L medulla pons, midbrain, thalamus, RT frontal, LT parietal				
29	2	MRI	B/L frontal	No	No	No	
30	2	MRI	B/L fronto-parietal	Nodular	No	No	CH/CR ratio=1.2
31	4	MRI	Right basal ganglia, B/L fronto-parietal, CC	No	No	No	
32	4	MRI	Right MCP, cerebellar W.M., left occipital	No	No	No	
33	1	MRI	Corpus callosum				
34	3	MRI	Midbrain, thalamus, left parietal				
35	4	MRI	Brainstem, B/L cerebellum, B/L MCP, left frontal	No	No	No	CH/CR ratio=1.4
36	2	MRI	Fronto-parietal				
37	3	MRI	Left frontal, B/L parietal	No	No	No	
38	5	MRI	Right fronto-parietal, left frontal, right P/L I.C. brainstem, cerebellum	No	No	No	CH/CR ratio=1.6

B/L bilateral; *RT* right; *LT* left; *P/L IC* Posterior limb Internal capsule; *MCP* middle cerebellar peduncle; *WM* white matter; *CC* Corpus callosum; *ext.* external

presentation. Five patients were available for follow-up; two patients have improved with HAART; one of them is the longest survivor in our series followed for 7 years and 3 months.

Two unique imaging findings noted in the series included (a) discrete involvement of pyramidal tract in the internal capsule on the right crossing over to the left side of the brainstem (Sobha et al. 2005) and (b) T2 and FLAIR

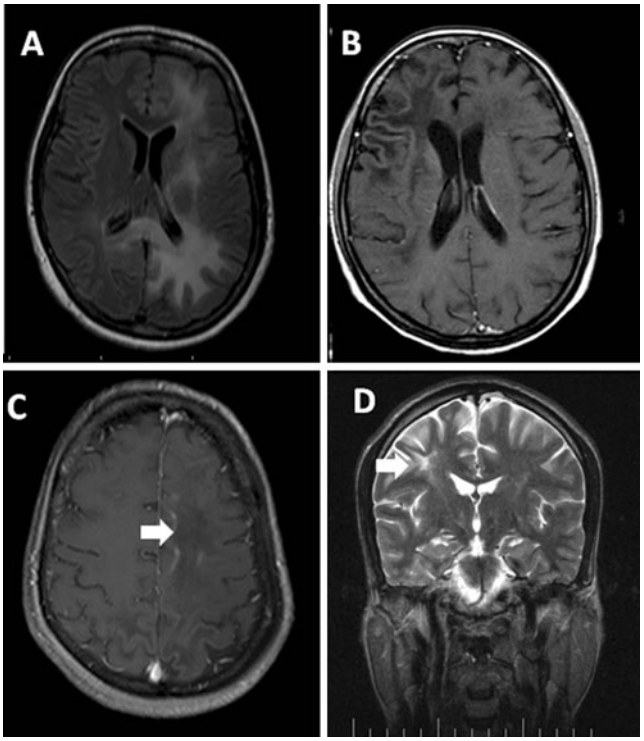

Fig. 3 Imaging. **a** Axial FLAIR hyperintensity involving the left cerebral white matter and the corpus callosum. **b** Axial T1 hypointensity in the right fronto-temporal white matter. **c** Axial T1 gradient image showing mild peripheral contrast enhancement in left frontal region. **d** Coronal T2 hyperintensity involving the right parietal white matter and extending along the internal capsule

cruciform hyperintensities in the Pons resulting in Hot cross bun sign due to the involvement of transverse pontocerebellar fibers, previously reported by Yadav et al (2011).

Pathology Brain biopsy was obtained stereotaxically from radiologically evident lesions in four cases for diagnosis. The lesions were multiple non-enhancing or vaguely enhancing white matter lesions in which diagnosis of tuberculomata, lymphoma, vasculitis, ADEM, glioma, or HIV encephalitis was considered as differential diagnosis. Histology revealed foci of demyelination with variable histiocytic response and perivascular inflammation in all the cases bordered by hypertrophic reactive or bizarre astrocytes with large pleomorphic nuclei. The classical enlarged inclusion-bearing oligodendroglia was seen in only two out of four biopsies, immunostaining for JC viral nucleocapsid demonstrated the presence of the viral antigen within oligodendroglia or within the processes of reactive infected astrocytes confirming the diagnosis in all the cases. No viral antigen was demonstrable within the perivascular inflammatory infiltrates.

Consent for autopsy was obtained in six of the cases who succumbed. Complete autopsy was performed in one, while consent was available for removal of brain alone in five. The brains retrieved at autopsy were fixed in 10 % buffered formalin for 4 weeks before sectioning. On gross examination of the brain, multifocal lesions were found that corresponded to the white matter hyperintense lesions seen on imaging in centrum semiovale, extending along the superior longitudinal fasciculus (Fig. 4a, b). Demyelinating foci were detected in subcortical white matter of frontal, parietal, and occipital white matter extending along the optic radiation (Fig.4c) and tended to involve the subcortical U fibres and commesural fibres of corpus callosum and splenium, cerebellar white matter, cerebellar peduncles, and occipital radiation. The JC viral nucleocapsid on immunohistochemistry was localised to the enlarged oligodendroglia within the basophilic intranuclear inclusions (Fig. 4d, e). The presence of viral capsid was detectable occasionally within the cytoplasm of astrocytes as well. Perivascular inflammation was minimal to absent in all the cases. Lack of significant inflammation reflects the lowered immune response of the host. Ante-mortem biopsies however showed significant perivascular inflammation reflecting relatively heightened immune response of the host early in the disease process and faint enhancement on neuroimaging studies.

Treatment details All the 38 patients were advised HAART regimen (2 NRTI—nucleoside reverse transcriptase inhibitors along with 1 NNRTI—non-nucleoside reverse transcriptase inhibitors). Fifteen patients received HAART. None of them received protease inhibitors or cytosine arabinoside.

Follow-up Patients were discharged after stabilization with anti-retroviral therapy. Follow-up information was available in 22 (59.5 %) patients:

a. Ten (45.5 %) patients expired at home (confirmed by telephonic conversation) within 2–3 months following discharge. Six patients expired in hospital following cardiorespiratory arrest (4 cases) or bronchopneumonia (2 cases).
b. Twelve (54.5 %) patients were followed up with a median duration of 16.5 months (range—3–87 months). All of them were on HAART therapy and had improved completely; and nearly half (50 %) of them had residual neurological dysfunction. The average duration of survival of these patients was 23.8 months.

In our study, the survival exceeded one year in ten patients, the longest survival being 87 months (7 years 3 months). This gentleman had developed recurrent diarrhea during which he was diagnosed to be seropositive. Three months later, he presented with behavioral disturbances. MRI brain revealed left parieto-temporal T2 hyperintense lesions with mild peripheral enhancement on contrast administration. His CD4 count was 111 cells/μL. HIV

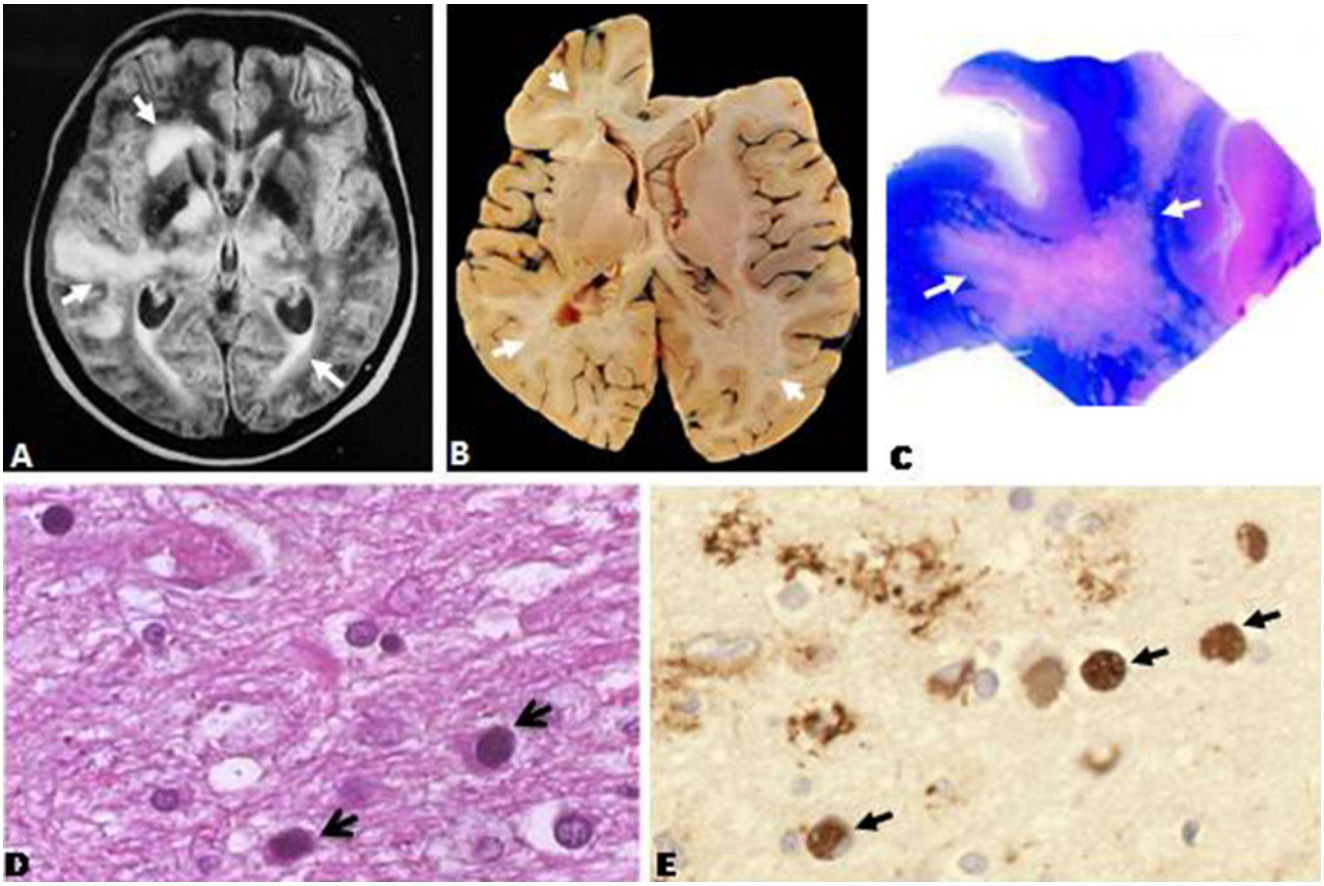

Fig. 4 Neuopathological examination. **a** Multiple white matter hyperintensities seen involving long fibre tracts, subcortical U fibres in bilateral frontal and temporal white matter (*arrows*) extending to involve the optic radiations on both sides (*arrows*) on FLAIR sequences. **b** Brain sliced approximately at same level in axial plane shows granular breakdown of white matter corresponding to hyperintensities on MRI (*arrows*). **c** Luxol Fast Blue stained sections for myelin from frontal cortex reveals large plaque-like demyelination (*arrow*) with multiple smaller satellite pale zones representing multifocal demyelination. d: Section from border of demyelinated zone shows multiple enlarged oligodendroglia with intranuclear basophilic inclusion (*arrow*) and reactive astrocytes. **e** Immunohistochemsitry with antibody to JC viral nucleocapsid highlights JC viral antigen within oligodendroglial nuclei (*arrow*). In addition, astrocytic processes also reveal irregular labeling. [**c** Luxol fast Bluex4, **d** H&ExObj.40, **e** Immunoperoxidase, DAB chromogenxObj.40]

viral load was not available. Stereotaxic brain biopsy was performed showed definite evidence of PML. He was started on HAART. He showed complete improvement (both clinical and radiological) within 1 year of the diagnosis.

Follow-up MRI was available in three (7.9 %) patients (duration, 9 months and 1 year each in the other two patients) which revealed radiologic recovery in the form of gliosis of the initial affected areas without contrast enhancement. Follow-up CD4 count was available in 7 patients (18.4 %) ranging from 72 to 834 cells/μL (mean±SD= 399.9±239.5). None of them developed any other opportunistic infections, although two patients had developed drug induced neuropathy secondary to anti-retroviral therapy. Immune reconstitution inflammatory syndrome was not observed in any of the patients. Although this contradicts previous studies, this could be due to the retrospective nature of the study.

Statistical analysis did not reveal any predictive prognostic factors on comparing variables such as age at presentation, gender, past/associated opportunistic illness, treatment with antiretrovirals, CD4 count at presentation, HIV-1 viral load amongst those who survived (n=12), and those who succumbed (n=16). Complete information regarding CD4 counts, prior HAART therapy, follow-up following HAART therapy, etc., was not available in all cases to determine if these influence survival.

Discussion

This is the first case series reviewing clinical, radiological, and pathological features of HIV-PML patients from a tertiary, university teaching hospital from India. Fifty-five patients were diagnosed to have PML among the 1,965 HIV seropositive patients over a period of January 2001–May 2012,

representing a prevalence of 2.8 % which is comparable with the reports in the Western literature. The prevalence of PML in HIV patients from India was deemed to be low in the past (Shankar et al. 2003). Only three cases of PML were diagnosed clinically and radiologically over a decade (1989–2000) from our institute. Between 2000 and 2012, 55 patients with PML were diagnosed. Underdiagnosis, under reporting of cases, patients succumbing to other commoner opportunistic infections like tuberculosis that occur at a higher CD4 count, possible interaction of HIV Clade C Tat protein with JC virus, and genetic polymorphisms in p53 were the considered causes for low prevalence. The spurt in the number of cases after year 2000 could be attributed to availability of PCR for JC virus and more sophisticated imaging modalities making diagnosis easier without recourse to biopsy/autopsy.

Table 4 presents comparison with other studies reported in the literature. The number of patients in this study was considerably lower compared to the large series reported by Berger et al. 1998a, b, Gillespie et al. (1991), and Khanna et al. (2009). This could be attributed to (a) stringent inclusion criteria as our study included only definitive/probable cases. We excluded cases in whom only CT scans were performed and no other parameter like JCV PCR or histopathological diagnosis were not available, (b) under-reporting, (c) referral bias as ours is a tertiary referral center, and (d) advances in imaging features, wherein those with HIV-encephalopathy were excluded which forms a close differential with PML on imaging. These patients may have been included in previous studies. Other important factor is that predominant HIV infection is due to Clade C virus in India (Siddappa et al. 2004)

Majority of the patients in our study was male (75.7 %). This reflects the high male to female ratio of patients with HIV infection (3:1) in India (Shankar et al. 2003). Due to socioeconomic reasons in India, men are more likely than women to seek medical attention in our country. In our cohort, heterosexual mode of HIV transmission was prevalent. There was no history of intravenous drug abuse, blood transfusion or homosexuality forthcoming. This is in contrast to homosexual behavior and use of intravenous drugs as a common risk factor noted in other studies (Table 4).

Gradually progressive motor weakness (hemiparesis/monoplegia/quadriparesis/paraparesis) was the commonest neurological presentation seen in 24 (64.9 %) patients comparable with the previous studies and reflects the involvement of subcortical white matter tracts. Cognitive changes were less frequent (only 27 %) in contrast to other studies (36–65 %) from West. Cerebellar involvement was noted in 37.8 % of cases constituting the second most common clinical symptom. In a population-based study from Europe, however, the incidence of cerebellar involvement was even higher (68 %; Engsig et al. 2009). Visual deficits due to involvement of optic radiation were seen in 10.8 %,

Table 4 Comparison of the present study with the previous studies reported in the literature

Clinical manifestation	Berger et al. (1998a, b)	Brook and Walker et al.	Gillespie et al. (1991)	Berenguer et al. (2003)	Wyen et al. (2004)	Vidal (2008)	Engsig et al (2009)	Khanna et al. (2009)	Nery et al. (2011)	Present Study 2013
Period of study type of study	1981–1994/ retrospective	To be done	1981–1989	Retrospective	1996–2002/ retrospective	2003–2004/ retrospective	1995–2006	1995–2007	1992–2009/ retrospective	Jan 2001–May 2012/ retrospective or perspective
No. of patients (M/F)	154 (136:18)	74	94 (92:2)	118 (98:20)	35 (34:1)	12 (9:3)	47 (35:12)	159 (118:41)	25 (21:4)	38 (29:9)
Definite histopathology cases	72 (47 %)		48 (81 %)	42	9	0	14 (30)	26 (16 %)	4	11
Definite lab proves				–	17	4	13 (42)	38 (24 %)	2	9
Probable cases	82 (53 %)		46 (49 %)	76	9	8	25 (53)	95 (80 %)	19	18
Median (range) age	39 (5–68)			36	38 (21–55)	36 (25–52)	48.7 (43.3–53)	37 (33–42)	39 (31.5–46)	39 (25–68)
Motor weakness (%)	59 (42 %)	29 (39.2 %)	31 (39 %)	82 (69.5)	18 (51 %)	75 %	20 (43 %)		72 %	24 (64.9 %)

which is similar to other studies. Hemisensory loss secondary to thalamic/spinothalamic tract involvement was seen in 8.1 % of cases. The spectrum of clinical symptomatology was essentially similar to that of the series reported by Berger et al. (1998a, b), except for the low incidence of headache (13.5 %) in this series in contrast to 32 % in the former, and was likely to be related to HIV per se or secondary to depression if all other neurological causes are ruled out (Satishchandra et al. 2000). Seizures were recorded in 13.5 % of our patients, though PML is a white matter disease, reflecting cortical involvement by JC virus. Several of our patients were alcohol dependent and this may explain the higher incidence of seizures in our study.

Movement disorders are noted in 11 % of HIV patients; most commonly due to toxoplasma abscess (Fontoura et al. 2002). These are rarely reported in cases of PML (0–2.6 %) mostly as anecdotal case reports (Fontoura et al. 2002). The various movement disorders reported in literature include Parkinsonism, isolated limb dystonia, and head tremor (Rieder and Ziomkowski 2005; Williams-Gray et al. 2007). Two patients in our series had tremors, and one patient was on HAART for 3 years prior to presentation. Both cases had motor weakness in addition to tremor. MRI brain revealed white matter lesions in the cerebellum in one and the fronto-parietal white matter in another suggesting cortico-striatal or cortico-thalamic pathways involvement as etio-pathogenesis since neither had basal ganglia or thalamic involvement. Both cases showed significant improvement with HAART (one of them required concomitant beta-blockers for some time as adjuvant) on follow-up (18 and 20 months).

Sixteen (43.2 %) patients were detected to be immunocompromised at present admission in our Institute, while 13 (35.1 %) patients were already on HAART prior to hospital admission. The duration of HAART treatment was less than 6 months in all except four patients (36, 60, 60, and 180 months). The prognosis of HIV-PML patients is unpredictable. In the pre-HAART era, the prognosis was uniformly dismal, most succumbing within 4–6 months of diagnosis. Survival has considerably improved with the introduction of HAART; one third of the patients showing improvement (Berenguer et al. 2003). A CD4 count of <100 cells/μL or a JCV DNA levels >3.64 log copies/mL has been correlated with poor outcome (Berenguer et al. 2003; Bossolasco et al. 2005). The longest surviving patient in our series was 7 years and 3 months.

On neuroimaging, the frontal and parietal white matter was the commonest sites involved (44.3 %). Isolated involvement of the posterior fossa was noted in 5 % of cases. In other studies, parietal involvement was more common than frontal (Berger et al. 1998a, b; Whiteman et al. 1993; Giancola et al. 2008; Wyen et al. 2004; Table 5), the temporal white matter being least frequently involved. Other AIDS associated neurological complication such as cerebral toxoplasmosis and primary CNS lymphoma can present as multifocal lesions, but demonstrate contrast enhancement and perilesional edema. CMV infection involves the gray matter and the ventricular ependyma rather than pure white matter. Mild and diffuse white matter involvement is the most common radiologic finding in patients with AIDS dementia complex. Patchy white matter pattern may be seen in patients with cryptococcal meningitis.

PML lesions are classically non-enhancing lesions, though contrast enhancement has been described in 10–15 % patients (Thurnher et al. 2001). Several reasons have been cited to explain this feature like: (a) breakdown in blood brain barrier with intense inflammatory reaction especially in patients who develop PML lesions when they are on HAART and (b) in drug-naïve patients, it represents a positive predictor for prolonged survival (Thurnher et al. 2001). Our series showed a high rate of contrast enhancement (21 %). But, the exact correlation with the survival and CD4 could not be correlated.

PML was the initial AIDS defining illness in 75.7 % of patients in our study, as compared to 25 % in study by Berger et al. (1998a, b). In patients who are not suspected to be at risk for HIV, the initial presentation of PML can present diagnostic difficulties. A clinical possibility of PML

Table 5 Compares the MR imaging features in different studies

Anatomical sites of involvement	Whitemen et al. (1993; %)	Berger et al. (1987; %)	Giancola et al. (2008; %)	Present study (2013; %)
Frontal	19 (40 %)	30 (27 %)	20 (64.5 %)	21 (21.6 %)
Temporal	13 (27 %)	17 (15 %)	15 (48.4 %)	7 (7.2 %)
Parietal	37 (78 %)	39 (35 %)	28 (90.3 %)	22 (22.7 %)
Occipital	17 (36 %)	23 (21 %)	14 (45.2 %)	8 (8.3 %)
Corpus callosum	7 (15 %)	21 (19 %)	4 (12.9 %)	3 (3.1 %)
Internal capsule/basal ganglia	7 (15 %)	13 (12 %)	6 (19.4 %)	9 (9.3 %)
Thalamus	8 (17 %)	16 (14 %)	0 (0 %)	5 (5.2 %)
Posterior fossa—cerebellum	15 (31 %)	38 (34 %)	12 (38.7 %)	11 (11.3 %)
Posterior fossa—brainstem	0 (0 %)	30 (35 %)	17 (%)	11 (11.3 %)

was entertained in nearly half of our patients at the initial visit. Due to multifocal deficits, acute disseminated encephalomyelitis (ADEM) was suspected in 7.7 % patients. A diagnosis of cervical myelopathy was considered in one patient who presented with a slowly progressive motor weakness of all four limbs, intracranial space occupying lesion, or granuloma were considered in five cases due to insidious onset and gradually progressive nature of the neurological deficits, cerebrovascular accident was entertained in four patients who presented with motor weakness in one side of the body. Toxoplasmosis and tubercular meningitis being the more frequent opportunistic neurological infections in seropositive patients, were considered in five patients. High level of suspicion for HIV is required in patients presenting with focal neurological deficits for diagnosis of PML; along with the imaging characteristics as described. Early diagnosis followed by treatment with HAART therapy definitely is useful in the management of HIV associated PML.

Conclusions PML in HIV positive patients is not that uncommon contrary to earlier belief in India and constituted 2.3 % of HIV associated opportunistic infections. PML is being more frequently recognized among HIV seropositives in India in the recent years. The diagnosis of PML however was considered in only half of the patients initially indicating that a high index of suspicion is essential for diagnosis. There are no significant differences between clinical and radiological manifestations of PML between Indian and Western countries. Hemiparesis was the commonest neurological manifestation. Any seropositive individual presenting with progressive neurological deficit with or without cerebellar signs/cognitive decline in the absence of fever and symptoms and signs of raised intracranial tension suggests the diagnosis of PML. It is usually seen in patients with CD4 count less than 200 cells/μL. MRI brain is more sensitive than CT in the diagnosis of PML. Imaging revealed multifocal, non-enhancing frontal and parietal subcortical white matter involvement without mass effect. Increase in CD4 counts was observed following initiation of HAART resulting in prolonged survival. Early diagnosis and aggressive antiretroviral therapy is suggested to treat patients with PML as they can recover and lead a normal life.

Acknowledgments We are thankful to Dr. Avindra Nath, Chief, Section of Infections of the Nervous System, Clinical Director, NINDS, NIH, for his inputs and critical review of the manuscript. The authors wish to acknowledge assistance of Mrs. Rajasakti, Mr. Prasanna Kumar, and Mr. Shivaji Rao, Human Brain Tissue Repository (Brain Bank), NIMHANS for assistance with whole mount histological preparations and immunohistochemistry as well as Mr. K. Manjunath, Department of Neuropathology, NIMHANS for assistance with microphotography and preparation of montages.

Funding source This publication was partly supported by a subaward from The Johns Hopkins University, with funds provided from National Institute of Neurological Disorders and Stroke (NINDS) [Grant no: 1RO1NS055628-01A2]. Its contents of the study are solely the responsibility of the authors and do not represent the official view of NINDS or JHU.

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