Primary central nervous system lymphoma: A profile of 26 cases from western India

Pankaj A. Agarwal, Suresh Menon, B. K. Smruti[1], B. S. Singhal

Departments of Neurology and [1]Oncology, Bombay Hospital Institute of Medical Sciences, 12, New Marine Lines, Mumbai 400 020, Maharashtra, India

Abstract

Background: Primary central nervous system (CNS) lymphoma (PCNSL) is a rare malignant non-Hodgkin's lymphoma and it accounts for 1% of all intracranial tumors. Only a few PCNSL studies have been reported from India, and studies on prognostic factors determining outcome, or evaluation of the response to currently accepted treatment, are lacking. **Aims:** This study attempts to further delineate the clinical, radiological and pathological profile of PCNSL in India, to evaluate response to treatment and to assess usefulness of the International Extranodal Lymphoma Study Group (IELSG) score. **Settings and Design:** All patients with pathologically proven PCNSL admitted over three years at a large tertiary care institution were studied. **Materials and Methods:** Clinical features, IELSG prognostic score, imaging and pathological features, and response to treatment were evaluated. Results were analyzed using χ^2 test. **Results:** Of 26 patients found, all except two were immunocompetent. Median age at diagnosis was 59 years. Focal deficits (76.9%) and neuropsychiatric symptoms (57.6%) were the commonest presenting complaints. Except for one case, at least some contrast enhancement was seen in brain lesions of all patients. Pathological studies showed high grade diffuse large B-cell (DLBCL) histology in 96.2% of patients. Of 22 patients who received methotrexate (MTX) based chemotherapy with/without radiotherapy; six died, with a response rate of 72.7%. Median survival was 10 months. Median follow-up duration was 14.5 months. Four patients developed treatment-related cognitive decline. All six patients with IELSG score of 4/5 died, while all 16 patients with a score of 0-3 survived. **Conclusions:** PCNSL presents most commonly in the sixth decade with focal neurological deficit, behavioral symptoms and cognitive decline. High grade DLBCL is the commonest histological subtype. Steroids should ideally be withheld until biopsy as they may confound the diagnosis. Most immunocompetent patients respond well to high dose MTX-based chemotherapy with/without radiation. High IELSG scores correlate with worse prognosis in patients with PCNSL

Key words: *India, International eEtranodal Lymphoma Study Group prognostic score, primary central nervous system lymphoma*

Address for correspondence:
Dr. Pankaj Agarwal,
Department of Neurology, Room No. 131, 1st Floor, MRC Building, Bombay Hospital Institute of Medical Sciences, 12, New Marine Lines, Mumbai, Maharashtra, India.
E-mail: drpankaj.agarwal@rediffmail.com

DOI: 10.4103/0028-3886.59472

Introduction

Primary central nervous system (CNS) lymphoma (PCNSL), an aggressive, malignant high grade B cell neoplasm, is a rare form of Non-Hodgkins lymphoma of the CNS and eye, and accounts for 1% of all intracranial tumors[1] and 4-7% of primary brain tumors.[2] Over the last few decades an increasing incidence of PCNSL has been documented in the developed nations both in the immunocompromised and immune competent population.[2,3] Left untreated, most patients succumb to the disease within months. High dose methotrexate (MTX) has been shown to significantly improve outcome in PCNSL, and various treatment regimens have been

used, that include MTX and other chemotherapeutic agents, with or without whole brain radiotherapy (WBRT).[1] The International Extranodal Lymphoma Study Group (IELSG) prognostic score has been shown to be a useful predictor of survival in PCNSL patients managed according to modern therapeutic guidelines.[4,5] A few studies of PCNSL have been reported from India[6-8] but none have studied prognostic factors determining the outcome or evaluated the response to currently accepted treatment in PCNSL. The present study was undertaken in an attempt to further examine the clinical, radiological and pathological profile of PCNSL, to evaluate response to treatment in subjects with pathologically confirmed PCNSL and to assess usefulness of the IELSG prognostic scoring system in Indian patients.

Materials and Methods

In the present study, all patients with pathologically proven PCNSL admitted between 2003 and 2006 to a large tertiary-care institution were studied. Clinical features including age, sex, and presenting symptoms were noted. Performance status, as per the Eastern Cooperative Oncology Group -Performance Status (ECOG-PS) score[9] was recorded. Serological tests for the human immunodeficiency virus (HIV), by ELISA, were obtained in all the patients. Computed tomography (CT) scan of the chest, abdomen, and pelvis, and bone marrow biopsy were done in all the patients to rule out systemic lymphoma. A contrast-enhanced magnetic resonance imaging (MRI) brain scan was performed in all the patients. Imaging features including number, location and enhancement characteristics of lesions were recorded. Alternative diagnoses considered prior to brain biopsy, on the basis of clinical and imaging features were noted. The time interval from onset of symptoms to establishment of the diagnosis was recorded. All patients had undergone a stereotactic brain biopsy to establish the diagnosis of PCNSL.

Histological subtype of the tumor with grading of tumor cells on hematoxylin and eosin-stained slides, and immunohistochemical details, including typing for leucocyte common antigen (LCA), CD20 (B cell marker) and CD3 (T cell marker), performed on formalin-fixed, paraffin-embedded tissue samples, were recorded. Cerebrospinal fluid (CSF) examination including cytological evaluation for malignant cells was performed in all the patients, except if contraindicated. Complete ophthalmologic examination was performed in all the patients. Serum lactate dehydrogenase (LDH) was measured. The IELSG prognostic score[4,5] was calculated for each patient based on five variable patient characteristics i.e. age, performance status, deep brain structure involvement, CSF protein elevation and serum LDH level.[4] Each variable was assigned a value of "0" if favorable, or "1" if unfavorable; and the values of the five variables were added to arrive at a final score.

Details of treatment (chemotherapy/radiotherapy) were documented. Follow-up imaging was performed after completion of therapy, and then after 3 months. 'Complete response' was defined as the disappearance of all signal enhancement on MRI. Overall survival (OS) was calculated from the date of pathologic diagnosis to death or to the last date of follow-up. Presence or absence of cognitive decline at last follow-up was recorded and graded as mild: Mini mental status examination score (MMSE) 25-18; moderate: MMSE 17-10 or severe: MMSE <10. The Chi-Square test was used to test for significance of difference in treatment response between following patient groups: IELSG score 0-3 vs. score 4-5; age <60 vs. age >60 years; WBRT received vs. not received; ECOG-performance score 0-1 vs. score 2-3. A P value of <0.05 was considered significant.

Results

Twenty-six patients (16 male, 10 female) were seen during the study period. Median age at diagnosis was 59 years (range 27-80 years). Two patients (7.6%), aged 44 and 48 years were seropositive for HIV (absolute CD4 counts 56 and 171/mm^3) and the rest (92.3%) were immunocompetent. The most common clinical features at presentation were focal neurologic deficits (76.9%), neuropsychiatric symptoms (apathy, depression, confusion or cognitive decline; 57.6%), symptoms of raised intracranial tension (headache, vomiting or impaired consciousness; 26.9%) and seizures (11.5%). [Table 1]. Multiple (two/more) parenchymal lesions were seen in 77% of patients. A periventricular location (basal ganglia, corpus callosum or periventricular white matter) was found in 61.5%. Callosal lesions were seen in 23%. In immunocompetent patients, except for one case, all lesions showed dense homogenous contrast enhancement. In the two HIV patients, ring-enhancing lesions were seen in the corpus callosum and thalamus.

Twenty-five of the 26 patients (96.1%) showed high grade diffuse large B-cell lymphocytic (DLBCL) type PCNSL, while T-cell histology was noted in one patient. Immunohistochemistry was performed on 18 specimens and showed positivity for LCA and CD20 in 17 samples. The T-cell variant sample was LCA and CD3-positive and CD20-negative. Median interval from symptoms to establishment of pathological diagnosis was 13 weeks (range one week-two years).

Five (19.2%) patients had meningeal spread from parenchymal lesions, seen as meningeal enhancement on MRI. CSF studies, performed in all but one patient, showed protein elevation in 52% of patients. CSF cytology

Table 1: Comparison between present and previous studies of primary central nervous system lymphoma

Study, year, no. of pts.	Median age (yrs)	Sex ratio M: F	Clinical features (%)				Immune compromised* (n)[HIV/AIDS]	Time to diagnosis	Contrast enhancing lesions	Site/number of lesions (%)								Histology, IHC profile	Treatment	Out come
			FD	RICP	Npsy	Sz				Multiple (2/more)	Supratentorial	Periventricular	Callosal	F	T	P	O			
Fine[12] 1993 Non HIV n = 792	55.2	1.35:1	56	32	35	11	0	2.8 mo	97.2%	25	NA	>60%	NA	NA	NA	NA	NA	22% high grade, IHC-NA	None/RT/CT	OMS 18.9 mo
HIV n = 315	30.8	7.38:1	51	14	53	27	315 [315]	1.8 mo	90.1%	52	NA	NA	NA	NA	NA	NA	NA	60% high grade, IHC-NA	RT	OMS 2.6 mo
Miller[13] 1994 n = 104	52.4	1.6:1	NE	NE	NE	NE	16 [11]	2 mo	NE	NE	NE	NE	NE	NE	NE	NE	NE	41/42 B- cell, 1 T-cell	RT/RT +CT (MTX/other)	OMS 19 mo
Tomlinson[14] 1995 n = 89	60	2.0:1	73	3	28	9	14 [0]	<8 wks†		25.8	NA	NA	7.8	42.6	10.1	29.2	1.1	70.7% B-cell, 3.3% T-cell	Surgery, RT/ RT +CT	OMS 20.9 mo
Herrlinger[15] 1998 n = 26	58	1.0:1	42.3	38.4	73.0	23.0	0	2.5 mo	100%	61.5	NA	NA	NA	NA	NA	NA	NA	17 high grade, 2 low grade, all B-cell	RT/RT +CT (MTX, cyta, others)	CR in 6/7 pts recvg. RT + CT, OMS 12 mo.
Bataille[16] 2000 n = 248	61	0.95:1	70	33	43	14	0‡	12 wks§	>99%	34	86	60	12	20	18	15	4	96.4% B-cell (62% DLBCL), 3.6% T-cell	RT/CT/ RT + CT (anth, MTX, cyta)	RR 48.3%, OMS 12 mo
Tiwari[6] 2002 n = 46	50	1.8:1	41	74	41	0	3[0]	NE	100%	28.4	97.8	34.8	NA	10.8	6.5	8.6	4.3	20 diffuse large cell, 9 small cell cleaved‖ IHC-NA	RT + CT (COP, CHOP, CCNU)	RR- NE OMS 8 mo
Ferreri[4] 2003 n = 378	61	58:42	NE	NE	NE	NE	0	NE	NE	34	NE	NE	NE	44	14	13	6	LG, IG and HG 3, 58 and20% unclassified 19%, 2% T cell	CT(MTX± alkylating agent, cyta, anth,) ± RT, RTalone	RR 61%, 2y-OS 37%
Pels[17] 2003 n = 65	62	34:31	NE	NE	NE	NE	0	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	100% B cell	CT-MTX, vinc, Ifosfamide; Dexa; ICV pred, MTX, Cyta	RR 71% OMS 50 mo
Poortmans[18] 2003 n = 52	51	35:17	NE	NE	NE	NE	0	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	CT(MBVP,T MTX, cyta, ydrocort) +RT	RR 81% OMS 46 mo

Contd...

Table 1 Contd...

Study, year, no. of pts.	Median age (yrs)	Sex ratio M:F	Clinical features (%)				Immune compromised* (n)[HIV/AIDS]	Time to diagnosis	Contrast enhancing lesions	Site/number of lesions (%)								Histology, IHC profile	Treatment	Out come
			FD	RICP	Npsy	Sz				Multiple (2/more)	Supratorial	Periventricular	Callosal	F	T	P	O			
Sarkar[7] 2005 n = 186	39.5-44.4	2.2-2.3:1	NE	NE	NE	NE	2[1]	NE	NE	NA	80-86.2	NA	NA	55	25	31	NA	99% B-cell (99% DLBCL) 1 T-cell	NE	NE
Paul[8] 2008 n = 56	42	1.5:1	42.8	71.4	12.5	19.6	1[1]	NE	NE	21.4	94.6	3.5	7.0	32.1	14.2	28.4	3.5	86% B-cell (most DLBCL), 1 T-cell	NE	NE
Present study 2006 n = 26	59	1.6:1	76.9	26.9	57.6	11.5	2[2]	13 wks	96.2 (all except 1 case)	75	70	58	20	41	8	16	0	96.2% B cell (all DLBCL), 3.8% T-cell	RT/RT + CT (MTX, proc, vinc, cyta, IT MTX)	RR 72.7%, OMS 10 mo

IHC - Immunohistochemistry; FD - Focal deficit; RICP - Raised intracranial pressure; NPsy - Neuropsychiatric symptoms (such as apathy, depression, cognitive decline); Sz - Seizures; F - Frontal; T - Temporal; P - Parietal; O - Occipital; NA - Information not available; NE - Not evaluated; OMS - Overall median survival; CR - Complete response; mo - Months; MTX - Methotrexate; anth - Anthracyclines; cyt - Cytarabine; vinc - Vincristine; proc - Procarbazine; LG,IG and HG - Low grade, Intermediate grade and High grade; Dexa - Dexamethasone; Pred - Prednisolone; ICV - Intraventricular; MBVP - MTX, teniposide, carmustine, and methylprednisolone; IT - Intrathecal; * - by congenital immune deficiency/autoimmune disorders i.e. systemic lupus erythematosus, sarcoidosis, Sjogren's syndrome, vasculitis, idiopathic thrombocytopenic purpura; † - in 48% of patients; ‡ - study of immunocompetent only; § - time from symptom onset to admission; ‖ - Also present: 5 cases of immunoblastic lymphoma, 5 diffuse mixed small and large cleaved cell lymphoma, 1 diffuse small non-cleaved cell lymphoma; Histotype defined as per working formulation classification

was negative for malignant lymphocytes in all the patients. Intraocular/intraspinal lesions were not found in any of the patients. Serum LDH was elevated in 34.6% of patients. Alternative diagnoses considered before biopsy were glioma (n = 11), tubercular granuloma (n = 11), metastases (n = 7), demyelination (n = 6), meningioma (n = 2) and toxoplasmosis (2 HIV patients).

Both HIV-positive patients were treated with highly active anti-retroviral therapy (HAART) and WBRT, but died at three and five weeks respectively, after diagnosis. Of the 24 immunocompetent patients, one was unfit for chemotherapy, received WBRT only, and died after five months, while one other patient was given MTX and carmustine, and died at three months. Twenty two patients received chemotherapy with MTX, vincristine and procarbazine, (MPV) plus cytarabine, as per the protocol used by Abrey *et al*.[10] Chemotherapy was administered for five cycles over a 10-week period. Each cycle consisted of MTX 2.5 g/m^2 and vincristine 1.4 mg/m^2. MTX was followed by hydration, urine alkalinization, and leucovorin rescue. Procarbazine 100 mg/m^2/d for seven days was administered on cycles 1, 3 and 5. Intrathecal MTX (12 mg) was given for five cycles the week after each dose of intravenous MTX. Of the above 22 patients, all patients aged <60 y (n = 10) received WBRT (total dose of 45 Gy), while in all those aged > 60 y (n = 12), WBRT was withheld due to a perceived higher risk of delayed neurotoxicity. At completion of WBRT or initial chemotherapy, all 22 patients received two courses of cytarabine; each consisting of two doses, 24 hours apart, of 3 g/m^2/day. The 22 patients who received chemotherapy with MPV+ cytarabine (±WBRT) were followed up for a median duration of 14.5 months (range 1 to 36 months), and further analyzed for treatment response. Six patients died (median duration 15.5 months) and 16 survived. Complete response i.e. no enhancing disease on MRI imaging after completion of therapy, was seen in all surviving patients (16 of 22, 72.7%). One patient suffered relapses twice over three years. Overall median survival duration was 10 months.

Of the 22 patients further analyzed, eight had IELSG scores of 0 or 1, eight had a score of 2 or 3, while another six patients had a score of 4 or 5. All patients (n = 6) with an IELSG score of 4 or 5 were dead at the last follow up, while all patients (n = 16) with a score of 0 to 3 survived ($P < 0.0001$). Six of 12 patients aged >60 y, and all 10 patients <60 y survived ($P < 0.05$); four of nine patients with ECOG-PS score 2 or 3, and 12 of 13 patients with ECOG-PS score of 0 or 1 survived ($P < 0.05$). Higher IELSG score (of 4 or 5), age >60 years, and a higher ECOG-PS score of 2 or 3, were associated with lower survival rate after treatment. Of the 16 treated survivors, five developed cognitive decline on follow-up for a median duration of 12.2 months. One patient had

severe dementia due to recurrent frontal lesions, while in the other four, cognitive symptoms were likely due to treatment-related neurotoxicity. Dementia was mild in two (both aged <60 y, not received WBRT) and moderate in the other two patients (of which one pt. aged <60 y, not received WBRT).

Discussion

PCNSL is being increasingly diagnosed in both immunocompromised and immunocompetent patients. In previously reported Indian case series, the proportion of immunocompromised patients has been low, 0.01-0.06%.[6-8] Also, in an autopsy study from Mumbai, no PCNSL was found in brains of 85 AIDS patients with CNS pathology.[11] Similarly, in the present series only two of 26 (0.07%) patients were found to be immunocompromised. PCNSL incidence in this study was higher in males, and the average age at presentation was in the sixth decade, similar to the findings from earlier western studies. However in the previous Indian series the reported age at presentation was a decade earlier [Table 1].[6-8] The relative incidence of presenting clinical features is comparable to that of series reported from India and the west, although a few studies have found a higher occurrence of raised ICT symptoms[6,8] and seizures [Table 1].[8,15]

On imaging solitary lesions generally are considered to be more common than multiple lesions. In our series, multiple lesions were more common, which is also the experience of some other workers.[15] Typical locations are periventricular white matter and corpus callosum. [Figure 1]. Dense homogenous enhancement is typically seen in all lesions on MRI with contrast administration.[19] Non-contrast enhancement may be seen in the immunocompromised, but is distinctly rare in immunocompetent patients who have not received steroids. We found one such immunocompetent patient with basal ganglionic and brainstem lesions that showed complete lack of contrast enhancement [Figure 2]. A recent large MRI study of 100 consecutive PCNSL cases reported only one case of non-enhancing PCNSL in an immune-competent individual.[20] We could find three other reports in literature, each of a single case of non-contrast enhancing, immunocompetent PCNSL.[21-23]

A high index of suspicion is needed to suspect PCNSL. Lesions can disappear with the use of corticosteroids only to reappear when steroids are discontinued. This was noted in three of our patients who were initially misdiagnosed to have relapsing demyelination, until lymphoma was suspected and a biopsy was performed. Steroids have been associated with initial complete remission in 15% and partial remission in 25% of PCNSL patients,[24] due to their apoptotic effect on lymphoma cells, even to the point that lesional cells disappear completely from the biopsy material. Ideally, steroids should be withheld in all cases of suspected PCNSL until biopsy is performed to avoid false-negative biopsies.[1] However, a recent retrospective study found that prior corticosteroid administration did not seem to prevent pathological diagnosis of PCNSL.[25]

Majority of the reported PCNSL cases in literature (≥95%) are high-grade DLBCL, both in immunocompetent as well as AIDS patients.[12] Low-grade B-cell PCNSLs, typically composed of small lymphocytes, are distinctly uncommon. All but one of our cases were high-grade DLBCL [Figure 3]. T-cell lymphomas have been reported as primary CNS tumors but are rare and appear to comprise less than 5% of all cases of PCNSL.[12] There was a single case of T-cell lymphoma in the present series.

The incidence of positive CSF cytology in immunocompetent PCNSL patients is reported to be 26-31%.[26] The small number of morphologically recognizable malignant cells found in CSF is thought to account for this low incidence.[27] Although a fifth of our patients demonstrated meningeal spread on MRI, none had positive CSF cytology despite serial cytological evaluation. This was possibly because several patients had previously received corticosteroids, which are known to decrease the incidence of positive CSF cytology.[27] Other tests to establish monoclonality of a lymphocyte population in CSF include DNA flow cytometry and immunohistochemistry with antibodies against B-cell markers and immunoglobulin light chains.[26] Epstein-Barr virus (EBV) DNA-PCR testing may be used in HIV-PCNSL, however, there seems to be no etiologic role of EBV in immunocompetent PCNSL.[28]

The introduction of chemotherapy with MTX-based regimens has improved survival in PCNSL patients, and several approaches have been successfully used, including a variety of drugs, and varying doses and timing of WBRT.[1] Current research focuses on maximizing survival while minimizing WBRT- and MTX-related toxicity. Newer approaches such as immunotherapy with monoclonal antibodies, and autologous stem cell rescue after myeloablative chemotherapy are being evaluated. Table 2 compares results of treatment in the present study to the other series. The response rate of 72.7% in immunocompetent patients treated with MPV, with or without WBRT, is comparable to other reports. Overall median survival, at 10 months, reflects the short follow-up duration in our study. A longer-term study would provide more data regarding survival in these patients.

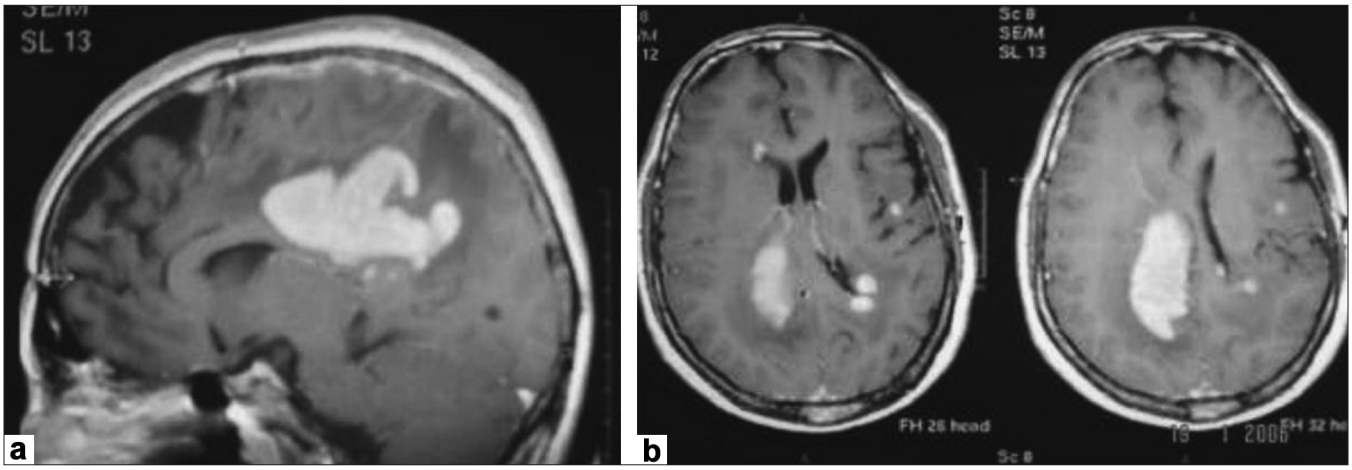

Figure 1: Typical magnetic resonance imaging appearance of primary central nervous system lymphoma; T1-weighted (a) sagittal and (b) axial post-contrast MR images of brain show corpus callosal, periventricular and subcortical lesions, with dense homogenous contrast enhancement and moderate edema

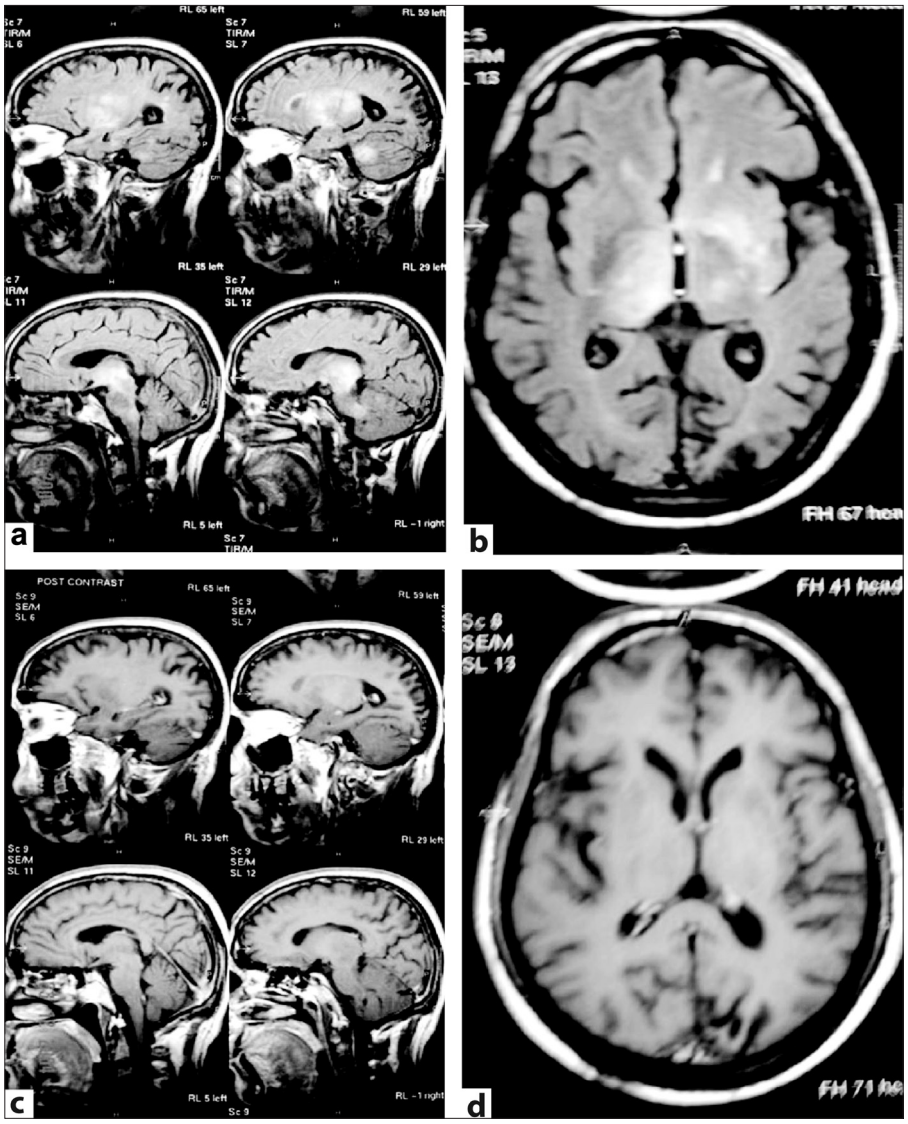

Figure 2: Non contrast-enhancing primary CNS lymphoma. (a) Sagittal and (b) axial T2- FLAIR images show hyperintense signals in lesions in the basal ganglia, thalami, brainstem and cerebellum. T1-weighted (c) sagittal and (d) axial images after administration of contrast exhibit complete lack of contrast enhancement

Table 2: Comparison of trials using chemotherapy + whole brain radiotherapy in primary central nervous system lymphoma

Study	No. of pts	Regimen	R T (Gy)	Resp.rate (%)	OMS (months)
Glass[29] 1994	25	IV MTX (3.5 g/m^2)	30-44	88	33
Abrey[10] 2000	52	MPV (IV MTX 3.5 g/m^2) + IV ara-C + IT MTX (12 mg × 3)	45 in 35/52 pts	90	60
de Angelis[30] 2002	102	MPV (IV MTX 2.5 g/m^2) + IT MTX (12 mg × 5)	45	94	30+
Present study 2006	22*	MPV (IV MTX 2.5 g/m^2) + IV ara-C + IT MTX (12 mg × 5)	45 in 10/22 pts	72.7	10

*- Out of a total of 26 pts. 4 patients not included in analysis (two pts. HIV +, received WBRT only; one pt. received MTX + carmustine only, one pt. received WBRT alone) RT - Radiotherapy; Resp. Rate - Response rate; OMS - Overall median survival; MTX - Methotrexate; MPV - Methotrexate, procarbazine, vincristine; ara-C - Cytarabine; IT - Intrathecal

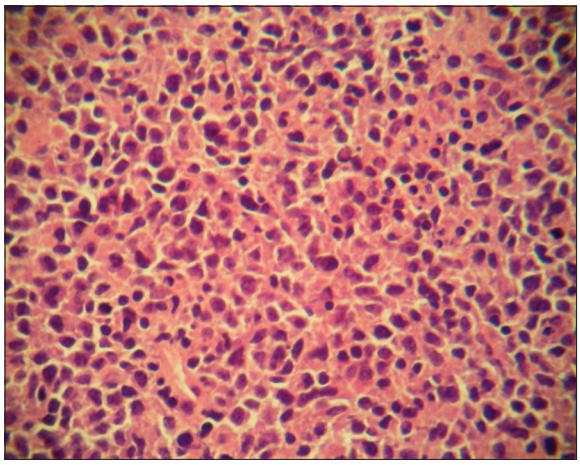

Figure 3: Primary central nervous system lymphoma specimen shows diffuse sheets of high grade, large lymphomatous B-cells, (H and E, ×400)

In previous retrospective multicentric studies, the IELSG score was found to correlate with survival rates.[4,5] In our small study of 26 patients, a high IELSG score of 4 or 5 was significantly associated with poorer response to chemotherapy with MPV ±WBRT in 22 immunocompetent patients. Other groups have been unable to validate the IELSG score and have found age and performance status to be the only two factors predictive of outcome.[31] In the present study too, these two factors were found to be associated with a poorer response to treatment. More than half of the patients achieving a remission after treatment for PCNSL eventually relapse.[1] Relapse is associated with significantly shorter survival than newly diagnosed disease; 35% to 60% of patients with recurrent disease die within a few months.[1] In our series, one patient suffered two relapses and failed to respond after the second relapse.

When a combination of WBRT and chemotherapy is used, the incidence of treatment-related neurotoxicity ranges from 8 to 50%,[29,30] especially in long-term survivors over 60 years of age.[32] Further, most trials have used chemotherapy prior to WBRT because there is evidence that MTX administered after WBRT increases the risk of neurotoxicity.[33] Neurotoxicity most commonly manifests as cognitive decline, and can include gait disturbance, parkinsonism and seizures. 25% (four of 16) survivors in this series developed cognitive decline due to treatment-related neurotoxicity. Since cognitive changes develop months to years after therapy, their incidence is proportionate to the duration of survival. Longer follow-up is likely to uncover more cognitive deficits in our patients.

Conclusion

PCNSL in the immunocompetent individuals most commonly presents in the sixth decade with focal neurological deficits, behavioral symptoms and cognitive decline. Dense homogenous contrast enhancement is typical of immunocompetent PCNSL. However, the absence of enhancement may rarely be found. A high index of suspicion is necessary for the correct diagnosis. Ideally steroids should be withheld until the biopsy as they may delay or confound the diagnosis. High grade diffuse large B-cell lymphoma is the commonest histological PCNSL subtype. Most immunocompetent patients respond well to high dose MTX-based chemotherapy with or without radiation. High IELSG scores correlate with worse prognosis in Indian patients.

Acknowledgments

Dr. Girish Muzumdar, Department of Pathology; Dr. Sunila Jaggi, Department of Radiology; Drs. CE Deopujari, SN Bhagwati, KE Turel, Department of Neurosurgery; and Dr. BK Goyal, Dean, Bombay Hospital Institute Of Medical Sciences.

References

1. Shah GD, deAngelis LM. Treatment of primary central nervous system lymphoma. Hematol Oncol Clin North Am 2005;19:611-27.
2. Surawicz TS, McCarthy BJ, Kupelian V, Jukich PJ, Bruner JM, Davis FG. Descriptive epidemiology of primary brain and CNS tumors: Results from the Central Brain Tumor Registry of the United States, 1990-1994. Neuro Oncol 1999;1:14-25.
3. Corn BW, Marcus SM, Topham A, Hauck W, Curran WJ Jr. Will primary central nervous system lymphoma be the most frequent brain tumor diagnosed in the year 2000? Cancer 1997;79:2409-13.
4. Ferreri AJ, Blay JY, Reni M, Pasini F, Spina M, Ambrosetti A, *et al*. Prognostic scoring system for primary CNS lymphomas: The International Extranodal Lymphoma Study Group experience. J Clin Oncol 2003;21:266-72.
5. Ferreri AJ, Reni M, Pasini F, Calderoni A, Tirelli U, Pivnik A, *et al*. A multicenter study of treatment of primary CNS lymphoma. Neurology 2002;58:1513-20.
6. Tiwari MK, Singh DP, Pathak A, Khandelwal N, Radotra BD, Mathuriya SN, *et al*. Primary central nervous system lymphoma: Experience of 46 cases with review of literature. Neurol India 2002;50:424-9.

7. Sarkar C, Sharma MC, Deb P, Singh R, Santosh V, Shankar SK. Primary central nervous system lymphoma-a hospital based study of incidence and clinicopathological features from India (1980-2003). J Neurooncol 2005;71:199-204.
8. Paul TR, Challa S, Tandon A, Panigrahi MK, Purohit AK. Primary central nervous system lymphomas: Indian experience, and review of literature. Indian J Cancer 2008;45:112-8.
9. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al*. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
10. Abrey LE, Yahalom J, deAngelis LM. Treatment for primary CNS lymphoma: The next step. J Clin Oncol 2000;18:3144-50.
11. Lanjewar DN, Jain PP, Shetty CR. Profile of central nervous system pathology in patients with AIDS: An autopsy study from India. AIDS 1998;12:309-13.
12. Fine HA, Mayer RJ. Primary central nervous system lymphoma. Ann Intern Med 1993;119:1093-104.
13. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma: The Massachusetts General Hospital experience 1958-1989. Cancer 1994;74:1383-97.
14. Tomlinson FH, Kurin P, Suman VJ, Scheithauer BW, O'Fallon JR, Kelly PJ, *et al*. Primary intracerebral malignant lymphoma: A clinicopathological study of 89 patients. J Neurosurg 1995;82:558-66.
15. Herrlinger U, Schabet M, Clemens M, Kortmann RD, Petersen D, Will BE, *et al*. Clinical presentation and therapeutic outcome in 26 patients with primary CNS lymphoma. Acta Neurol Scand 1998;97:257-64.
16. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, *et al*. Primary intracerebral malignant lymphoma: Report of 248 cases. J Neurosurg 2000;92:261-6.
17. Pels H, Schmidt-Wolf IG, Glasmacher A, Schulz H, Engert A, Diehl V, *et al*. Primary central nervous system lymphoma: Results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. J Clin Oncol 2003;21:4489-95.
18. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H, Van't Veer M, Hansen M, Soubeyran P, *et al*. European Organization for Research and Treatment of Cancer Lymphoma Group. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. J Clin Oncol 2003;21:4483-8.
19. Bühring U, Herrlinger U, Krings T, Thiex R, Weller M, Küker W. MRI features of primary central nervous system lymphomas at presentation. Neurology 2001;57:393-6.
20. Kuker W, Nagele T, Korfel A, Heckl S, Thiel E, Bamberg M, *et al*. Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. J Neurooncol 2005;72:169-77.
21. Agrawal D, Mahapatra AK. Unusual radiological presentation of PCNSL. J Neurooncol 2005;74:155-6.
22. Carlson BA. Rapidly progressive dementia caused by nonenhancing primary lymphoma of the central nervous system. Am J Neuroradiol 1996;17:1695-7.
23. Terae S, Ogata A. Nonenhancing primary central nervous system lymphoma. Neuroradiology 1996;38:34-7.
24. Herrlinger U, Schabet M, Bitzer M, Petersen D, Krauseneck P. Primary central nervous system lymphoma: From clinical presentation to diagnosis. J Neurooncol 1999;43:219-26.
25. Porter AB, Giannini C, Kaufmann T, Lucchinetti CF, Wu W, Decker PA, *et al*. Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: A pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma. Ann Neurol 2008;63:662-7.
26. Jellinger K, Radaskiewicz T, Slowik F. Primary malignant lymphomas of the central nervous system in man. Acta Neuropathol (Berl) 1975;6: S95-102.
27. Fitzsimmons A, Upchurch K, Batchelor T. Clinical features and diagnosis of primary central nervous system lymphoma. Hematol Oncol Clin North Am 2005;19:89-703.
28. Tandon A, Challa S, Shanmugam M, Gopalan S, Paul RT, Digumarthi R. Epstein-Barr virus as a possible etiologic agent in primary central nervous system lymphoma in immunocompetent individuals. Neurol India 2009;57:36-40.
29. Glass J, Gruber ML, Cher L, Hochberg FH. Preirradiation MTX chemotherapy of primary central nervous system lymphoma: Long-term outcome. J Neurosurg 1994;81:188-95.
30. DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz CJ. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002;20:4643-8.
31. Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, *et al*. Primary central nervous system lymphoma: The Memorial Sloan-Kettering Cancer Center prognostic model. J Clin Oncol 2006;24:5711-5.
32. Abrey LE, deAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol 1998;16:859-63.
33. Shenkier TN, Blay JY, O'Neill BP, Poortmans P, Thiel E, Jahnke K, *et al*. Primary CNS lymphoma of T-cell origin: A descriptive analysis from the international primary CNS lymphoma collaborative group. J Clin Oncol 2005;23:2233-9.

Accepted on 02-11-2009
Source of Support: Nil, **Conflict of Interest:** None declared.