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

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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 $\chi^2$ 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 Extranodal Lymphoma Study Group prognostic score, primary central nervous system lymphoma

Introduction

Primary central nervous system (CNS) lymphoma (PCNSL), an aggressive, malignant high grade B cell neoplasm, is a rare form of Non-Hodgkin's 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.\(^3,4\) 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).[11] 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/mm³) 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>
<thead>
<tr>
<th>Study, year, n of pts.</th>
<th>Median age (years)</th>
<th>Sex ratio M:F</th>
<th>Immune compromised*</th>
<th>Clinical features (%)</th>
<th>Site/number of lesions (%): F</th>
<th>Histology, IHC profile</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine et al. 1993 n=72</td>
<td>55.2</td>
<td>1.35:1</td>
<td>NA</td>
<td>25</td>
<td>NA</td>
<td>20% high grade, IHC+NA</td>
<td>None/RT/CT</td>
<td>97.2%</td>
</tr>
<tr>
<td>Kuhlmann et al. 1993 n=75</td>
<td>792</td>
<td>1.35:1</td>
<td>NA</td>
<td>792</td>
<td>55.2</td>
<td>20% high grade, IHC+NA</td>
<td>None/RT/CT</td>
<td>97.2%</td>
</tr>
<tr>
<td>Miller 1994 n=5</td>
<td>52.4</td>
<td>1.6:1</td>
<td>NA</td>
<td>104</td>
<td>NE</td>
<td>B-cell, T-cell</td>
<td>RT/RT</td>
<td>NE</td>
</tr>
<tr>
<td>Herrlinger 1998 n=5</td>
<td>60</td>
<td>2.0:1</td>
<td>NA</td>
<td>89</td>
<td>NE</td>
<td>20% high grade, B-cell</td>
<td>Surgery/RT</td>
<td>NE</td>
</tr>
<tr>
<td>Herrlinger 1998 n=5</td>
<td>58</td>
<td>1.0:1</td>
<td>NA</td>
<td>104</td>
<td>NE</td>
<td>B-cell, T-cell</td>
<td>RT/RT</td>
<td>NE</td>
</tr>
<tr>
<td>Bataille 2002 n=46</td>
<td>61</td>
<td>0.95:1</td>
<td>NA</td>
<td>62</td>
<td>NE</td>
<td>20% high grade, B-cell</td>
<td>RT/CT</td>
<td>NE</td>
</tr>
<tr>
<td>Ferreri 2003 n=378</td>
<td>61</td>
<td>0.95:1</td>
<td>NA</td>
<td>378</td>
<td>NE</td>
<td>20% high grade, B-cell</td>
<td>RT/CT</td>
<td>NE</td>
</tr>
<tr>
<td>Poortmans 2003 n=65</td>
<td>62</td>
<td>1.8:1</td>
<td>NA</td>
<td>65</td>
<td>NE</td>
<td>20% high grade, B-cell</td>
<td>RT/CT</td>
<td>NE</td>
</tr>
</tbody>
</table>

*Note: HIV/AIDS, PT, MTX, CT, CYTO, IFOSF.
### Table 1 Contd...

<table>
<thead>
<tr>
<th>Study, year, no. of pts.</th>
<th>Median age (yrs)</th>
<th>Sex ratio M:F</th>
<th>Clinical features (%)</th>
<th>Immune compromised* (n)(HIV/AIDS)</th>
<th>Time to diagnosis</th>
<th>Contrast enhancing lesions</th>
<th>Site/number of lesions (%)</th>
<th>Histology, IHC profile</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkar et al. 2005 n = 186</td>
<td>39.5-44.2</td>
<td>2.2-2.3</td>
<td>NE NE NE NE</td>
<td>2[1]</td>
<td>NE</td>
<td>NE</td>
<td>NA</td>
<td>80-86.2</td>
<td>NA</td>
<td>55</td>
</tr>
<tr>
<td>Paul et al. 2008 n = 56</td>
<td>42</td>
<td>1.5:1</td>
<td>42.8 71.4 12.5 19.6</td>
<td>1[1]</td>
<td>NE</td>
<td>NE</td>
<td>21.4</td>
<td>94.6</td>
<td>3.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Present study 2006 n = 26</td>
<td>59</td>
<td>1.6:1</td>
<td>76.9 26.9 57.6 11.5</td>
<td>2[2]</td>
<td>13 wks</td>
<td>96.2 (all except 1 case)</td>
<td>75</td>
<td>70</td>
<td>58</td>
<td>20</td>
</tr>
</tbody>
</table>

IHC - Immunohistochemistry; FD - Focal deficit; RICP - Raised intracranial pressure; NP sy - Neuropsychiatric symptoms (such as apathy, depression, cognitive decline); Sz - Seizures; 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 - Anthacyclines; 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, carbematine, 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.
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.[13] 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.[26]

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.
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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Regimen</th>
<th>RT (Gy)</th>
<th>Resp. Rate (%)</th>
<th>OMS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass[33] 1994</td>
<td>25</td>
<td>IV MTX (3.5 g/m²)</td>
<td>30-44</td>
<td>88</td>
<td>33</td>
</tr>
<tr>
<td>Abrey[16] 2000</td>
<td>52</td>
<td>MPV (IV MTX 3.5 g/m²) + IV ara-C + IT MTX (12 mg × 3)</td>
<td>45 in 35/52 pts</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>de Angelis[31] 2002</td>
<td>102</td>
<td>MPV (IV MTX 2.5 g/m²) + IT MTX (12 mg × 5)</td>
<td>45</td>
<td>94</td>
<td>30+</td>
</tr>
<tr>
<td>Present study 2006</td>
<td>22*</td>
<td>MPV (IV MTX 2.5 g/m²) + IV ara-C + IT MTX (12 mg × 5)</td>
<td>45 in 10/22 pts</td>
<td>72.7</td>
<td>10</td>
</tr>
</tbody>
</table>

* Out of a total of 26 pts. 4 patients not included in analysis (two pts. HIV +, one pt. received WBRT 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

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.

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