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# PRIMARY CNS LYMPHOMAS: AN IMMUNOMORPHOLOGICAL STUDY FROM A REGIONAL CANCER CENTRE

Pathology

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## ABSTRACT

Primary central nervous system lymphomas (PCNSL) are rare and aggressive type of non Hodgkin lymphomas which form about 2-3% of all CNS tumors.

We undertook a retrospective study of PCNSL at our Institute over a period of 6 years, wherein the clinical and immunomorphological features of PCNSL were studied.

There were 27 cases of PCNSL, males were more commonly affected with an age range of 12-68 years. Almost all were B cell lymphomas and diffuse large B cell lymphoma (DLBCL) was the commonest type, with most showing centroblastic morphology. Further subtyping into germinal centre B cell(GCB) and non germinal centre B cell(NGCB) groups by IHC was possible in 18 cases using Hans algorithm, which showed higher number of NGCB cases. There were one case each of anaplastic large cell lymphoma and follicular lymphoma.

## KEYWORDS

Primary CNS lymphomas; DLBCL; ALCL; Follicular lymphoma

**Introduction**:

Primary Central Nervous System lymphomas (PCNSL) are rare neoplasms with distinctive clinicopathological features, aggressive behaviour and poor prognosis. They account for 2-3% of all the brain neoplasms and 4-6% of all the extranodal lymphomas [1]. Majority of these are Diffuse Large B Cell Lymphomas(DLBCL) occurring in both immunocompromised and immunocompetent patients. The cell of origin is supposed to be a B cell of peripheral lymphoid tissue, which has crossed the blood brain barrier and then proliferates in an immunologically protected environment [2].

We undertook this work to study the clinicopathological and immunophenotypic features of PCNSL over a period of 6 years in our Institute which is a tertiary cancer centre.

**Methods:**

All cases of primary lymphomas occurring in the CNS over a period of 6 years were included in the study. The relevant clinical & demographic details and HIV status were obtained from the case records. Tumor samples received in 10% neutral buffered formalin were processed according to the laboratory protocol and embedded in paraffin. Five micron thick sections were cut and stained with Hematoxylin and Eosin(H&E). H&E stained sections of all the cases were reviewed and histomorphologic typing into different lymphoma subtypes was done. A wide panel of Immunohistochemistry was performed based on morphology for exact subtyping by avidin, streptavidin, biotin method using Diaminobenzidine(DAB) as chromogen. Details of antibodies are as follows: LCA(LCA88, 1:400, Biogenex); Ki67(Mib1, 1:100, Biogenex); CD3(PS1, 1:100, Biogenex); CD20 (L26, 1:70, Biogenex); CD10(56C6, 1:40, Biogenex), BCL-6 (LN22, 1:100, Biocare); MUM-1(EAU-32, 1:100, Biocare); BCL-2 (3.1, 1:100, Biocare); Cyclin-D1(EPR224, 1:60, Biogenex); ALK-1 (SP8, ready to use, Biogen X); CD30(HRS4, 1:40, Biogenex). All the clones used were mouse monoclonal except cyclin-D1 and ALK-1, which were rabbit monoclonal antibodies. Antigen retrieval was done at a pH of 9 with EDTA buffer.

**Results:**

There were 27 cases of primary lymphomas of the CNS in the study period of 6 years. The patients age at presentation ranged from 12 to 68 years, with a mean age of 40.9 years. There was a male preponderance with a male to female ratio of 2.4:1. All the patients were immunocompetent (serologic tests for HIV 1& 2 were negative). The commonest location was in the frontal lobe region. All the 27 cases were non Hodgkin lymphomas (NHL) and an overwhelming majority were of the B cell phenotype (26 cases-96.3%). The commonest subtype was DLBCL, which comprised 25(92.6%)cases. There were one case each of follicular lymphoma and anaplastic large cell lymphoma subtypes(Figure 1). Of the 25 cases of DLBCL analysed, 14 cases were morphologically of the centroblastic type with a prominent angiocentric pattern(figure 2). Most of them were high grade lymphomas with a high Ki67 proliferative index averaging 80%. In 18 out of the 25 cases of DLBCL, further immunologic subtyping into Germinal Center B type (GCB) and Non- Germinal Center B type (NGCB) was done with the antibodies CD10, BCL6 and MUM1 applying the widely used Hans algorithm. Majority of them (14 cases), belonged to the NGCB subtype.

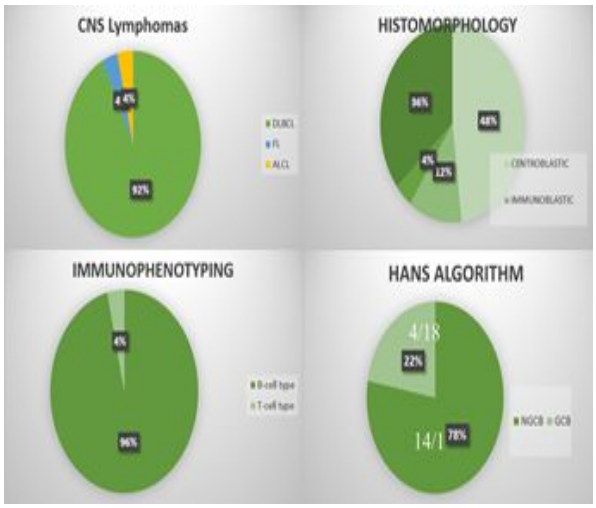


**Figure 1** Relative frequency of Primary Central Nervous System Lymphomas according to subtype. DLBCL, Diffuse Large B-Cell Lymphoma; FL, Follicular Lymphoma; ALCL, Anaplastic Large Cell Lymphoma; NGCB, Non-Germinal Centre B-type; GCB, Germinal Centre B-type.

One case of follicular lymphoma was immunoreactive for CD20, BCL2, CD10 and negative for CD5 and Cyclin D1.

The only case of T cell lymphoma was ALK positive anaplastic large cell lymphoma, in a 14 year old boy which was immunoreactive for CD3, CD30 and ALK1 antibodies.

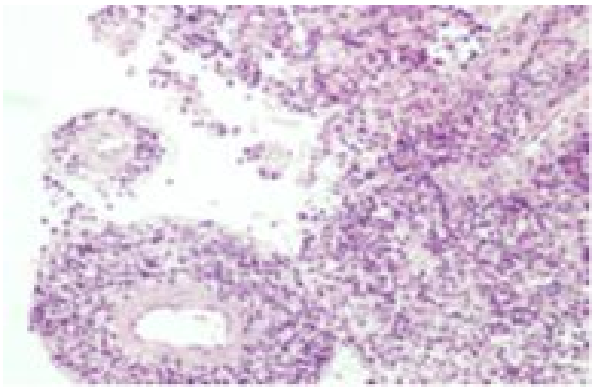

**Figure 2** Shows DLBCL with angiocentric pattern.

**Discussion:**

Primary CNS lymphomas are rare, aggressive neoplasms with distinctive clinicopathological features and with a poor outcome in majority of the cases. We evaluated the demographic, histomorphologic and immunophenotypic profile of PCNSL at a regional cancer centre in South India and compared the trend occurring in other parts of India and other countries.

**Demographic features:** The mean age at presentation in our study was 40.9 yrs which was similar to many Indian studies [3-6]. However in the study by Mahadevan et al [7] and some western studies the mean age of occurrence was slightly older [8-12]. There was male preponderance in our study which is similar to most Indian studies, however a few western studies have shown a female preponderance [8,10]. All the studies including ours showed supratentorial region as the commonest site of involvement by the neoplasm. All the patents in this study were immunocompetent and negative for serologic tests for HIV 1 and 2, which was the case in most other studies except a few studies which had a few HIV positive cases [4].

One case of ALCL in our study occurred in a 14 year old immunocompetent boy in the dura mater of the frontal region without any evidence of the disease outside of the CNS. ALCL primarily occurring in the CNS is very rare [13]. George et al reported a bimodal age distribution of ALCLs, with most patients occurring in the age group of <22yrs, supratentorially, and none showing association with immunosuppression, which correlates with the findings of our study [13].

The one case of follicular lymphoma in our study was seen in an elderly female patient aged 68 yrs in the duramater without any evidence of the disease elsewhere. Very few primary dural follicular lymphomas reported in the literature, which showed similar features with female preponderance [14,15].

**Histopathology:** Most of the cases of DLBCL in our study were of the centroblastic type on morphology, which correlated with other studies where morphologic subtyping was done [7,10,11,12,16]. The case of ALCL in our study resembled any other ALCL at nodal or extranodal site and was similar to the case series reports by George et al [13]. CNS follicular lymphoma in our study was low grade(grade 2 of 3), which was similar to the study by Berial et al [14].

**Immunohistochemistry**: DLBCLs can be subtyped into GCB and NGCB types using IHC markers, which has prognostic significance using any of the algorithms available of which the Hans algorithm [17] is the widely used and makes use of the IHC markers, CD 10, BCL6 and MUM1 and NGCB group has a relatively worse prognosis[17]. Eighteen of the 25 cases of DLBCL in our study were subtyped into GCB and NGCB using the Hans algorithm, and NGCB type was the most common subtype forming 77.8%(14 cases). Most other Indian and international studies have also shown that NGCB subtype is the commonest type of DLBCL in the CNS though the proportion of NGCB varied from 64.7% to 96.3% in different studies which are summarised in Table 1. The relative proportion of GCB subtype is higher in Asian studies as compared to the western studies [3,6,-9,11,12,16,18].

**Table 1:** Comparison of GCB vs NGCB in various studies with the present study.

| Study group(year) | Country / Study duration | Total no. of cases | GCB | NGCB |
|---|---|---|---|---|
| Sharma et al (2016)[6] | India / 10yrs | 64 | 13 (20.3%) | 51 (79.7%) |
| Patel et al (2015)[3] | India / 13yrs | 51 | 18 (35.3%) | 33 (64.7%) |
| Mahadevan et al (2015)[7] | India / 13yrs | 24 | - | 22 (91.6%) |
| Aki et al (2013)[19] | Turkey / 15yrs | 39 | 6 (15.4%) | 33 (84.6%) |
| Hattab et al (2010)[8] | USA / 7yrs | 31 | 5 (16%) | 26 (84%) |
| Raoux et al (2010)[11] | France / 12yrs | 39 | 13 (25.7%) | 26 (74.3%) |
| Preusser et al (2010)[12] | Austria / 39yrs | 75 | 3(4%) | 72 (96%) |
| Bhagavathi et al (2008)[9] | USA / 20yrs | 21 | 2 (9.5%) | 19 (90.5%) |
| Broet et al (2006)[18] | France / - | 82 | 3 (3.7%) | 79 (96.3%) |
| Lin et al (2006)[16] | Taiwan / 12yrs | 51 | 11 (21.6%) | 40 (78.8%) |
| Present study | India / 6yrs | 18 | 4 (22.2%) | 14 (77.8%) |

ALK positive ALCLs of the CNS, typically express CD 30 and ALK1 on IHC, and occur in patients younger than 18 years, and carry a good prognosis like ALCL at any other location [13]. The case of ALCL in our study is also disease free after completing chemotherapy and is on regular follow up.

Follicular lymphomas of the CNS are very rare and IHC is useful in differentiating them from other low grade lymphomas and meningiomas, particularly when they are dura based [15].

**Conclusions:**

In this 6 year retrospective study of 27 cases of PCNSL, presenting at a regional cancer centre in South India, all the patients were immunocompetent with DLBCL being the commonest type of primary CNS lymphoma, and NGCB type was the most common among DLBCL. The proportion of GCB type to NGCB type was higher in our study which is similar to other Asian studies. There was one case each of ALCL and FL with typical morphoimmunologic features.

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