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Original Article

Clinicopathological features of primary central nervous system diffuse large B cell lymphoma: Experience from a Tertiary Center in North India

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ABSTRACT

Background: Primary central nervous system-diffuse large B-cell lymphoma (PCNS-DLBCL) is a rare extra-nodal Non-Hodgkin lymphoma. There is relative paucity of literature on PCNSL from Indian subcontinent. We aimed to analyze the clinicopathological features of PCNSL and categorize them into germinal center B cell (GCB) and non-GCB subtypes to assess their prognostic significance in Indian context.

Methods: All patients with histopathologically diagnosed PCNSLs at our center over a period of 6 years were recruited and classified into GCB and non-GCB using Han's algorithm (immunohistochemistry for CD10, BCL6 and MUM1). *In situ* hybridization (ISH) for Epstein-Barr virus (EBV)-encoded RNA was performed.

Results: Eighty-six cases of PCNS-DLBCL were included with median age of 55 years. Majority of them were supratentorial in location (n = 62). All patients were immunocompetent. On immunohistochemical assessment, 69 (80.2%) were of NGCB subtype, 10 (11.6%) were of GCB subtype, and 7 (8.1%) were unclassified. Overall, MUM1, BCL-6, and CD10 expressions were seen in 69 (80.2%), 28 (32.6%), and 2 cases (2.3%), respectively. Four cases (4.6%) showed C-MYC expression. The median overall survival (OS) was 675 days. None of the factors (age, sex, location, immunomarkers, and GCB vs. NGCB phenotype) showed correlation with OS; however, BCL6 positive cases showed slight better OS ($P > 0.05$). All cases were negative for EBV-LMP1 on ISH.

Conclusion: The majority of the CNS DLBCL belongs to non-GCB phenotype and uniformly carry poor prognosis, irrespective of their phenotype. Individual markers, such as BCL-6, MUM1, or CD10, are unable to predict outcome in PCNS-DLBCL.

Keywords: Central nervous system, Diffuse large B-cell lymphoma, Han's algorithm, Immunocompetent, Non-germinal center B cell type

INTRODUCTION

Primary central nervous system (PCNS) lymphomas (PCNSLs) are extranodal, malignant non-Hodgkin lymphomas that are confined to the brain, eyes, leptomeninges, or spinal cord, in the absence of systemic lymphoma.[14] PCNSL account for 2.4–3% of all brain tumors and 4–6% of

all extranodal lymphomas; their overall annual incidence is 0.5 cases per 100,000 population.[14,17] The peak age of occurrence is 6th decade (median patient age is 56 years) and shows slight male predominance. The incidence rate of PCNSL is known to be high in immunodeficient individuals, such as in patients with acquired immune deficiency syndrome (AIDS), organ transplant recipient; however, due to the current promising highly active retroviral therapy, its incidence has declined in AIDS patients.[9,15] Even, patients with autoimmune disorders and immune system senescence are also more prone to develop CNS lymphoma.[20] There is a recent trend of increased incidence of PCNSL among immunocompetent individuals, although the cause remains unknown.[13] Most of these cases have diffuse large B-cell lymphoma (DLBCL) histology and carries a dismal prognosis than systemic DLBCL.[20] In view of aggressive behavior, these lymphomas are associated with multiple relapses and unflavored remissions. Methotrexate-based chemotherapy, with or without whole brain irradiation, provides longer survival, but increases the patient's risk of subsequent debilitating neurotoxicity. A broad consensus is emerging in the current ongoing clinical research that high dose methotrexate-based induction, as the sole first-line treatment followed by some consolidation chemotherapy is best option.[14,17] Median survival is 17–45 months in immunocompetent patients, while it is only 13.5 months in those with AIDS.[4] Prognostic factors include patient age, clinical performance state, involvement of deep brain structures, and cerebral spinal fluid findings.[10] Older patient age (>65 years) is a major negative prognostic factor and is associated with reduced survival and an increased risk of neurotoxicity.[17]

Systemic nodal DLBCL is divided into two subgroups named germinal center B-cell (GCB) such as and non-GCB such as using cDNA microarray and immunomarkers (CD10, BCL6, and MUM1), according to Hans *et al*. algorithm.[11] Many studies have confirmed that the GCB group has a much better prognosis compared to non-GCB nodal DLBCL.[6] Few subsequent studies on CNS-DLBCL have also described similar findings; however, most of these are small series with limited follow-up data.[1,3,7,13,16,18,19,24,25,28,29,34,35] There is relative paucity of the literature on PCNSL from Indian subcontinent.[21,22,26,28,31,32] In our study, we aimed to analyze the clinicopathological features of PCNSL and categorize them into GCB and non-GCB phenotype to assess their prognostic significance in Indian context.

MATERIALS AND METHODS

Study population, samples, and clinical data

The surgical pathology database of single institution (Post Graduate Institute of Medical Education and Research, Chandigarh, India) was searched for cases of PCNS-DLBCL, from January1, 2014, to December 31, 2019 (6 years). Cases of systemic DLBCL with secondary CNS involvement were excluded.[33] For all cases, the slides were screened for confirmation of the diagnosis. Cases were excluded if the tumor material was insufficient for immunohistochemical analysis. The clinical data collected such as age at diagnosis, sex, tumor location, radiological findings (magnetic resonance imaging or computed tomography scan), and any history of immunosuppression, systemic investigations such as positron emission tomography scan, bone marrow findings, and serological findings (where available) were collected. Patients were followed up in the Departments of Radiation Oncology and Internal Medicine (hematology division). Follow-up data were collected in all available patients in terms of death, recurrence, and disease-free survival.

Tissue microarrays (TMA) and immunohistochemistry (IHC)

TMA were constructed by punching cores of 2 mm from formalin fixed paraffin embedded blocks of cases with adequate tissue sample and were inserted in a grid pattern into a recipient paraffin block using an automated tissue microarrayer (Quick Ray Master UATM-272B, Korea). TMA blocks contained three cores from each case. Tonsillar tissue was included as internal control. A hematoxylin and eosin stained slide of each TMA block was generated to assess their quality. For cases where TMA could be prepared, IHC was performed on TMA blocks. Cases with limited material such as stereotactic biopsy and brain biopsy with small amount of tumor were not included in TMA, but immunohistochemical study was performed on whole slides. IHC was carried out on TMA block for 46 cases and on whole slide in 40 cases. For IHC, 5-μm sections of a representative block were obtained. The following antibodies were used: glial fibrillary acidic protein (GFAP; clone EP672Y, Cell Marque, dilution 1:100), leukocyte common antigen (LCA; clone 2B11+PD7/26, Dako, dilution 1:100), CD3 (Rabbit polyclonal, Cell Marque, dilution 1:500), CD20 (clone L26, Dako, dilution 1:300), CD10 (clone 56C6, Cell Marque, dilution 1:20), B-cell lymphoma 6 (BCL6; cone G1191E/A8, Cell Marque, dilution 1:300), Multiple Myeloma 1 (MUM1; clone MRQ-43, Cell Marque, dilution 1:300), B-cell lymphoma 2 (BCL2; clone 124, Dako, dilution 1:50), c-myc (clone EP121, Cell Marque, dilution 1:50), and Ki-67 (clone SP6, Cell Marque, dilution 1:300). These were performed on Ventana, Biotek automated system with appropriate positive and negative controls run concurrently. Briefly, paraffin sections were mounted on charged glass slides, air-dried over-night, and then deparaffinized. To enhance the immunostaining, a heat-induced epitope-retrieval procedure was performed. After incubation with blocking serum, sections were incubated with primary antibodies, followed by a biotinylated

polyvalent secondary antibody solution. Sections were then incubated with horseradish peroxidase conjugated avidin-biotin complex, followed by 3,3-diaminobenzidine and hydrogen peroxidase.

Three pathologists independently evaluated the stained slides. For each immunostain, the percentage of positive cells was estimated for each of the 10 high power fields evaluated, and an average calculated. Immunostaining for CD10, BCL-6, and MUM1 was considered positive if >30% of the tumor cells were immunoreactive. The intensity of staining was also evaluated but was not used to determine positivity because the variability in tissue fixation and processing appeared to affect the intensity of staining. Sub-classification was carried out as described earlier, according to the schema proposed by Hans *et al*.[11] Only nuclear staining was considered positive for MUM1, BCL-6, c-myc, and Ki-67; membranous for CD10; and cytoplasmic and membranous for BCL2.

In situ hybridization (ISH) for Epstein-Barr virus (EBV)

ISH for EBV-encoded RNA (EBER-1) (Ventana) was performed on formalin-fixed paraffin-embedded tissue sections for all cases with sufficient tissue with the appropriate positive and negative controls. All cases were assessed for EBV-encoded LMP1 by IHC.

Statistical analysis

The results were analyzed by employing appropriate statistical methods. Group comparisons were performed with Fisher's exact test. Overall survival (OS) was defined as the time from diagnosis to death from any cause. OS was estimated using the Kaplan–Meier method, and group comparisons were made with the log-rank test.

RESULTS

Of total 101 cases of PCNS-DLBCL obtained from the archives, 15 were excluded due to inadequate material ($n = 9$) and non-availability of blocks ($n = 6$). Thus, a total 86 cases were included for final analysis.

Clinical findings

Out of 86 cases, 56 were male (62.8%) and 32 were female (37.2%) patients with M:F ratio of 1.68:1. The median age was 55 years (range: 22–82 years) with 34 patients of elderly (≥60 years) age group. Majority of these cases were supratentorial ($n = 68$) in location while only seven cases were infratentorial. Site could not be determined in 11 cases as it was not mentioned in the biopsy request form. All patients tested negative for HIV by enzyme immunoassay. None of the patients had history of organ transplantation, chronic illness, or any other form of immunodeficiency. Five patients had other coexisting diseases, which included chronic hepatitis due to Hepatitis B virus ($n = 3$), cytomegalovirus colitis ($n = 1$), and Type 2 diabetes mellitus ($n = 1$). Follow-up was performed for 66 patients, as 20 were lost to follow-up.

Histology and IHC

Our material consisted of both stereotaxic ($n = 35$, 40.7%), and open ($n = 51$, 59.3%) biopsies. In all cases, the brain parenchyma was replaced and diffusely infiltrated by tumor in prominent sheet-like pattern. The histology revealed characteristic angiocentric distribution, large pleomorphic nuclei with irregular thick nuclear membrane, prominent nucleoli, brisk mitotic figures, and apoptotic bodies. Most of the cases showed areas of geographic necrosis. Five cases showed interspersed histiocytes, giving starry sky appearance. No case showed plasmacytoid morphology. The tumor cells showed immunoreactivity for CD20 (cell membrane; diffuse and intense) but were completely negative for CD3 and GFAP immunostains.

On IHC assessment, 69 (80.2%) were of the NGCB subtype, 10 (11.6%) were of germinal center (GCB) subtype, and 7 (8.1%) were unclassified (UC). The median age for NGCB, GCB and UC was 55 years, 51.5 years, and 53 years, respectively ($P = 0.98$). Among NGCB subtype, all the cases ($n = 69$) showed nuclear positivity for MUM1. Eighteen of these MUM1 positive cases also demonstrated nuclear immunoreactivity for BCL6; one of which displayed BCL2 cytoplasmic positivity. Four MUM1 positive cases expressed c-MYC and none of them showed BCL6 immunoreactivity. Ten cases (11.6%) were categorized as GCB type, and all showed nuclear BCL6 expression and were negative for MUM1. Two of the ten GCB cases were CD10 positive (membranous). Seven cases could not be classified using Han's algorithm. They did not show expression of either MUM-1, BCL-6, or CD10. The Ki-67 labeling index ranged between 70 and 100% with median of 87.5% [Figures 1 and 2]. BCL-2 positivity was seen in 12/46 cases (26%). Overall MUM1 expression was seen in 69 cases (80.2%), BCL-6 in 28 cases (32.6%), and CD10 in 2 cases (2.3%). c-MYC expression was seen in 4 cases, all of these belonged to non-GCB phenotype, were negative for both BCL-2 and BCL-6. The c-MYC and BCL2 immunoexpression was not seen in any of the cases in GCB subtype. Since there was no case with dual immunoexpression (among BCL-2, BCL-6, and c-MYC), no case was subjected to fluorescent ISH (FISH) for BCL-2, BCL-6, or c-MYC rearrangement to detect a double or triple hit lymphoma. All cases were negative for EBV-LMP1 on IHC and EBER for ISH. The clinical and pathological features are shown in [Table 1].

Treatment and follow-up

The follow-up data were available in 66 patients (76.74%) with intervals ranging from 322 to 1028 days. The median follow-

up time was 675 days. Rest 20 patients were lost to follow-up. The treatment details were available in 66 patients (76.74%) and were in the form of variable combination of radiotherapy and chemotherapy (methotrexate, rituximab, vincristine, and dexamethasone) in 41 patients (62.12%), chemotherapy alone in 13 patients (19.7%), and radiotherapy alone in ten patients (11.62%). Two patients did not receive any therapy because of poor general condition. Thirty of 66 patients (45.45%) were found to be alive (26 NGCB, 3GCB, and 1UC) while 36 of 66 patients (54.54%) were found to be dead (28 NGCB, 4 GCB, and 4UC) at the time of last follow-up. The median OS was 675 days. There was no statistically significant difference in survival between non-germinal center, germinal center, and UC subtypes (Log-Rank chi-square = 1.083, df = 2, $P = 0.582$). The median OS for MUM1 positive and MUM1 negative cases were 675 and 399 days, respectively ($P = 0.966$). The median OS for BCL-6 positive and BCL-6 negative cases were 823 and 426 days, respectively ($P = 0.301$) [Figure 3]. Since there were only two CD10 positive cases, its significance on patient survival could not be determined. Other variables such as age of presentation, location of the tumor or sex did not show any correlation with OS [Table 2].

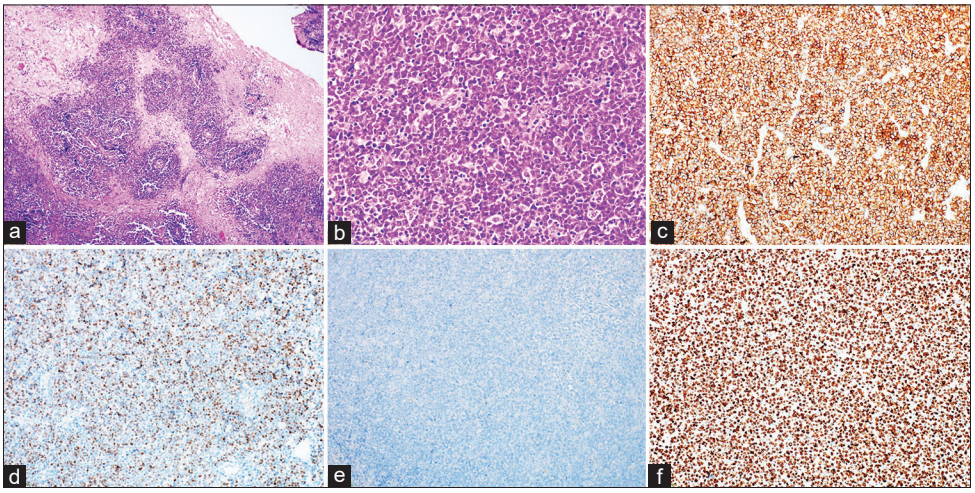

Figure 1: Primary diffuse large B-cell lymphoma of central nervous system, germinal center B-cell phenotype. (a) Characteristic angiocentric distribution is seen (hematoxylin and eosin [H&E], 100×). (b) Tumor cells are arranged in diffuse sheet with starry sky appearance (H&E, 200×). (c) CD20 shows diffuse membranous positivity (immunoperoxidase, 200×). (d) Nuclear expression for BCL6 immunomarker (immunoperoxidase, 200×). (e) MUM1 immunomarker is negative (immunoperoxidase, 200×). (f) Mitotic activity is brisk; Ki-67 proliferation index is more than 90% (immunoperoxidase, 200×).

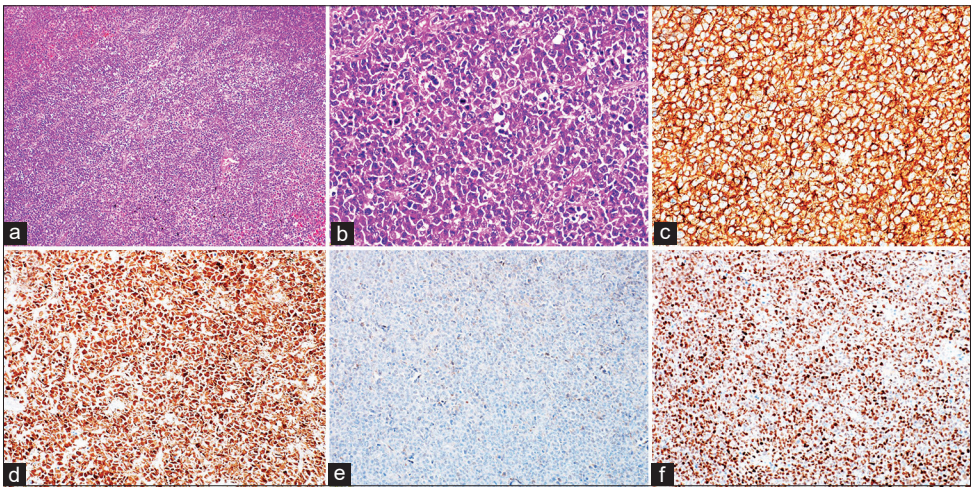

Figure 2: Primary diffuse large B-cell lymphoma of central nervous system, non-germinal center B-cell phenotype. (a) Tumor cells are arranged in diffuse sheet (hematoxylin and eosin [H&E], 100×). (b) Large B-cell morphology with thick nuclear membrane and single to multiple prominent nucleoli (H&E, 400×). (c) CD20 shows diffuse membranous positivity (immunoperoxidase, 200×). (d) Strong nuclear expression of MUM1 immunostain (immunoperoxidase, 200×). (e) BCL6 immunomarker is negative (immunoperoxidase, 200×). (f) Nuclear expression for c-MYC (immunoperoxidase, 200×).

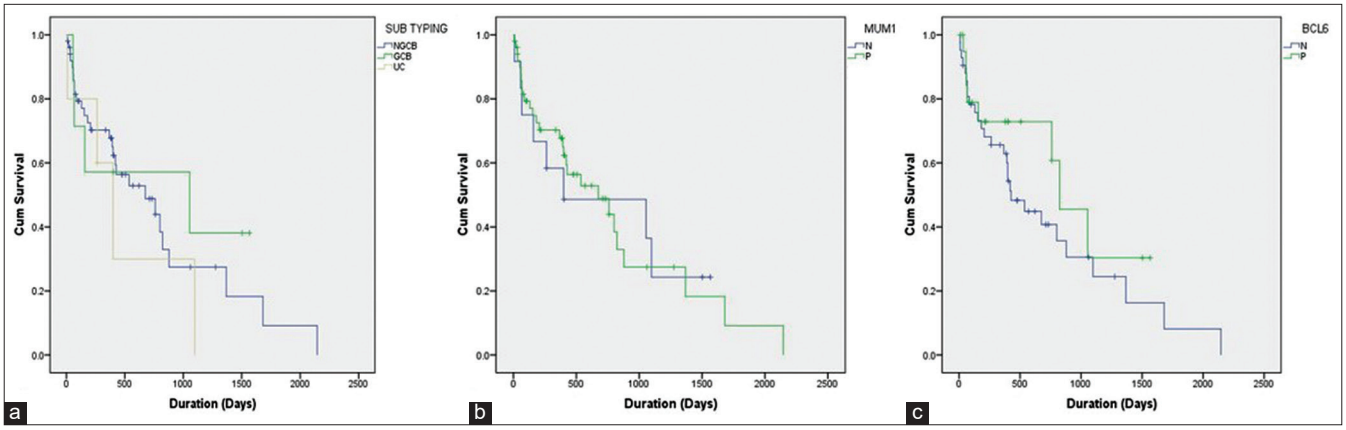

Figure 3: Kaplan–Meier curve. (a) No statistically significant difference in survival between the germinal center B-cell (GCB), non-GCB and unclassified subgroups. (b) No statistically significant difference in survival between the BCL6 positive and BCL6 negative cases. The patients with BCL6 expression exhibited slight better overall survival. (c) No statistically significant difference in survival between the MUM1 positive and MUM1 negative cases.

Table 1: The clinical and pathological details of primary central nervous system diffuse large B-cell lymphoma.

Parameters	Number (%)
Age (*n*=86) (years)	
Median	55
Range	22-82
Gender (*n*=86)	
M:F	1.68:1
Location (*n*=86)	
Supratentorial	68 (79)
Cerebral cortex	39 (45.34)
Basal ganglia	3 (3.5)
Thalamus	9 (10.4)
Periventricular	16 (18.6)
Dura matter	2 (2.3)
Infratentorial	7 (8.13)
Cerebellum	6 (6.97)
Cerebellopontine angle	1 (1.2)
Not available	11 (12.8)
Phenotype (*n*=86)	
GCB	10 (11.6)
NGCB	69 (80.2)
UC	7 (8.1)
Immunomarkers (*n*=86)	
CD10 positive	2 (2.3)
BCL6 positive	28 (32.6)
MUM1 positive	69 (80.2)
EBER-ISH (*n*=86)[#]	0

M: Male, F: Female, GCB: Germinal center B-cell, NGCB: Non-germinal center B-cell, UC: Unclassified, BCL6: B-cell lymphoma 6, MUM1: Multiple myeloma 1, EBER-ISH: Epstein-Barr virus-encoded RNA – *in situ* hybridization. [#]All cases were also negative for EBV-LMP1 on immunohistochemistry

Table 2: Analyses of risk factors for overall survival.

Parameters	Number (%)	OS (days)	*P*-value
Age (years)			
<60	52 (60.5)	734	0.891
≥60	34 (39.5)	833	
Gender			
Male	54 (62.8)	392	0.941
Female	32 (37.2)	578	
Location			
Supratentorial	68 (79)	455	0.721
Infratentorial	7 (8.13)	502	
Phenotype			
GCB	10 (11.6)	1054	0.582
NGCB	69 (80.2)	675	
UC	7 (8.1)	399	
CD10			
Positive	2 (2.3)	57	0.241
Negative	84 (97.7)	760	
BCL6			
Positive	28 (32.5)	823	0.091
Negative	58 (67.5)	426	
MUM1			
Positive	69 (80.2)	675	0.737
Negative	17 (19.8)	399	

GCB: Germinal center B-cell, NGCB: Non-germinal center B-cell, UC: Unclassified, BCL6: B-cell lymphoma 6, MUM1: Multiple myeloma 1, OS: overall survival

DISCUSSION

In this study, we analyzed 86 cases of primary CNS DLBCL in tertiary health care center of North India, one of the largest cohorts in Indian population. All the patients were immunocompetent. The median age of presentation was 55 years. Using Han's algorithm, these cases were further subcategorized into GCB and non-GCB subgroups.[16] In the literature, several immunohistochemical algorithms[8,23] have been used for subdividing DLBCL, but Hans *et al*. algorithm is still most frequently used and considered.

In the present study, most of the cases (80.2%) belonged to non-GCB category which is in agreement with most of the previous studies. Almost all studies have reported a high frequency of MUM1 expression, low frequency of CD10 expression, while the reported frequency of Bcl-6 expression is highly variable [Table 3]. The variability of Bcl-6 expression may either be due to different cutoff criteria used in various studies or due to true biological variation of primary CNS DLBCL.

There is a paucity of literature on PCNSL from Indian subcontinent. In a previous study from our institute, Powari *et al*.[27] reviewed 3325 intracranial tumors diagnosed over a period of 15 years (1985–1999). Of 40 cases of PCNSL included in that study, the majority belonged to category of DLBCL and most of them were immunocompetent individuals. Subsequently, Sarkar *et al*.[31] reviewed all biopsy proven PCNSL cases from the neurosurgical databases of two large referral hospitals in India from the period 1980 to 2003. PCNSL cases constituted 0.95% (n = 116) and 0.92% (n = 70) of the total intracranial neoplasms in those two hospitals, respectively. Mahadevan *et al*.[21] conducted immunophenotyping of PCNS-DLBCLs using Hans *et al*. algorithm. They included 24 cases of PCNS-DLBCL, 91.7% (22/24) of them belonged to non-GCB subtype while there were none belonging to GCB subtype; the other two cases did not show positivity for any of the three markers (MUM1, CD10, and BCL6) and were UC. In a subsequent study, Patel *et al*.[26] from South India found 33/51 (64.7%) and 18/51 (35.3%) of primary CNS DLBCL cases belonging to non-GCB and GCB subtypes, respectively, which is different from our study and most western studies. The higher frequency of GCB type may be explained due to either different source or dilutions of antibodies used; in the present study, we have used antibodies from Cell Marque whereas Patel *et al*. have used antibodies from Novocastra. Besides, this they have not provided the breakup of individual markers such as CD10 and BCL6 positivity to label PCNSL cases as GCB type in their study.

In the current study, c-MYC expression was detected in four cases, all of which were MUM1 positive. BCL2 and BCL-6 immunoreactivity was not seen in association with c-MYC expression. Double or triple hit is very uncommon in primary CNS DLBCL. Nosrati *et al*.[25] examined rearrangement of MYC, BCL2, and BCL6 by interphase FISH and found BCL-6, MYC, and BCL-2 translocation in 12%, 3.8%, and 1.2% cases, respectively. Only one (1.2%) double hit lymphoma was identified showing both MYC/BCL2 translocations. Villa *et al*.[34] found BCL-6 rearrangement in 33% cases but did not find any case with double or triple hit molecular signature. No double or triple hit lymphomas were evident in our study based on immunohistochemical screening, although we did not perform FISH. Hattab *et al*.[13] also did not find any case of double or triple hit lymphoma in their series. EBV has been suggested as a causative agent of PCNS-DLBCL in immunocompromised individuals and elderly patients. Camilleri-Broet *et al*.[3] tested 70 PCNSLs cases for EBV by ISH and found all of them EBER-1–mRNA negative. Mahadevan *et al*.[21] found all their cases negative for EBV by ISH for EBER and IHC for LMP1 antigen. Our study also reflected similar results and thus substantiates that EBV is unlikely to be involved in the pathogenesis of PCNS-DLBCL in immunocompetent patients, and an alternate mechanism or causative factor needs to be explored. Our experience with autopsy cases of PCNSL (unpublished data) is also similar and none of our autopsy cases showed EBV positivity by ISH.

The prognosis of CNS DLBCL is poor. Compared with systemic DLBCL, primary CNS DLBCL carries a much worse prognosis. Various studies have evaluated different clinical and pathological parameters to predict the prognosis in CNS DLBCL [Table 4]. Camilleri-Broet *et al*.[3] and Villa *et al*.[34] found that younger age of presentation (<60 years) was associated with longer OS; however, several other studies failed to demonstrate similar relationship.[1,35] We also did not find any significance of age on patient outcome. Higher lactate dehydrogenase level and poor performance status have been inconsistently shown to be associated with

Table 3: Comparison of CD10, BCL-6, and MUM1 expression in primary CNS DLBCL in different studies.

Antigen	CD10	BCL-6	MUM1
Levy *et al*.[18] (n=66)	5/60 (8.3%)	26/57 (45.6%)	17/18 (94.4%)
Camilleri-Broet *et al*.[3] (n=83)	2/82 (2.4%)	45/81 (55.6%)	75/81 (92.6%)
Lin *et al*.[19] (n=51)	9/51 (17.6%)	30/51 (58.8%)	43/51 (84.3%)
Braaten *et al*.[2] (n=33)	6/32 (18.8%)	26/33 (78.8%)	31/32 (96.9%)
Kinoshita *et al*.[16] (n=32)	6/32 (18.8%)	21/32 (65.6%)	27/32 (84.4%)
Mahadevan *et al*.[21] (n=24)	0/24 (0%)	12/24 (50%)	22/24 (91.7%)
Momota *et al*.[24] (n=27)	6/27 (22.2%)	13/27 (48.1%)	22/27 (81.5%)
Hattab *et al*.[13] (n=31)	4/31 (12.9%)	26/31 (83.9%)	27/31 (87.1%)
Villa *et al*.[34] (n=115)	4/110 (3.6%)	33/109 (30.27%)	85/108 (78.7%)
Yuan *et al*.[35] (n=150)	21/133 (16%)	94/124 (76%)	112/130 (86%)
Present study (n=86)	2/86 (2.3%)	20/86 (32.6%)	69/86 (80.2%)

CNS: Central nervous system, DLBCL: Diffuse large B cell lymphoma

Table 4: Prognostic comparison of clinicopathological parameters and treatment response between different studies.

Authors	*P*-value (<0.05)				Treatment related factors
	Age	GCB versus nGCB phenotype	MUM1 expression	BCL6 expression	
Aki *et al.*[1] (2013) (*n*=35)	No significance	No significance	No significance	No significance	CT+RT had significantly better outcome in comparison to those who received RT or CT alone
Braaten *et al.*[2] (2003) (*n*=33)	No significance	NA	NA	Associated with improved OS	NA
Camilleri-Broet *et al.*[3] (2006) (*n*=83)	Younger age (<60 years) associated with better survival	No significance	No significance	No significance	NA
Hattab *et al.*[13] (2010) (*n*=31)	NA	No significance	NA	NA	NA
Kinoshita *et al.*[16] (2010) (*n*=33)	No significance	No significance	NA	No significance	HDMTX - better response
Momota *et al.*[24] (2010) (*n*=27)	No significance	No significance	No significance	Associated with poor PFS	NA
Villa *et al.*[34] (2019) (*n*=115)	<60 years associated with better survival	No significance	No significance	No significance	HDMTX based therapies – poor survival
Yuan *et al.*[35] (2019) (*n*=150)	<72 years associated with better survival	No significance	No significance	No significance	HDMTX based CT – improved OS
Present study (*n*=86)	No significance	No significance	No significance	No significance	NA

GCB: Germinal center B-cell, nGCB: Non-germinal center B-cell, MUM1: Multiple myeloma 1, BCL6: B-cell lymphoma 6, NA: Not available, CT: Chemotherapy, RT: Radiotherapy, HDMTX: High dose methotrexate, PFS: Progression-free survival, OS: Overall survival

poor prognosis in CNS-DLBCL.[35] Several authors have evaluated pathological prognostic factors in CNS DLBCL. It is well-known that GCB phenotype is associated with a better outcome compared to non-GCB phenotype in systemic DLBCL. However, most of the studies on CNS DLBCL failed to demonstrate any survival advantage in GCB group.[1,34,35] Some authors have evaluated the prognostic significance of individual markers, such as MUM1, BCL-6, and CD10. None have shown any prognostic significance of MUM1 and CD10. There are, however, conflicting results about the prognostic significance of BCL-6 expression. Some authors found BCL-6 expression to be an independent predictor of improved survival,[2,19] whereas many others did not demonstrate any prognostic significance of BCL-6 expression.[1,3,5,35] Neither BCL-6 expression nor rearrangement was associated with patient outcome in a study by Villa *et al.*[34] Our patients with BCL6 expression (32.6%) carried a slightly better OS, although it was not statistically significant.

This study, as well the previous studies have shown that the biology and behavior of primary CNS DLBCL differ from systemic DLBCL. Compared to systemic DLBCL, most of the CNS DLBCL belong to non-GCB phenotype, and carry uniformly poor prognosis. Even cases with GCB phenotype also carry poor prognosis. Compared to systemic DLBCL, PCNS DLBCL carries an extremely high load of somatic mutations of immunoglobulin genes and other proto-oncogenes. Based on these findings, some researchers have proposed that PCNS DLBCL is a separate entity. However, comparative genomic hybridization analysis of chromosomal imbalances showed similar abnormalities in PCNSL and systemic DLBCL, arguing against this hypothesis.[12,30]

CONCLUSION

To summarize, the majority of the CNS DLBCL belong to non-GCB phenotype and uniformly carries poor prognosis, irrespective of their phenotype. Double or triple hit lymphomas are very rare. Individual markers such as BCL-6, MUM1, or CD10 are unable to predict outcome in PCNS DLBCL. The reason for poor prognosis needs to be further evaluated.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

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