

Clinicopathological Features and Predictors of Survival in Primary CNS Lymphoma

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ABSTRACT

Background: Primary CNS lymphoma (PCNSL) is a rare form of extranodal lymphoma, representing 3 to 4% of brain tumors. We aim to report the clinicopathological features and predictors of survival in patients with PCNSL.

Materials and Methods: This retrospective study was conducted at Shifa International Hospital, Pakistan. Patients diagnosed with PCNSL from 2018 to 2023 were included. The Hans algorithm was used to further categorize cases of high-grade lymphoma. Data were analyzed using IBM® SPSS Statistics Software Version 26.

Results: Fifty-two patients were diagnosed with PCNSL during the study period, out of whom twenty-seven patients had complete clinical and laboratory data available. From these 27 patients, 14 (52%) were male. Mean age was 48.78 ± 13.46 years. Twenty-four (88.9%) patients were immunocompetent and none had HIV infection. On radiology, a solitary lesion was seen in 19 (70.4%) patients with parietal lobe being the most common location in 8 patients. Twenty-six patients were diagnosed with high-grade non-Hodgkin B-cell lymphoma whereas one patient had low-grade non-Hodgkin B-cell lymphoma. Seven patients expired, with median survival of five months (range 1–31 months). Ki-67 proliferative index >80% was the only factor identified as significantly associated with decreased overall survival ($p < 0.05$).

Conclusion: PCNSL is a rare and aggressive disease. High Ki-67 proliferative index is a significant predictor of overall survival in these patients. Lack of association of HIV, frequent occurrence of Bcl6 positivity and a single case of low-grade lymphoma were unique features identified in our study population.

Keywords: Primary central nervous system lymphoma; Immunohistochemistry; Ki-67; Survival

INTRODUCTION

Primary Central Nervous System Lymphomas (PCNSL) comprise a group of aggressive, extranodal lymphomas involving the Central Nervous System (CNS) including brain, eyes, leptomeninges or spinal cord, in the absence of systemic evidence of lymphoma at the time of diagnosis¹. PCNSL is a rare entity, representing 4 to 6% of extranodal lymphomas and 3 to 4% of intracranial neoplasms². The fifth edition of the World Health Organization classification of haematolymphoid tumours includes PCNSL in the new entity of Large B-cell lymphomas of immune-privileged sites³.

The diagnosis of PCNSL requires a high index of suspicion due to diversity of clinical signs and

symptoms. Depending on the involved region, patients may present with focal neurological deficits, altered mental status, seizures, vomiting, visual field defects, sensory changes, bowel or bladder dysfunction⁴. Magnetic Resonance Imaging (MRI) is usually among the first line investigations, however definitive diagnosis requires histopathological examination⁵. Furthermore, Positron Emission Tomography (PET) Scan and/or Computed Tomography (CT) Scan as well as bone marrow biopsy are performed to document the absence of systemic disease⁶.

A study by Hattab et al. found that that majority of PCNSL are diffuse Non-Hodgkin B-cell lymphomas of non-germinal center origin, with high proliferative

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activity⁷. Immunohistochemistry plays a significant role in diagnosis and risk stratification⁸. Previous studies have shown that immunophenotypic markers including expression of Bcl-6, MUM1 and CMYC can predict prognosis in PCNSL^{9, 10}. However, there is wide variation in the reported literature as most studies are based on case series with limited sample size.

Due to the uncommon nature of this condition, data regarding the clinicopathological features and predictors of survival is limited. Knowledge of these predictors is necessary to aid clinicians in the process of pre-treatment risk stratification. Therefore, the aim of this study is to document the clinicopathological features and identify predictors of survival in patients diagnosed with PCNSL – a rare entity with a challenging diagnosis and prognosis.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Pathology at Shifa International Hospital (SIH), a 550-bed quaternary care hospital in Pakistan that is accredited by the Joint Commission International (JCI). SIH is a high-volume center which receives more than 30,000 specimens for histopathological analysis per annum. Patients of all ages and both genders were included. Those patients who had a diagnosis of PCNSL from January 2018 to December 2023 were identified through the Electronic Medical Record system by their respective ICD code. We excluded patients with evidence of systemic involvement by lymphoma, such as those with significant radiological findings or presence of lymphoma in biopsies of bone marrow, lymph nodes or extranodal masses. We also excluded patients who did not have a basic panel of immunohistochemistry done.

Hans algorithm was used to classify our cases of High-grade CNS lymphoma into two categories: Germinal center (GC-DLBCL) and non-Germinal center B-cell Lymphoma (non GCB-DLBCL), also known as Activated B-Cell type Diffuse Large B-Cell Lymphoma (ABC-DLBCL). This algorithm has been adapted from the landmark publication of Hans et al. in 2004¹¹.

A standardized data collection form was used to collect information regarding the demographics,

clinical presentation, radiological and histopathological features of these patients. Data was analyzed using IBM® SPSS Statistics Software Version 26. Mean and standard deviation were reported for quantitative variables whereas frequencies and percentages were reported for qualitative variables. Our primary outcome measure was overall survival, reported from the time of diagnosis of PCNSL until expiry or last available follow up. Clinicopathological characteristics of survivors and non-survivors were compared using Independent samples t-test for normally distributed quantitative variables, whereas Chi-square test or Fisher's exact test for qualitative variables. Cox regression analysis was performed to assess the factors associated with overall survival. Kaplan-Meier curve analysis was done to compare the overall survival among PCNSL patient subgroups based on Ki67 proliferative index. A p value of less than 0.05 was considered statistically significant for all data analysis.

This study was commenced after receiving ethical approval from the Institutional Review Board of SIH. No funding was required due to the retrospective nature of this study.

RESULT

Fifty-two patients were diagnosed with PCNSL during the study period out of whom follow up data and immunohistochemistry was available for 27 patients. Thus, a total of 27 patients met the inclusion criteria. Fourteen (52%) were male. Mean age was 48.78 ± 13.46 years. The median follow-up duration was five months (range 1 to 31 months). A focal neurological deficit such as unilateral sensory or motor loss was the initial symptom in majority of the cases (14 cases, 52%). Other presenting complaints included occurrence of headache in 7 patients (25.9%), visual defects (6 cases, 22.2%), seizures (5 patients, 18.5%) altered mental state (4 cases, 14.8%) and vertigo in 4 patients (14.8%). On radiology, a solitary lesion was seen in 19 (70.4%) patients. Rest of our patients had multiple lesions with more than three lesions seen on MRI in 5 (18.5%) patients. Parietal lobe was the most common location of CNS lymphoma, seen in 8

(29.63%) patients, followed by the temporal lobe in 5(18.5%), frontal lobe in 5(18.5%), thalamus in 5(18.5%), basal ganglia in 3(11.1%), occipital lobe in 2(7.4%) and cerebellum in 2(7.4%) patients. A single case showed spinal cord involvement. Twenty-four (88.9%) patients were immunocompetent and none of the patients had a history of HIV infection. Three patients were considered immunosuppressed due to a history of Tuberculosis or malignancy.

Twenty-four (88.9%) patients were immunocompetent and none of the patients had a history of HIV infection. Three patients were considered immunosuppressed due to a history of Tuberculosis or malignancy.

Twenty-six patients were diagnosed with High grade Non Hodgkin B-Cell Lymphoma (NHBCL) whereas one patient had a Low grade NHBCL. Among the high-grade NHBCL cases, 6 out of 26 (23.08%) were GCB-DLBCL whereas majority (20, 76.92%) were non-GCB type of DLBCL.

Figures 1 – 2 show the characteristic histopathological and immunohistochemical features of our patients.

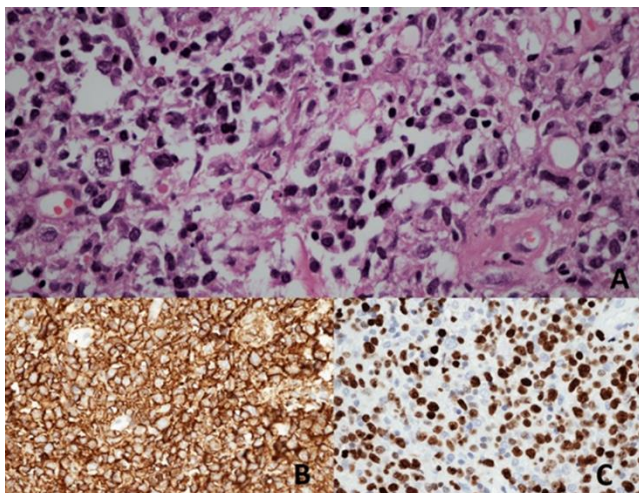


Figure 1. High grade PCNSL. A: Haematoxylin and eosin stain (atypical lymphoid infiltrate with reactive background and increased mitotic activity), B: CD20 immunostain (positive), C: Ki67 immunostain (high proliferative index).

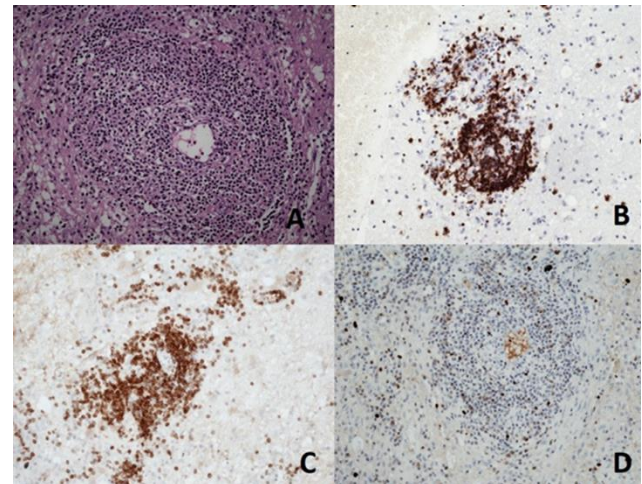


Figure 2. Low grade PCNSL. A: Haematoxylin and eosin stain (atypical lymphoid infiltrate in perivascular area), B: CD20 immunostain (positive), C: Bcl2 immunostain (positive), D: Ki67 immunostain (low proliferative index).

All patients underwent debulking surgery for treatment of PCNSL, while 16 out of 27 (59.3%) patients who received radiotherapy and 18 out of 27 (67%) patients received methotrexate based chemotherapy regimens.

Overall, seven patients (25.9%) expired, while 20 patients (74.1%) survived during the follow up period. Median overall survival was five months (range 1 to 31 months). Table 1 compares the characteristics of survivors and non-survivors. Table 2 shows the results of cox regression analysis, used to identify predictors of overall survival in our patients.

Table 1: Comparison of characteristics of survivors and non-survivors

	Survivors	Non-survivors	P
	(N = 20)	(N = 7)	
Age (years)	49.25 ± 13.84	47.43 ± 13.26	0.765
Gender			
Male	10 (50.0%)	4 (57.1%)	1.000
Female	10 (50.0%)	3 (42.9%)	
Comorbidities			
Immunocompetent	17 (85.0)	7 (100.0)	0.545
Immunosuppressed	3 (15.0)	0 (0.0)	
Number of lesions on radiology			
1	13 (68.4%)	6 (85.7%)	
3	2 (10.5%)	0 (0%)	0.586
>3	4 (21.1%)	1 (14.3%)	
Diagnosis			
GC-DLBCL	4 (20.0%)	2 (28.6%)	
Non GCB-DLBCL	15 (75.0%)	5 (71.4%)	0.767
LG-NHBCl	1 (5.0%)	0 (0%)	
Ki67			
> 80%	2 (10.0%)	3 (42.9%)	0.054
≤ 80%	18 (90.0%)	4 (57.1%)	
CD10 positive	4 (20.0%)	2 (28.6%)	0.633
Bcl6 positive	12 (70.6%)	7 (100%)	0.272
MUM1 positive	16 (80%)	7 (100%)	0.512
Background CD3 activity			
Low	11 (64.7%)	5 (71.4%)	
Moderate	3 (17.6%)	1 (14.3%)	0.951
High	3 (17.6%)	1 (14.3%)	

P values of Independent samples t-test for quantitative variables and chi-square test/Fisher's exact test for qualitative variables

Table 2: Factors associated with overall survival in patients with PCNSL (Univariate cox regression analysis)

Variable	HR	95% CI	p
Gender	1.373	0.307-6.139	0.678
Comorbidities	0.037	0.000-228.605	0.458
Number of lesions on radiology			
1	0.943	0.111-8.021	0.957
3	0	0	0.992
Diagnosis			
GC-DLBCL	0.867	0.167-4.500	0.865
Non GCB-DLBCL	0	0	0.990
Ki67			
> 80%	4.594	1.014-20.804	0.048
CD10 positive	1.247	0.240-6.467	0.793
Bcl6 positive	27.916	0.008-96072.047	0.423
Background CD3 activity			
Low	0.670	0.074-6.025	0.721
Moderate	0.718	0.044-11.680	0.816

A high proliferative index defined as Ki67 more than 80% was significantly associated with poor overall survival in patients with PCNSL ($p < 0.05$). Figure 3

shows the Kaplan-Meier curve of our patients with Ki-67 as a predictor of overall survival.

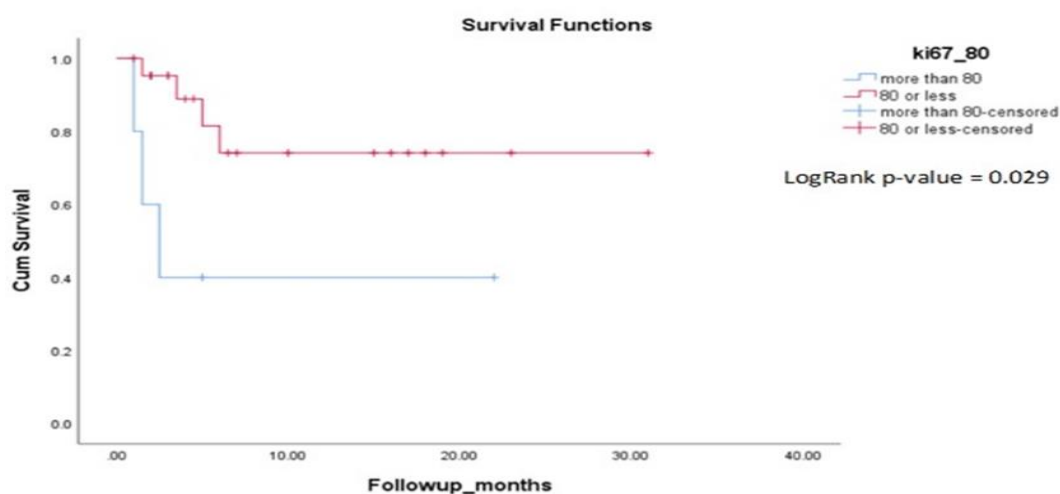


Figure 3. Kaplan Meier analysis of overall survival with Ki-67 as a predictor of survival in patients with High grade PCNSL

DISCUSSION

This study reports the clinical presentation, pathological features and outcomes of patients with PCNSL. A high Ki-67 proliferative index was identified as the only significant predictor of poor overall survival in these patients.

Ki-67 proliferative activity is documented to be an independent prognostic marker in various lymphoproliferative disorders, which include DLBCL, follicular lymphoma, mantle cell lymphoma and NK/T cell lymphomas¹². Ki-67 proliferative index more than 80% was significantly associated with decreased overall survival in our patients. However, the cut-off of Ki-67 expression used to predict clinical outcomes has varied in different studies. Cho et. al assessed 45 patients with PCNSL and found that cases in which Ki-67 immunostain showed a high proliferative index ($\geq 90\%$) were associated with poor overall survival¹³. Another study reported that Ki67 index $\geq 80\%$ was the only factor associated with prognostic significance among thirty PCNSL patients from India¹⁴.

Over 70% of our patients (19 out of 27) showed greater than 30% expression of Bcl-6. The role of Bcl-6 as a prognostic marker is conflicting in previous studies. Preusser et.al performed a comprehensive analysis of 75 patients with PCNSL, using a panel of 16 immunostains, in situ hybridisation for Epstein-Barr virus (EBV) RNA and fluorescence in situ hybridisation (FISH) for Bcl6 and FOXP1 genes¹⁵. They found that Bcl-6 expression was an independent marker associated with good prognosis in PCNSL patients. This association of Bcl-6 with prognosis was not seen on immunohistochemistry of our patients, whereas FISH for Bcl-6 was not performed in this study. Another study that also showed association of Bcl-6 expression with favourable outcomes reported that among their patients, Bcl-6 was more commonly expressed among older patients who already had a poor performance status. In this study of 66 PCNSL patients, Bcl-6 expression was significantly associated with improved progression-free survival on univariate analysis, however on multivariate analysis, only age and performance status remained significant predictors of survival¹⁶. This raises the possibility of bias while reporting associations as majority of the data on PCNSL is based on studies

with a small sample size. We also encountered a single rare case of Low grade NHBCL, the first such case from Pakistan. Few low-grade CNS lymphomas which have been documented earlier in the form of case reports include Marginal zone lymphoma (CNS-MZL), Lymphoplasmacytic lymphoma (PCNS-LPL) and follicular lymphoma (CNS-FL)¹⁷⁻¹⁸. Low-grade PCNSLs are difficult to diagnose, as they are extremely rare, however they are associated with favorable clinical outcomes in terms of response to treatment and overall survival¹⁹. Our patient remains well to date, with a current follow up of over 2.5 years.

In cases of DLBCL involving organs other than the CNS, the cell of origin has a significant impact on disease prognosis²⁰. In particular, GCB-DLBCL is associated with favorable outcomes as compared to non-GCB or ABC-DLBCL. However, in our patients, cell of origin was not a significant predictor of survival. Our results corroborate the findings of another study by Woo et al. who reported that cell of origin classification did not predict survival in their 74 patients with PCNSL²¹.

Majority of our patients were immunocompetent. Furthermore, none of our patients had HIV/AIDS. Historically, immunodeficiency especially in the setting of HIV/AIDS was the main predisposing factor for PCNSL²². However, more recently, due to substantially improved treatment of HIV/AIDS and the advent of highly active anti-retroviral drugs, PCNSL is now encountered more frequently in immunocompetent patients²³. The lack of HIV positivity in our patient population may also be a consequence of the overall low prevalence of HIV in Pakistan, which is estimated to be less than 1%²⁴.

This study is limited by the small sample size and retrospective nature due to which some patients were lost to follow-up. Additionally, heterogeneity in treatment regimen is also expected to have had an impact on survival in our patients. Prospective studies with a larger sample size with subgroup analysis based on treatment regimens are needed to verify the findings of our study. Other pathological markers which were not available in our study such as expression of Bcl-2 and CMYC should also be assessed for their prognostic value.

CONCLUSION

PCNSL is associated with poor prognosis. High Ki67 proliferative index greater than 80% is the only significant predictor of overall survival in our patients. Lack of HIV infection and frequent Bcl-6 positivity were unique features identified in our study population. We also report a rare case of Low-grade Non-Hodgkin B-cell lymphoma involving the CNS.

CONFLICT OF INTERESTS

None of the authors has any conflicts of interest to declare.

REFERENCES

- Grommes C, Rubenstein JL, DeAngelis LM, et al. Comprehensive approach to diagnosis and treatment of newly diagnosed primary CNS lymphoma. *Neuro Oncol*. 2019;21(3):296-305.
- Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer*. 2011;105(9):1414–1418.
- Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022; 36(7):1720-48.
- Grommes C, DeAngelis LM. Primary CNS Lymphoma. *J Clin Oncol*. 2017;35(21):2410-2418.
- Lukas RV, Riedell P, Horowitz PM, et al. Diagnostic Evaluation in Primary CNS Lymphoma. *Neurologist*. 2018;23(2):53-54.
- Scott BJ, Douglas VC, Tihan T, et al. A systematic approach to the diagnosis of suspected central nervous system lymphoma. *JAMA neurology*. 2013 1;70(3):311-9.
- Hattab EM, Martin SE, Al-Khatib SM, et al. Most primary central nervous system diffuse large B-cell lymphomas occurring in immunocompetent individuals belong to the nongerminal center subtype: a retrospective analysis of 31 cases. *Modern Pathology*. 2010;23(2):235-43.
- Citterio G, Reni M, Gatta G, et al. Primary central nervous system lymphoma. *Crit Rev Oncol Hematol*. 2017;113:97-110.
- Momota H, Narita Y, Maeshima AM, et al. Prognostic value of immunohistochemical profile and response to high-dose methotrexate therapy in primary CNS lymphoma. *Journal of neuro-oncology*. 2010;98:341-8.
- Chang CC, Kampalath B, Schultz C, et al. Expression of p53, c-Myc, or Bcl-6 suggests a poor prognosis in primary central nervous system diffuse large B-cell lymphoma among immunocompetent individuals. *Archives of pathology & laboratory medicine*. 2003;127(2):208-12.
- Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-82.
- He X, Chen Z, Fu T, et al. Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis. *BMC cancer*. 2014;14:1-3.
- Cho U, Oh WJ, Hong YK, et al. Prognostic significance of high ki-67 index and histogenetic subclassification in primary central nervous system lymphoma. *Applied immunohistochemistry & molecular morphology*. 2018;26(4):254-62.
- Phalak P, Rajamma BM, Pradeep A, et al. Prognostic significance of immunohistochemical markers in Primary CNS lymphomas. *IP Arch Cytol Histopathol Res*. 2023;6(3):160-5.
- Preusser M, Woehrer A, Koperek O, et al. Primary central nervous system lymphoma: a clinicopathological study of 75 cases. *Pathology*. 2010;42(6):547-52.
- Levy O, DeAngelis LM, Filippa DA, et al. Bcl-6 predicts improved prognosis in primary central nervous system lymphoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2008;112(1):151-6.
- Kaji FA, Martinez-Calle N, Sovani V, et al. Rare central nervous system lymphomas. *Br J Haematol*. 2022;197(6):662-78.
- Abbi KK, Muzaffar M, Gaudin D, et al. Primary CNS lymphoplasmacytic lymphoma: a case report and review of literature. *Hematology/Oncology and Stem Cell Therapy*. 2013;6(2):76-8.
- Lim T, Kim SJ, Kim K, et al. Primary CNS lymphoma other than DLBCL: a descriptive analysis of clinical features and treatment outcomes. *Annals of Hematology*. 2011;90:1391-8.
- Woo HY, Chae SW, DO SI, et al. Clinicopathological Characterization of Primary Diffuse Large B-Cell Lymphoma of the Central Nervous System. *Anticancer Research*. 2022;42(11):5601-8.
- Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. *Journal of clinical oncology*. 2011;29(2):200-7.
- Brandsma D, Bromberg JE. Primary CNS lymphoma in HIV infection. *Handbook of clinical neurology*. 2018;152:177-86.
- Sierra del Rio M, Rousseau A, Soussain C, et al. Primary CNS lymphoma in immunocompetent patients. *The oncologist*. 2009;14(5):526-39.

24. Ahmed A, Hashmi FK, Khan GM. HIV outbreaks in Pakistan. The Lancet HIV. 2019;6(7):e418.