Article published online: 2022-09-20

ORIGINAL ARTICLE

Primary intracranial lymphomas

Shagufta T. Mufti[1], Saleh S. Baeesa[2], Jaudah A. Al-Maghrabi[1,3]

Departments of [1]Pathology, and [2]Surgery, Faculty of Medicine, King Abdulaziz University, Jeddah, [3]Department of Pathology, King Faisal Specialist Hospital and Research Centre, Jeddah, Kingdom of Saudi Arabia

ABSTRACT

Background: Primary CNS lymphoma (PCNSL), a rare form of aggressive extranodal non-Hodgkin's lymphoma (NHL), has increased in incidence during the last three decades and occurs in both immune compromised and immune competent hosts. It has an overall poor prognosis.

Objective: This study attempts to further delineate the clinico-pathological, immunohistochemical and radiological profile of PCNSL at Jeddah to King Faisal Hospital and Research Center.

Methods: Computerized search through the archives of King Faisal Hospital and Research Centre between July 2000- December 2012 identified 15 patients with pathologically confirmed PCNSL.These were analyzed retrospectively. Their clinico-pathological, immunohistochemical and radiological data were analyzed.

Results: Of the 15 PCNSL patients, 8 (53.3%) were females and 7 (46.6%) were males. There was female predilection especially in the age group of 40-59 years. Mean age at diagnosis for all patients was 50.4 years. There was no patient in the pediatric age group. The most common location in the brain was the frontal region in 7 patients (46.6%), 7 (46.6%) had multiple intracranial masses; all 15 (100%) were Non Hodgkin B-cell lymphomas, among which 13 (86.6%) were diffuse large B-cell lymphomas. All 15 (100%) cases showed diffuse and strong positivity for CD 45, and CD 20. Fourteen patients were immune competent while one was immune compromised.

Conclusions: PCNSL often occurs in middle-aged and aged patients. There is female predilection especially in the middle age. Frontal region is the most common location with diffuse large B-cell lymphoma being the predominant subtype.

Key words: Central nervous system, lymphoma, primary

Introduction

Primary central nervous system lymphoma (PCNSL) is defined as an aggressive extranodal, high-grade B-cell neoplasm of the CNS and eye. Excluded are lymphomas of the dura and those with evidence of systemic disease, CNS secondary lymphomas and all immunodeficiency-associated lymphomas arising in the brain, spinal cord, cerebrospinal fluid and eyes in the absence of lymphoma outside the nervous system at the time of diagnosis. In the updated 2008 World Health Organization (WHO) classification of lymphomas, primary diffuse large B-cell lymphoma (DLBCL) of the CNS is recognized as a separate entity under "Aggressive lymphoma/leukemia".[1,2]

The incidence of CNS lymphoma has been increasing over the past two decades[3] and according to the most recent central brain tumor registry of united states (CBTRUS)[4] statistical reports it now represents 2.3% of all primary brain and central nervous system tumors in USA. The age-adjusted incidence is 0.46/100,000 and appears to be increasing over time. Approximately 1,000 new cases are diagnosed annually in the United States.[4]

The study of PCNSL is important for several reasons. Firstly because nothing is known about how lymphoma arises in an organ, which is immunologically privileged and gives sanctuary to the malignant lymphocytes among immune competent individuals.[5]

Secondly once a rare tumor and the subject of individual case reports, PCNSL now afflicts approximately 1,000 people in the United States each year[6] and has shown a trend towards an increase in incidence over the past three decades[3,7] contributing to an increasingly important differential diagnosis of intracranial mass lesions.

Access this article online	
Quick Response Code:	Website: www.asianjns.org
	DOI: 10.4103/1793-5482.145082

Address for correspondence:
Prof. Jaudah A. Al-Maghrabi, Department of Pathology, Faculty of Medicine, King Abdulaziz University, P. O. Box 80205, Jeddah 21589, Kingdom of Saudi Arabia.
E-mail: jalmaghrabi@hotmail.com

Third, the blood-brain barrier (BBB) is critically important because much of the tumor resides behind an intact BBB and often cannot be visualized radiologically.[8] Finally, because the brain is the non-regenerative organ there has been a longstanding concern that even if effective therapy were to become available for malignant primary brain tumors, eradication of the tumor may not necessarily translate into improved neurologic outcome. However, PCNSL serves as a shining example that this is not the case. Since PCNSL is a highly radio and chemo sensitive tumor if treatment is effective and does not damage the brain, it can prolong remission and even cure patients.[6]

Objective

This study attempts to present the clinico-pathological, immunohistochemical and radiological profile of PCNSL at King Faisal Hospital and Research Center, Jeddah. We also present the most recent literature review in the understanding of PCNSL.

Method

A computerized search through the archives of the Anatomical Pathology Department at King Faisal Hospital and Research Center, Jeddah between the years January 2000 and December 2012, was performed to identify all cases of PCNSL inclusive of all regions of the brain. For inclusion into this analysis, patients had to have a confirmed histological diagnosis of central nervous system lymphoma in the absence of any radiologic evidence of systemic involvement. The patient had to have a follow-up of 6 months to be included in this analysis. The data was filtered using appropriate morphology Systematized Nomenclature of Medicine codes indicating the following parameters: Date of receiving biopsy, personal identity (medical record number, age, sex etc.,) clinical diagnosis, morphology and topography. The data was rechecked manually to delete duplications. Computerized search was then exported to Microsoft Excel format and used for analysis. Specific target group of PCNSL was identified. 15 cases of PCNSL were retrieved. These were analyzed retrospectively. The clinical data analyzed were: Age at diagnosis, date of clinical onset, symptoms described, imaging data, tissue sampling method, primary CNS origin, past medical history, immune status and human immunodeficiency virus (HIV) serology findings, number and location of lesions, involvement of deep brain structures and outcome. Data were analyzed using the program Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive and frequency statistics were obtained for the variables studied. The procedures followed in the present study were in accordance with the ethical standards of the hospital ethical committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Lesions were reclassified using the Revised European American Lymphoma Classification WHO classification updated in 2008.[2]

The patients underwent magnetic resonance imaging (MRI) scan of the brain at diagnosis as well as computerized tomography (CT) scans of the chest, abdomen and pelvis and lumbar puncture at diagnosis. A repeat MRI scan to assess response was done after the end of chemotherapy in those who were managed with combined modality therapy. All patients had an evaluation of response at the end of all planned treatment with an MRI and were then followed at 3 monthly intervals with a follow-up MRI scan as well as clinical evaluation to assess residual neurologic deficit and/or long-term toxicity from treatment. Biopsies taken were subjected to five-micron-thick sections stained with hematoxylin and eosin which were reviewed by two pathologists for morphological features of the lymphoma. Immunohistochemical staining using Ventana automated stainer with the avidin-biotin-peroxidase complex method was performed using the antibodies CD45 (dilution 1:0; Dako, Denmark), CD20 (dilution 1:50; Dako, Denmark), CD3 (dilution 1:50; Nova, UK), CD30 (dilution 1:25 Dako, Denmark), CD79a (dilution 1:50; Dako, Denmark), CD10 (dilution 1:100; Nova, UK), Bcl-2 (dilution 1:25 Dako, Denmark), Bcl-6 (dilution 1:25; Nova, UK), Tdt (dilution 1:10 Dako, Denmark), CD68 (dilution 1:100; Dako, Denmark), CD1a (dilution 1:10; Cell Marque, USA), Cyclin D1 (dilution 1:10; Cell Marque, USA), Pancytokeratin (dilution 1:50; Dako, Denmark), GFAP (dilution 1:50; Dako, Denmark), Chromogranin (dilution 1:200; Nova, UK), Lambda light chain (One drop, Dako, Denmark) and Synaptophysin (dilution 1:10 Dako, Denmark). Antibodies were used to highlight the cell lineage and as the case scenario necessitated. Results were scored as follows: −, not seen; +/−, rare/focal positivity; and +/, diffuse positivity. Positive and negative controls were performed for the stains. Clinical data were obtained from the patients' hospital records and follow-up was obtained on a personal basis from the concerned neurosurgical and medical teams. Initial investigations performed in these patients were as follows CT MRI brain, chest X-ray, CT abdomen and chest and lesional biopsy, MRI was available in 13 cases while in two cases only CT findings were available.

Results

All patients in the study group were Saudi nationals. Of the 15 PCNSL patients, 8 (53.3%) were females and 7 (46.6%) were males. There was female predilection especially in the age group of 40-59 years. Mean age at diagnosis for all patients was 50.4 years. Five patients (33.3%) were more than 45-year-old. There was no patient in the pediatric age group. The most common location in the brain was the frontal region in 7 patients (46.6%). Seven patients (46.6%) had multiple intracranial masses. All 15 (100%) were non Hodgkin B-cell lymphomas, among which 13 (86.6%) were DLBCL. All the cases displayed a characteristic nuclear and cytoplasmic pattern of lymphoid cell with an angiocentric pattern and variable

parenchymal infiltration [Figure 1]. All cases showed diffuse and strong positivity for CD 20 [Figure 2]. A total of 14 patients were immune competent while one was immune compromised. Seven (46.6%) of the patients had multiple lesions. Three out of seven cases with multiple lesions were also bilateral.

Table 1 and Illustration 1 presents the age and sex distribution of PCNSLs, Table 2 presents the radiological features and Table 3 presents the histological subtype and immunohistochemical features. Illustration 2 illustrates the location and Illustration 3 the number (frequency) of PCNSLs. Thirteen patients were diagnosed on MRI brain while 2 cases were diagnosed by CT brain. Radiological studies of chest, abdomen, pelvis and neck showed no evidence to suggest a nodal primary source.

Medical and radiological follow-up (MRI) was available in 5 cases with a mean survival time of 1 year 2 months.

Discussion

The increase in incidence of PCNSL could be related partly to the acquired immune deficiency syndrome (AIDS) epidemic.[9-11] the other risk factors for PCNSL have included acquired or hereditary immune deficiency states, i.e. infection with human immune deficiency virus, organ transplantation, severe combined immmune deficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome as well as autoimmune or inflammatory disorders requiring long term immune suppression such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, myasthenia gravis and vasculitides.[12] It is over 1000 times greater in HIV positive than in non-HIV populations.[10,11,13]

Table 1: Age and sex distribution of PCNSLs at KFHRC, Jeddah, Saudi Arabia

Age group *n*=15	0-19 years		20-39 years		40-59 years		60 years and more	
Gender	M	F	M	F	M	F	M	F
	-	-	1	1	3	6	3	1
Total %			6.6	6.6	20	40	20	6.6

PCNSLs – Primary central nervous system lymphoma; KFHRC – King Faisal Hospital and Research Center

As in the present study, the incidence rates of PCNSL are also increasing among immune competent patients. Similar studies have been reported to literature.[3,11,14]

Evidence of Epstein-Barr virus (EBV) genome is present in more than 95% of AIDS-related PCNSL which suggests its major role in lymphoma pathogenesis in this group.[15] Incidence of EBV positive PCNSL is higher in Japanese than previously reported from western countries reflecting additional role of variable epidemiological factors.[16]

However, the etiology of PCNSL in immune competent patients is still unclear. Several hypotheses have been proposed to explain how lymphomas arise and grow primarily in the CNS. The theory of highly selective tropism of PCNSL suggests that B-cells may be transformed outside the CNS and then develop adhesion molecules specific for CNS tropism.[17] Recently, some specific genes involved in CNS tropism of PNCSL such as SPP1, a member of the extracellular matrix-related genes and DDR1, a member of a family of receptor tyrosine kinases involved in cell adhesion in several brain tumors, were found to be unregulated in PCNSL.[18] These findings support the theory of highly selective tropism of PCNSL. Alternatively polyclonal inflammatory cells in the brain may transform to monoclonal PNCSL. This theory is supported by occasional reports of "sentinel lesions" which are biopsy-proven demyelinating or non-neoplastic lesions but ultimately lead to PCNSL months to years later.[19]

We compared our results to other recent national and international studies on PCNSL Tables 4 and 5.[20-26]

Most of these studies indicate that percutaneous nephrolithotomy (PCNL) is common between 4th and 6th decade of life, with a male to female ratio of near unity, being predominantly of DLBC type located mainly in the cerebral hemispheres and having a mean survival time between 4 months and 17 months. An epidemiological study reported that PCNSL incidence for ages 20-49 years for Black patients was twice that for Whites.[27] Incidence for ages over 49 years for Whites was twice that for Blacks.[27] Earlier acquisition of PCNSL in Black populations could reflect

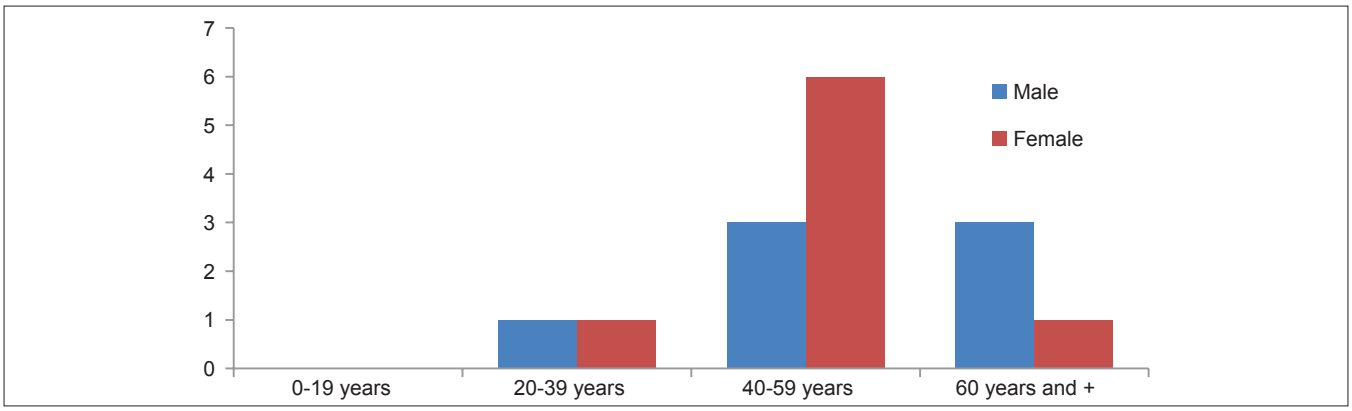

Illustration 1: Age and Sex diustribution of PCNSL at KFSHRC, Jeddah *n*=15

Table 2: Radiological features of PCNSLs at KFSHRC, Jeddah, Saudi Arabia

Features	Number of cases
Contrast CT characteristics *n*=2	
Homogeneously enhancing lesions	2
Surrounding vasogenic edema	2
Mass effect	2
MRI characteristics with gadolinium contrast *n*=13	
Mean size	
APD	5.5 cm
TRD	3.6 cm
Homogeneously enhancing lesions	13
Surrounding vasogenic edema	13
Mass effect	13
Herniation	
Subfalcine and uncal	2
Tonsillar and thalamic	1
Hydrocephalus	3
Subcutaneous extension	1
Involvement of deep structures	
Present	3
Absent	10
Follow-up MRI *n*=5	
Median survival	1 year 6 months
Outcome	
No evidence of residual tumor post	
Chemo+radiotherapy	2
Debulking	1
Resolution with lesional hemorrhage post chemo+radiotherapy	1
Recurrent multiple enhancing lesions post chemo+radiotherapy	1

PCNSLs – Primary central nervous system lymphomas; CT – Computerized tomography; MRI – Magnetic resonance imaging; KFSHRC – King Faisal Specialist Hospital and Research Centre; APD – Anterioposterior diameter; RD – Transverse diameter

Table 3: Histological subtype and immunohistochemical characteristics of PCNSLs at KFSHRC, Jeddah, Saudi Arabia

Features	Number of cases	% *N*=15
Histological subtype		
DLBCL	13	86.6
High grade NHBCL Burkitt type	1	6.6
Low grade lymphoma favoring marginal zone	1	6.6
Immunohistochemical expression		
CD45 and CD20 positive	15	100
CD3 negative in tumoral cells, positive in reactive T cells	15	100

PCNSLs – Primary central nervous system lymphomas; KFSHRC – King Faisal Specialist Hospital and Research Centre; DLBCL – Diffuse large B-cell lymphoma; NHBCL – Non-Hodgkin's B-cell lymphoma

environmental factors separate from HIV infection and genetic risks Survival at 12 months, 24 months and 60 months was higher among Whites than Blacks. Research is needed to determine the origin of these differences.[27]

Table 4: Analytical comparison of PCNSL at KFSHRC, Jeddah with other national studies[20-22]

Study/year	Number of cases (*n*)	Mean age	M: F ratio	Predominant histological type (%)	Immune status	Median survival time
El Husseiny 2002[20]	29	53	15:14	DLBCL 44.8	ICC	13 months
Abdelsalam 2010[21]	62	48.2	17:19	DLBCL 91.9	ICC	11 months
Al Diab 2011[22]	20	53	2.3:1	DLBCL 73.3	*	*
Present study	15	50.4	7:8	DLBCL 86.6	14 ICC 1 ICP	14 months

*Not available. DLBCL – Diffuse large B cell lymphoma; ICC – Immune competent; ICP – Immune compromised; PCNSL – Primary central nervous system lymphoma; KFSHRC – King Faisal Specialist Hospital and Research Centre

DLBCL accounts for approximately 90% of all PCNSLs, affecting the brain parenchyma with or without concomitant ocular or leptomeningeal involvement. The remaining 10% of cases comprise even more rare pathological entities such as low-grade PCNSLs, T-cell lymphomas and Burkitt's lymphomas.[7,28,29] The indolent course of low-grade PCNSL, long-term survival compared with patients who have high-grade PCNSL and the possibility of disease control with focal treatment or even no treatment, all denote similarities to the clinical course of systemic low-grade lymphomas.[30] In most of the cases, the malignant B cells have a centroblastic morphology and are CD79a+, CD20+, PAX-5+, BCL-2+, MUM1/IRF4+. BCL-6 is frequently positive and CD10 is less so. PCNSL cells also express high levels of c-MYC, which has been associated with adverse prognosis in systemic DLBCL.[31]

Histologically, PCNSL is indistinguishable from systemic non-Hodgkin's lymphoma (NHL). Biologically, PCNSL behaves in an aggressive fashion and it should be considered a high-grade tumor.[5] Genetically, PCNSL has been found to demonstrate clonal abnormalities of chromosomes 1, 6, 7 and 14, identical to those detected in systemic NHL. Analysis of cell surface markers including neural cell adhesion molecule and integrins is also identical to that of systemic lymphoma. p15 and p16 deletions have also been reported in PCNSL tumors.[5] Pan genomic analyses of chromosomal imbalances by comparative genomic hybridization have shown frequent chromosome 6q loss (60-75%) in PCNSL patients.[32] Nakamura *et al*.[33] refined the candidate region suspected to contain a lymphoma-related tumor suppressor gene in the 6q22-23 locus by a fine loss of heterozygosity deletion mapping of 6q in PCNSL. The protein tyrosine phosphatase, receptor type, K (PTPRK) gene seems a relevant candidate gene, because it is involved in the regulation of cell contact and adhesion and a loss of protein expression was observed in most (76%) of the PCNSLs tested. The protein that this gene encodes belongs to the protein tyrosine phosphatase superfamily of enzymes. Further studies to identify gene mutations and/or rearrangements are needed to ascertain the involvement of PTPRK in PCNSL tumorigenesis. Interestingly,

the authors showed that chromosome 6q loss was found at a significantly higher rate in PCNSL than in systemic DLBCL and was correlated with shorter survival.[32] An independent study of 75 newly diagnosed HIV-negative PCNSL patients investigated by interphase fluorescence *in situ* hybridization analysis confirmed frequent del (6)(q22) chromosome deletion, with prevalence of 45% and its negative impact on overall survival.[34] Chromosome 6q loss therefore represents a prognostic marker in PCNSL.

Recently, expression profiling and genomic screening have provided new insight into understanding the poor prognosis of PCNSL patients. Based on lymphochip complementary deoxyribonucleic acid (cDNA) microarrays, recently, three molecularly distinct forms of systemic DLBCL in immune competent patients were identified as germinal center B-cell–like (GCB), the activated B-cell–like (ABC) and the so-called type III.[35] Interestingly, patients with the GCB signature had a significantly better outcome than those with the ABC profile.[35] PCNSLs have been shown to frequently express BCL-6[31,36] and to carry an extremely high load of somatic mutations of immunoglobulin genes and several oncogenes demonstrating aberrant ongoing hypermutation.[37] Because such ongoing hypermutation and BCL-6 expression are considered as germinal center (GC) markers, it has been postulated that the cell of origin of PCNSL passes through the GC microenvironment and that these neoplasms correspond to the GCB subgroup as defined for DLBCL[38] However, recent immunoprofiling[36] and gene expression studies using cDNA microarrays[31] demonstrated that PCNSL may exhibit characteristics associated with both the ABC and GCB subtypes. Thus, PCNSLs may correspond to an overlapping B-cell differentiation time slot, that is, the late GC/early post-GC. The fact that several studies have shown that the DLBCLs of the GCB group have a significantly better outcome than the others and have correlated these results with distinct oncogenic mechanisms it seems reasonable to emphasize diagnostic differentiate between the two cell lineages in order to predict the better outcome groups.

The lesion is single in 60-70% of patients.[3] The most common localization sites of PCNSL (both B and T cells type) are in the supratentorial white matter of the frontal parietal lobes[39] accounting for 38%.[3,40] Other sites include thalamus/basal ganglia 16%, corpus callosum 14%, periventricular region 12%, cerebellum 9%, eyes 5-20%, meninges 16%.[3,40] Gliomas, metastases, toxoplasmosis, sarcoidosis, abscesses and progressive multifocal leukoencephalopathy are the main differential diagnoses, requiring brain biopsy for definitive diagnosis. In addition to brain involvement, the eye is involved in ~20% of patients, only half of whom have any visual complaints; visual symptoms are typically floaters or blurred vision.[3]

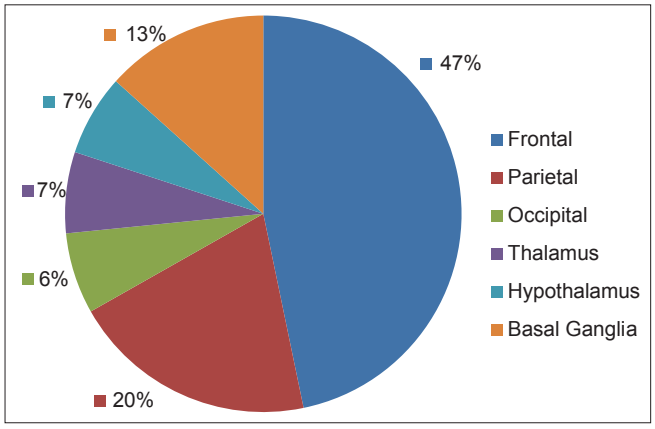

Illustration 2: Location of PCNLs in the brain at KFSHRC, Jeddah

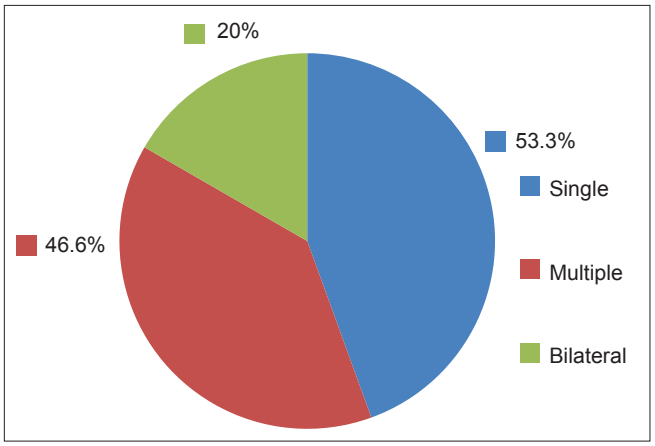

Illustration 3: Number of Lesions(%) of PCNSL at KFSHRC, Jeddah *n*=15

Table 5: Analytical comparison of PCNSL at KFSHRC, Jeddah with other recent international studies[23-26]

Study/year	Number of cases (*n*)	Mean age	M: F ratio	Predominant histological type	Immune status	Predominant location	Median survival
Shibamoto *et al.* Japan 2000-2004[23]	131	65	1.04:1	DLBCL	ICC	*	17 months
Moradi *et al.* Iran 2006[24]	110	42.02	1.6:1	DLBCL	ICC	Supratentorial	*
Pasricha 2011 India[25]	66	46	1:1	DLBCL	ICC	Frontal	*
Makhdoomi *et al.* 2011[26]	16	48	1:2.3	DLBCL	ICC	Frontoparietal	4.4 months
Present study	15	50.4	7:8	DLBCL	14 ICC 1 ICP	Frontal	14 months

*Not available. ICC – Immune competent; ICP – Immune compromised; DLBCL – Diffuse large B cell lymphoma; PCNSL – Primary central nervous system lymphoma; KFSHRC – King Faisal Specialist Hospital and Research Centre

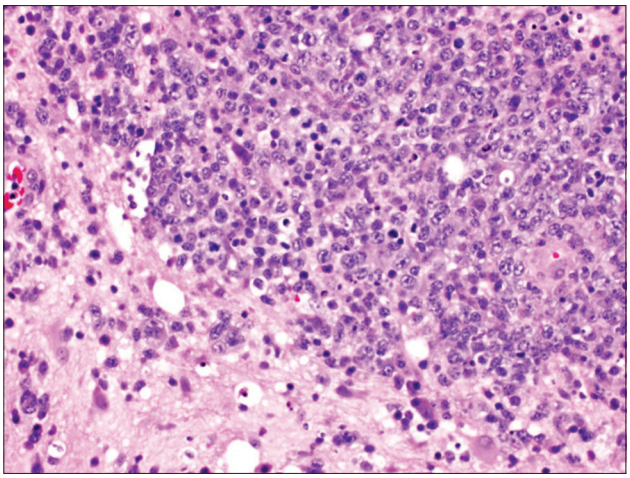

Figure 1: The diffuse infiltration of glial parenchyma by atypical lymphocytes with irregular nuclear contours and prominent nucleoli

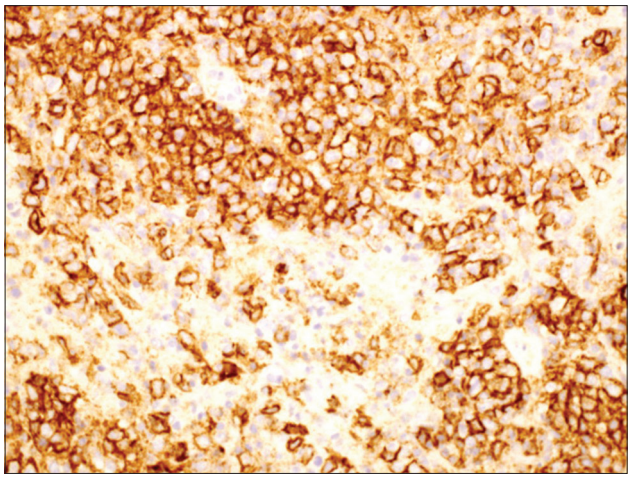

Figure 2: The immunohistochemical marker CD20 as staining strongly positive in the atypical lymphocytes

CT scans and MRI typically show characteristic single or multiple periventricular, homogeneously enhancing lesions in 100% of PCNSL.[41] However, PCNSL is potentially associated with a large spectrum of radiological presentations and can simulate inflammatory (sarcoidosis, multiple sclerosis) or infectious (acute disseminated encephalomyelitis) diseases or other brain tumors (meningiomas, malignant gliomas, gliomatosis cerebri, brain metastases) as such diagnosis may be difficult to establish.[11] As such, patients with a radiologic suspicion of gliomas, metastasis, meningiomas, or other tumors are routinely referred for complete resection, sometimes resulting in an unexpected diagnosis of lymphoma. Other unusual presentations of PCNSL reported are neurolymphomatosis and pituitary lymphomas.[42] Magnetic resonance spectroscopy and perfusion MRI seem helpful tools when showing some suggestive abnormalities.[43,44]

Chemotherapy and radiation, or chemotherapy alone may then be used as the primary treatment. Lymphomas are not usually treated with surgery as they tend to occur deep within the brain in which case the risk of neurological complications is high.[45] PCNSL surgery is therefore restricted to diagnostic biopsy. Stereotactic brain biopsy is the most appropriate method for diagnosis of PCNSL.[13,45,46]

Overall, PCNSL carries a worse prognosis compared with non-CNS extranodal DLBCL. With active chemotherapy/radiotherapy treatment, median survival up to 51 months has been reported.[45] In the present study, clinical follow-up at 12, 18, 24 months was available in 4 of 15 patients (26.66%) among which 3 (20%) are surviving at 24 months and one at 18 months. Three patients were declared as deceased. It remains unclear whether the dismal outcome of PCNSL patients compared with patients with systemic DLBCL is attributable to the immune-privileged cerebral location or reflects a specific aggressive intrinsic biologic behavior. The fact that unlike the western countries, the association of PCNSL with HIV/AIDS in India is very low in spite of substantial prevalence of HIV/AIDS[25] cases suggests that there is geographic variation in the risk factors.

The present study has certain limitations and the presented results should be interpreted keeping them in mind. The major limitation of the present study is the small number of cases and therefore the results do not reflect the pattern of PCNSL in the population of Saudi Arabia at large. The low overall median survival, also reflects the short follow-up duration in our study. A longer-term study would provide more data regarding survival in these patients.

Conclusion

PCNSL in the present study is more common among immune competent middle-aged and aged patients. There is female predilection especially in the middle age. Frontal region is the most common location with DLBCL being the predominant histological subtype. Our study also confirms the rare occurrence of Burkitt's lymphoma and low grade marginal zone lymphoma presenting as PCNSL. PCNL among older adults showed a more aggressive pattern and male to female ratio of near unity. These findings are concordant with other studies from the region.[20-22]

PCNSL, continues to be a diagnostic challenge in part due to lack of suspicion at presentation. In addition to the variation in the incidence, there may be regional and geographical differences in response to treatment, prognosis and survival for various types of lymphomas. In view of this, there is a need for further studies to elaborate on these issues for a disease that is heterogeneous and appears to be on the rise.

References

1. Kluin PM, Deckert M, Ferry JM. Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*., editors. WHO Classification of Tumours of

Haemopoietic and Lymphoid Tissues. Lyon: IARC; 2008. p. 240-1.
2. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood 2011;117:5019-32.
3. Marturano E, Ferreri AJ. Primary CNS lymphoma in immunocompetent patients. Ann Oncol 2011;22:iv41-3.
4. Primary brain and central nervous system tumors diagnosed in the United States in 2004-2008. CBTRUS Statistical Report Revised Version March 23, 2012. Available from: http://www.cbtrus.org/2012-NPCR-SEER/CBTRUS_Report_2004-2008_3-23-2012.pdf. [Last visited on 2013 Oct 23].
5. Haldorsen IS, Krossnes BK, Aarseth JH, Scheie D, Johannesen TB, Mella O, *et al*. Increasing incidence and continued dismal outcome of primary central nervous system lymphoma in Norway 1989-2003: Time trends in a 15-year national survey. Cancer 2007;110:1803-14.
6. DeAngelis LM. Primary central nervous system lymphoma: A curable brain tumor. J Clin Oncol 2003;21:4471-3.
7. Batchelor T, Loeffler JS. Primary CNS lymphoma. J Clin Oncol 2006;24:1281-8.
8. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: A whole-brain disease? Neurology 2002;59:1557-62.
9. A comprehensive introduction to brain tumors. Brain Tumor Primer. 9th ed. American Brain Tumor Association; 2010. p. 48. Available from: http://www.neurosurgery.mgh.harvard.edu/abta/ABTA_BrainTumorPrimer. [Last visited on 2014 Jul 23].
10. Kasamon YL, Ambinder RF. AIDS-related primary central nervous system lymphoma. Hematol Oncol Clin North Am 2005;19:665-87, vi-vii.
11. Bayraktar S, Bayraktar UD, Ramos JC, Stefanovic A, Lossos IS. Primary CNS lymphoma in HIV positive and negative patients: Comparison of clinical characteristics, outcome and prognostic factors. J Neurooncol 2011;101:257-65.
12. Bower M, Powles T, Nelson M, Mandalia S, Gazzard B, Stebbing J. Highly active antiretroviral therapy and human immunodeficiency virus-associated primary cerebral lymphoma. J Natl Cancer Inst 2006;98:1088-91.
13. Namas RA, Olugbemiga J, Shafique I, Gebregeorgis W, Hasan S, El Mortada M, *et al*. Primary central nervous system lymphoma in acquired immunodeficiency syndrome patient. Ibnosina J Med BS2012;4:53-9.
14. DeAngelis LM. Primary central nervous system lymphoma: Coming or going? Blood 2009;113:4483-4.
15. Knowles DM. Etiology and pathogenesis of AIDS-related non-Hodgkin's lymphoma. Hematol Oncol Clin North Am 2003;17:785-820.
16. Kitai R, Matsuda K, Adachi E, Saito Y, Nakajima T, Takeuchi H, *et al*. Epstein-Barr virus-associated primary central nervous system lymphoma in the Japanese population. Neurol Med Chir (Tokyo) 2010;50:114-8.
17. Deckert M, Paulus W. Tumours of the haematopoietic system, malignant lymphoma. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, editors. WHO Classification of Tumours of the Central Nervous System. Lyon Cedex, France: The International Agency of Research on Cancer (IARC); 2007. p. 187-92.
18. Tun HW, Personett D, Baskerville KA, Menke DM, Jaeckle KA, Kreinest P, *et al*. Pathway analysis of primary central nervous system lymphoma. Blood 2008;111:3200-10.
19. Habek M, Brinar VV, Zarković K, Ozretić D. Is there sentinel demyelination before development of primary CNS lymphoma? J Clin Neurosci 2008;15:1069-70.
20. El Husseiny G, Mourad WA, Shoukri M. Primary brain lymphoma in immunecompetent patients-Prognostic factors and treatment outcomes. Journal Of Egyptian Nat Cancer Inst 2002;14:51-8.
21. Abdelsalam M, El-Husseiny G, Akhtar S, Khafaga Y, Al-Shabana M, AlHusaini H, *et al*. Improved survival with combined chemo-radiotherapy in primary central nervous system lymphoma. Hematol Oncol Stem Cell Ther 2010;3:128-34.
22. Al Diab AR, Aleem A, Qayum A, Al Askar AS, Ajarim DS. Clinico-pathological pattern of extranodal non-Hodgkin's lymphoma in Saudi Arabia. Asian Pac J Cancer Prev 2011;12:3277-82.
23. Shibamoto Y, Ogino H, Suzuki G, Takemoto M, Araki N, Isobe K, *et al*. Primary central nervous system lymphoma in Japan: Changes in clinical features, treatment, and prognosis during 1985-2004. Neuro Oncol 2008;10:560-8.
24. Moradi A, Tajedini A, Mehrabian A, Sadeghi S, Semnani V, Khodabakhshi R, *et al*. Clinicopathological features of primary central nervous system lymphoma. Neurosciences (Riyadh) 2006;11:284-8.
25. Pasricha S, Gupta A, Gawande J, Trivedi P, Patel D. Primary central nervous system lymphoma: A study of clinicopathological features and trend in western India. Indian J Cancer 2011;48:199-203.
26. Makhdoomi R, Nayil K, Rayees A, Kirmani A, Ramzan A, Khalil MB, *et al*. Primary CNS lymphoma in immunocompetent: A review of literature and our experience from Kashmir. Turk Neurosurg 2011;21:39-47.
27. Pulido JS, Vierkant RA, Olson JE, Abrey L, Schiff D, O'Neill BP. Racial differences in primary central nervous system lymphoma incidence and survival rates. Neuro Oncol 2009;11:318-22.
28. Montesinos-Rongen M, Siebert R, Deckert M. Primary lymphoma of the central nervous system: Just DLBCL or not? Blood 2009;113:7-10.
29. 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.
30. Jahnke K, Korfel A, O'Neill BP, Blay JY, Abrey LE, Martus P, *et al*. International study on low-grade primary central nervous system lymphoma. Ann Neurol 2006;59:755-62.
31. Rubenstein JL, Fridlyand J, Shen A, Aldape K, Ginzinger D, Batchelor T, *et al*. Gene expression and angiotropism in primary CNS lymphoma. Blood 2006;107:3716-23.
32. Boonstra R, Koning A, Mastik M, van den Berg A, Poppema S. Analysis of chromosomal copy number changes and oncoprotein expression in primary central nervous system lymphomas: Frequent loss of chromosome arm 6q. Virchows Arch 2003;443:164-9.
33. Nakamura M, Kishi M, Sakaki T, Hashimoto H, Nakase H, Shimada K, *et al*. Novel tumor suppressor loci on 6q22-23 in primary central nervous system lymphomas. Cancer Res 2003;63:737-41.
34. Cady FM, O'Neill BP, Law ME, Decker PA, Kurtz DM, Giannini C, *et al*. Del (6)(q22) and BCL6 rearrangements in primary CNS lymphoma are indicators of an aggressive clinical course. J Clin Oncol 2008;26:4814-9.
35. Sierra del Rio M, Rousseau A, Soussain C, Ricard D, Hoang-Xuan K. Primary CNS lymphoma in immunocompetent patients. Oncologist 2009;14:526-39.
36. Camilleri-Broët S, Crinière E, Broët P, Delwail V, Mokhtari K, Moreau A, *et al*. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: Analysis of 83 cases. Blood 2006;107:190-6.
37. Montesinos-Rongen M, Van Roost D, Schaller C, Wiestler OD, Deckert M. Primary diffuse large B-cell lymphomas of the central nervous system are targeted by aberrant somatic hypermutation. Blood 2004;103:1869-75.
38. Montesinos-Rongen M, Brunn A, Bentink S, Basso K, Lim WK, Klapper W, *et al*. Gene expression profiling suggests primary central nervous system lymphomas to be derived from a late germinal center B cell. Leukemia 2008;22:400-5.
39. Slone HW, Blake JJ, Shah R, Guttikonda S, Bourekas EC. CT and MRI findings of intracranial lymphoma. AJR Am J Roentgenol 2005;184:1679-85.
40. Ferreri AJ. How I treat primary CNS lymphoma. Blood 2011;118:510-22.
41. Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: Characteristic findings on traditional and advanced imaging. AJNR Am J Neuroradiol 2011;32:984-92.
42. Da Silva AN, Lopes MB, Schiff D. Rare pathological variants and presentations of primary central nervous system lymphomas. Neurosurg Focus 2006;21:E7.
43. Hartmann M, Heiland S, Harting I, Tronnier VM, Sommer C, Ludwig R, *et al*. Distinguishing of primary cerebral lymphoma from high-grade glioma with perfusion-weighted magnetic resonance imaging. Neurosci Lett 2003;338:119-22.

44. Taillibert S, Guillevin R, Menuel C, Sanson M, Hoang-Xuan K, Chiras J, *et al*. Brain lymphoma: Usefulness of the magnetic resonance spectroscopy. J Neurooncol 2008;86:225-9.
45. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. J Clin Oncol 2006;24:4570-4.
46. Deangelis LM, Iwamoto FM. An update on therapy of primary central nervous system lymphoma. Hematology Am Soc Hematol Educ Program 2006;1:311-6.

How to cite this article: Mufti ST, Baeesa SS, Al-Maghrabi JA. Primary intracranial lymphomas. Asian J Neurosurg 2016;11:232-9.

Source of Support: Nil, **Conflict of Interest:** None declared.