Clinicopathological features of primary central nervous system lymphoma

Afshin Moradi, MD, Aram Tajedini, MD, Abbasali Mehrabian, MD, Sohrab Sadeghi, MD, Vahid Semnani, MD, Reza Khodabakhshi, MD, Noormohammad Arefian, MD, Maryam Afrakhteh, MD, Kayvan Keshvari, MD, Parvin Yavari, MD, Manouchehr Madani-Civi, MD.

ABSTRACT

Objectives: To investigate the anatomic location, immunologic, and clinicopathological features of patients with primary central nervous system lymphoma (PCNSL).

Methods: From May 1993 to December 2004, at Shohada Hospital, Tehran, Iran, the clinical data of 110 PCNSL patients, including the age, sex, duration of symptoms, radiological findings, site of tumors, immune status, and history of immunocompromised state (such as organ transplantation, radiotherapy, steroid therapy or AIDS) were assessed.

Results: The mean age of the patients with PCNSL was 47.02 ± 15.8 years. There were 42 female and 68 male patients. One hundred and six cases (96.3%) were diagnosed as B-cell lymphoma. Most of the PCNSL in our study are unifocal. More than 70% of tumors were in a cerebral hemisphere and periventricular location, usually involving the corpus callosum or basal ganglia. No patients had been in immunocompromised states. Symptoms of increased intracranial pressure or changes in personality, vision, or motor function are most common. Seizures are seen in approximately 10% of patients. The number of PCNSL cases showed a gradual rise in incidence.

Conclusion: The results of this single hospital 12-year survey of PCNSL are in agreement with data from other single institutions and regional surveys concerning clinical features. However, in contrast with the literature, most of our patients were immunocompetent. The age at diagnosis is also lower than in most reports.

Neurosciences 2006; Vol. 11 (4): 284-288

Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's lymphoma arising in the brain, the spinal cord, and the leptomeninges with the absence of lymphoma outside the nervous system at the time of diagnosis. In the last 2 decades, an increase in incidence of PCNSL in immunologically normal as well as in immunocompromised individuals has been reported in the United States.[1-3] A PCNSL may affect all age groups with a peak incidence in the fifth to seventh decade and a median age in the sixth decade in non-AIDS patients.[4] The most common clinical symptoms at time of diagnosis are personality change, focal neurological deficit, and symptoms of raised intracranial pressure.[5,6] The aims of this retrospective study were to investigate the anatomic location, immunologic, and clinicopathological features of patients with PCNSL admitted to Shohada Hospital, Tehran, Iran during a 12-year period.

From the Departments of Pathology (Moradi, Tajedini, Keshvari), Internal Medicine (Mehrabian), Neurosurgery (Sadeghi), Oncology (Khodabakhshi), Anesthesiology (Arefian), Obstetrics & Gynecology (Afrakhteh), and Epidemiology (Yavari), Shohada Hospital, Shahid Beheshti University of Medical Sciences, and the Research Department (Madani-Civi), THC Hospital, Tehran University of Medical Sciences, Tehran, and the Department of Pathology (Semnani) Semnan University of Medical Sciences, Semnan, *Iran*.

Received 9th May 2006. Accepted for publication in final form 28th June 2006.

Address correspondence and reprint request to: Dr. Afshin Moradi, Assistant Professor, Department of Pathology, Shohada Hospital, Shahid Beheshti University of Medical Sciences, Madani, PO Box 16765-3156, Tehran, *Iran*. Tel. +98 9121860059. Fax. +98 21 22719012. E-mail: madani_68@yahoo.com

Methods. A complete list of all patients recorded as CNS lymphoma from the pathology files of Shohada Hospital (Shahid Beheshti University of Medical Sciences, Tehran) from January 1993 to December 2004 (n=122) was obtained. The total number of intracranial tumors diagnosed during the same period was also obtained for the purpose of calculating the relative incidence. We excluded 12 of the 122 patients recorded as PCNSL because we found they had lymphoma in other locations at the time of diagnosis (n=5), Hodgkin lymphoma (n=3), or only clinical and radiological signs of PCNSL without histologic verification (n=4). Hematoxylin and eosin stained slides were reviewed by 2 independent pathologists and the diagnosis reconfirmed. We reviewed the preoperative brain CT scan and MRI and determined the location of the tumor and multiplicity. All of patients had a radiological study of other organs to rule out secondary lymphoma. The clinical data of 110 patients including the age, sex, duration of symptoms, radiological findings, site of tumors, immune status and history of immunocompromised state (such as organ transplantation or radiotherapy or steroid therapy or AIDS) were obtained from the medical records. Serology testing (ELISA), for HIV, was carried out for all cases. To evaluate the T- or B-cell lineage of PCNSL, immunophenotyping was performed using the antibodies against CD3 as T-cell marker and CD20 as B-cell marker (Dakopatts, Glostrup, Denmark) in all cases.

Statistical analyses were performed using SPSS for Windows, Version 11.0. All measurements are expressed as mean ± the standard error of the mean. Comparisons of results were carried out using the *t*-test. A *p*-value of less than 0.05 was considered to indicate a significant difference.

Results. Between May 1993 and December 2004, a total of 4885 intracranial tumors (ICT) were diagnosed at Shohada Hospital; of this, 110 (2.2%) cases were PCNSL. The mean age of the patients with PCNSL was 47.02 ± 15.8 years (range 8–85 years, median = 47.5). There were 42 female and 68 male patients (M/F = 1.6). The types of initial symptoms are shown in **Table 1**. The median intervals between the onset of the initial symptoms and admission were 8-36 weeks in PCNSL patients (mean = 22.28 weeks). All the cases displayed a characteristic nuclear and cytoplasmic pattern of lymphoid cell with an angiocentric pattern and variable parenchymal infiltration (**Figure 1**). Immunohistochemistry (IHC) revealed positively for leukocyte common antigen in all the 110 cases. Of 110 cases of PCNSL, 4 cases (3.7%) were diagnosed as T-cell lymphoma and 106 cases (96.3%) were diagnosed as B-cell lymphoma (positive for CD 20). Most of the PCNSLs are high-grade B-cell lymphoma (89%) with 4.5% of medium grade, and 6.4% of low grade. No patients had been in an immunocompromised state, such as organ transplantation, radiotherapy, systemic lupus erythematosus, rheumatoid arthritis, steroid therapy or AIDS. On CT and MRI, 61 patients (55.4%) had a single detectable lesion at the time of diagnosis. Multiple lesions were present in 49 (44.6%) patients. Findings from non-contrast CT scans were 36 of the 62 (58%) demonstrating isodense or hyperdense lesions. Most of the PCNSLs in our study are unifocal (**Table 2**). They developed in supratentorial sites 3 times as often as in infratentorial locations. Since

Table 1 - Clinical features of patients with PCNLS (n=110).

Features	No.	(%)
Gender		
Female	42	(38.2)
Male	68	(61.8)
Age range (years)	8-85	
<20 years	7	(5.5)
21-40 years	27	(24.5)
41-60 years	56	(51.8)
>60 years	20	(18.2)
Mean age ± SD (years)	47.02 ± 15.8	
Symptoms on admission		
Epilepsy	12	(10.9)
Headache/nausea/vertigo	28	(25.4)
Personality change	16	(14.5)
Motor deficit/paresis	42	(38.2)
Sensory deficit	7	(6.4)
Cranial nerve dysfunction	5	(4.5)
Lesion on MRI/CT scan		
Solitary	61	(55.4)
Multiple	49	(44.6)
Mean time until diagnosis (weeks)	22.28	

PCNSL - primary central nervous system lymphoma

Table 2 - Anatomic site of PCNSL (n=110).

Anatomic site	No.	(%)
Supratentorial		
Cerebral hemisphere	54	(49.1)
Frontal	26	(23.6)
Parietal	27	(24.5)
Temporal	18	(16.4)
Occipital	5	(4.5)
Diencephalon (Thalamus, epithalamus, and basal ganglia)	9	(8.0)
Corpus callosum	12	(10.9)
Infratentorial		
Brain stem	6	(5.4)
Cerebellum	9	(8.1)
Cerebello pontine angle	3	(2.7)
Spinal cord	16	(14.5)

PCNSL - primary central nervous system lymphoma

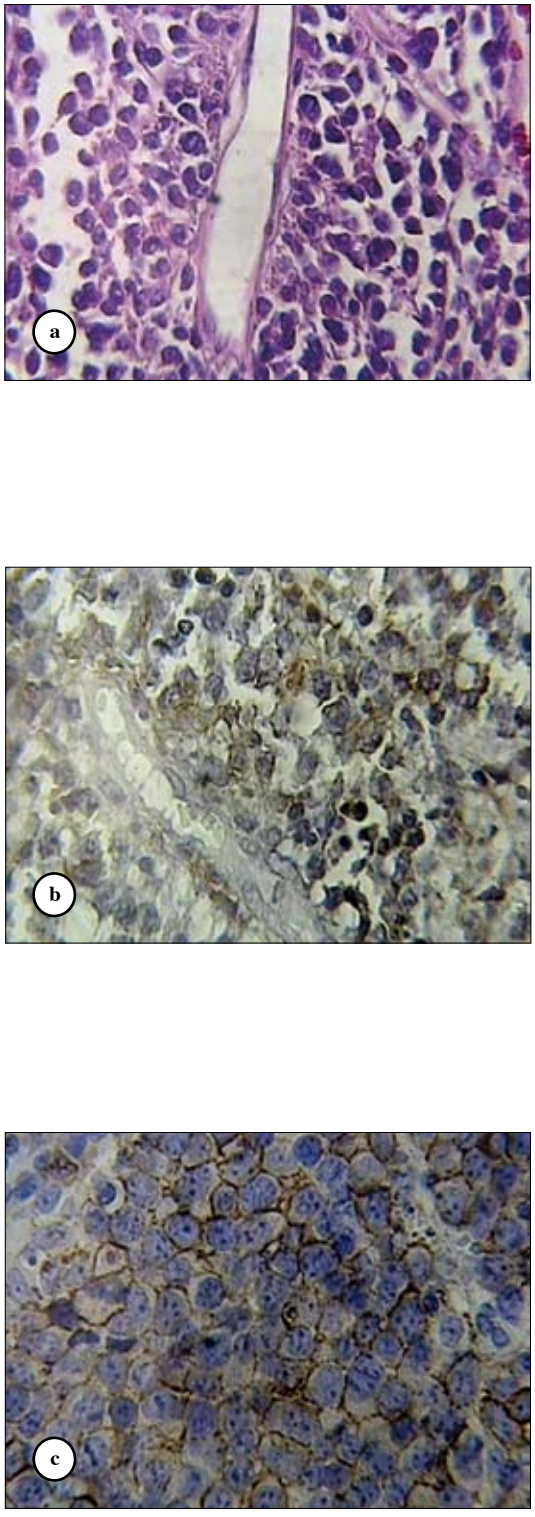

Figure 1 - Pathologic findings in primary cerebral lymphoma showing **a)** perivascular accumulation of tumor cells with parenchymal infiltration, **b)** immunocytochemistry for pan-leukocyte antigen CD45 shows positive reaction, and **c)** immuno-histochemistry for CD20 shows strong positivity.

the number of PCNSL cases recorded in each year was small, frequency rates for periods of 2 years were calculated to provide more stable estimates. The number of PCNSL cases showed a gradual rise in incidence from 15 cases in 1993–1994 to 27 cases in 2003–2004, with 2 peaks in 1999–2000 (21 cases), and in 2003–2004 (27 cases).

Discussion. Primary CNS lymphoma is an aggressive malignancy that is usually of B-cell origin, and is microscopically and immunologically indistinguishable from systemic non-Hodgkin's lymphomas.[7] Epidemiologic data strongly suggest that PCNSL is increasing in incidence. The increase was largely attributable to the increasing number of organ transplantations, coupled with improved survival of congenital immunodeficient patients and the outbreak of acquired immune deficiency syndrome (AIDS).[1,8] An unexplained increase in the incidence of PCNSL has recently been noted especially among the elderly (>60 years), HIV-negative, immunocompetent individuals. This trend appears independent of diagnostic techniques, the HIV epidemic, the increasing age of the population, or increases in brain tumors and systemic non-Hodgkin's lymphomas. Epstein-Barr Virus infections are not associated with PCNSL in this patient population.[1,9] In our study, all of the cases were immunocompetent individuals and HIV-negative. A possible explanation for this could be that AIDS cases in Iran were rare. However, organ transplantations were not routinely carried out in our country except renal transplantations. This explanation, however, cannot account for the incidence of PCNSL in immunocompetent individuals in Iran. Some observers have suggested that increased screening, with greater accessibility to MRI and CT technology, may partly account for the apparent increase in the incidence of this disease.[8] This explanation, however, cannot account for the higher percentage of PCNSL observed in resected or biopsied brain tumor specimens during the last decade. It therefore appears that the increase in the incidence of this disease is a true epidemiologic observation.

Primary CNS lymphomas can occur at all ages, but a peak in the sixth and seventh decade has been reported, among immunocompetent individuals.[10] In the immunodeficient patients, this age distribution is markedly altered, with a large peak in the fourth decade in individuals who are transplant recipients,[11] and those suffering from AIDS.[8] In our study, all of the patients though immunocompetent, were young, with a mean age of 47.2 years; approximately 2 decades younger than reported in the literature of immunocompetent patients.[10] There was no change

Table 3 - Relative frequency (%) of symptoms and signs in immunocompetent patients with PCNSL at the time of initial presentation.

Symptoms and signs	Our study	Hayakawa et al[18]	Henry et al[19]	Hochberg et al[20]	Braus et al[21]	Herrlinger et al[4]
No. of patients	110	119	83	66	54	26
Nausea/vomiting/headache	25	24	35	15	37	38
Behavioral changes/global cortical dysfunction	14	29	34	24	69	73
Seizures	10	2	-	13	15	23
Ataxia and/or other cerebellar signs	3	-	-	21	15	42
Hemiparesis/motor dysfunction	38	-	-	11	52	42
Cranial nerve dysfunction	5	-	-	-	31	19

Dash (—) means not specified, PCNSL – primary central nervous system lymphoma

in the trend of mean age at occurrence over the study period. Although approximately 18.2% of all PCNSL cases in our study were in the elderly age group (>60 years), there was no statistically significant increase in incidence in this age group, during the study period. A male preponderance of greater than 90% has been reported in PCNSL cases associated with inherited immunodeficiency.[10,12] However, in our series, a slight male predominance (1.61:1) was observed, which is a little less than that reported among the immunocompetent population in other studies.[10] In our study, the median time span between first symptom and diagnosis was found to be 22 weeks, this is consistent with reports from other groups.[5]

The PCNSL in immunocompetent patients is most commonly found adjacent to the ventricular surfaces and in deep white matter and subcortical structures, such as the basal ganglia, thalamus, and corpus callosum. Most of these tumors are supratentorial. In our series, more than 70% of tumors were in a cerebral hemisphere and periventricular location (usually involving the corpus callosum or basal ganglia). Approximately 50-70% of patients with this disease presented with solitary lesions, whereas the remainder had multifocal disease. These lesions characteristically enhance homogeneously with the administration of contrast agents.[13]

In evaluation of the T- or B-cell lineage of PCNSL, T-PCNSL is known to be very rare, constituting <5% of all PCNSL in Western countries. The incidence ranged from 1.8-4.6% in the reports from the United States.[14,15] In a recent survey of 248 cases of PCNSL in France, T-PCNSL accounted for 3.6%.[5] Of our cases, 3.7% were diagnosed as T-cell lymphoma.

The presenting symptoms from these tumors depend on the location and size of the tumor and the extent of mass effect, edema, and obstruction of the cerebrospinal fluid (CSF) flow pathways. Symptoms of increased intracranial pressure or changes in personality, vision, or motor function are most common. Seizures are seen in approximately 10% of patients. The clinical features in our patients corresponded well with the literature (**Table 3**). Personality change and focal neurological symptoms, usually hemiparesis, were the most frequent symptoms before diagnosis. Dexamethasone is routinely prescribed to patients who present with an intracranial mass and progressive neurologic symptom. This potent lympholytic agent may cause the PCNSL to shrink rapidly or even completely disappear on repeat neuroimaging studies.[16,17]

Although the diagnosis of PCNSL requires histologic confirmation of lymphoma, in the immunocompetent person who is found to have an intracranial mass suggestive of PCNSL, a tissue diagnosis should be made immediately. Although PCNSL can be effectively diagnosed by stereotactic biopsy techniques, nearly 23% of our patients during the last 12 years have had open craniotomy and resection rather than biopsy. It has been argued that craniotomy and resection allow a larger pathologic specimen to be obtained, thus ensuring an accurate histologic diagnosis. Recent studies, however, show that stereotactic biopsy provides a high rate of positive tissue diagnosis in PCNSL, especially when immunohistochemical staining is carried out. Stereotactic biopsy can be safely carried out by an experienced neurosurgeon in almost any area of the brain (<2% significant complications), a particularly important point given the deep periventricular location of most PCNSL.

In summary, the results of this single hospital 12-year survey of PCNSL are in agreement with data from other single institutions and regional surveys concerning clinical features. However, in contrast with the literature, most of our patients were immunocompetent. The age at diagnosis is also lower than most reports. There was a non-significant trend towards increased incidence, perhaps related to increased availability of diagnostic imaging (especially MRI) and stereotactic biopsy in our center.

References

1. Olson JE, Janney CA, Rao RD, Cerhan JR, Kurtin PJ, Schiff D, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. ***Cancer*** 2002; 95: 1504-1510.
2. Corn BW, Marcus SM, Topham A, Hauck W, Curran WJ Jr. Will primary central nervous system lymphoma be the most frequent brain tumor diagnosed in the year 2000? ***Cancer*** 1997; 79: 2409-2413.
3. Lutz JM, Coleman MP. Trends in primary cerebral lymphoma. ***Br J Cancer*** 1994; 70: 716-718.
4. Herrlinger U, Schabet M, Bitzer M, Petersen D, Krauseneck P. Primary central nervous system lymphoma: from clinical presentation to diagnosis. ***J Neurooncol*** 1999; 43: 219-226.
5. Bataille B, Delwail V, Menet E, Petersen D, Krauseneck P. Primary intracerebral malignant lymphoma: report of 248 cases. ***J Neurosurg*** 2000; 92: 261-266.
6. Schlegel U, Schmidt-Wolf IG, Deckert M. Primary CNS lymphoma-Clinical presentation, pathological classification, molecular pathogenesis and treatment. ***J Neurol Sci*** 2000; 181: 1-12.
7. Ferreri AJ, Abrey LE, Blay JY, Borisch B, Hochman J, Neuwelt EA, et al. Summary statement on primary central nervous system lymphomas from the Eighth International Conference on Malignant Lymphoma, Lugano Switzerland, June 12–15, 2002. ***J Clin Oncol*** 2003; 21: 2407-2414.
8. Cote TR, Manns A, Hardy CR, Yellin FJ, Hartege P. Epidemiology of brain lymphoma among people with or without immunodeficiency syndrome. AIDS/Cancer Study Group. ***J Nat Cancer Inst*** 1996; 88: 675-679.
9. Eby NL, Grufferman S, Flannelly CM, Schold SC Jr, Vogel FS, Burger PC. Increasing incidence of primary brain lymphoma in the US. ***Cancer*** 1988; 62: 2461-2465.
10. Basso U, Brandes AA. Diagnostic advances and new trends for the treatment of primary central nervous system lymphoma. ***Eur J Cancer*** 2002; 38: 1298-1312.
11. Martinez AJ. The neuropathology of organ transplantation: comparison and contrast in 500 patients. ***Pathol Res Prac*** 1998; 194: 473-486.
12. Fine HA, Mayer RJ. Primary central nervous system lymphoma. ***Ann Intern Med*** 1993; 119: 1093-1104.
13. Gliemroth J, Kehler U, Gaebel C, Arnold H, Missler U. Neuroradiological findings in primary cerebral lymphomas of non-AIDS patients. ***Clin Neurol Neurosurg*** 2003; 105: 78-86.
14. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma: The Massachusetts General Hospital experience 1958-1989. ***Cancer*** 1994; 74: 1383-1397.
15. Tomlinson FH, Kurtin PJ, Suman VJ, Scheithauer BW, O'Fallon JR, Kelly PJ, et al. Primary intracerebral malignant lymphoma: a clinicopathologic study of 89 patients. ***J Neurosurg*** 1995; 82: 558-566.
16. Bromberg JE, Siemers MD, Taphoorn M. Is a 'vanishing tumor' always a lymphoma? ***Neurology*** 2002; 10: 762-764.
17. Lachance DH, Brizel DM, Gockerman JP, Halperin EC, Burger PC, Boyko OB, et al. Cyclophosphamide, doxorubicin, vincristine, and prednisone for primary central nervous system lymphoma: short-duration response and multifocal intracerebral recurrence preceding radiotherapy. ***Neurology*** 1994; 44: 1721-1727.
18. Hayakawa T, Takakura K, Abe H, Yoshimoto T, Tanaka R, Sugita K, et al. Primary central nervous system lymphoma in Japan – a retrospective, co-operative study by the CNS-lymphoma study group in Japan. ***J Neuro Oncol*** 1994; 19: 197-215.
19. Henry JM, Meffner Jr RR, Dillard SM, Dillard SM, Earle KM, Davis RL. Primary malignant lymphomas of the central nervous system. ***Cancer*** 1974; 34: 1293-1302.
20. Hochberg FM, Miller DC. Primary central nervous system lymphoma. ***J Neurosurg*** 1988; 68: 835-853.
21. Braus DF, Schwechheimer K, Müller-Mermelink MK, Schwarzkopf G, Volk B, Mundinger F. Primary cerebral malignant non-Hodgkin's lymphomas: a retrospective clinical study. ***J Neurol*** 1992; 239: 117-124.