



12-2006

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Amar Lal
Aga Khan University

Nehal Masood
Aga Khan University

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Recommended Citation

Lal, Amar and Masood, Nehal (2006) "Current Approach to Primary Central Nervous System Lymphoma," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 1 : Iss. 3 , Article 5.

Available at: <https://ecommons.aku.edu/pjns/vol1/iss3/5>

CURRENT APPROACH TO PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

Amar Lal and Nehal Masood

Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan.

Correspondence to: Dr. Masood, Assistant Professor of Medicine (Oncology), Aga Khan University Medical College, Karachi 74800, Pakistan.
Tel. +92-21-493-0051, ext. 4663. Email: nehal.masood@aku.edu

Pak J Neurol Sci 2006; 1(3):138-44

ABSTRACT

Central nervous system involvement with Non-Hodgkin's Lymphoma (NHL), whether primary or secondary, is an uncommon but not rare condition. The incidence of Primary Central Nervous System Lymphoma (PCNSL) has dramatically increased during the last three decades in both immunocompromised and immunocompetent hosts. PCNSL is associated with unique diagnostic, prognostic, and therapeutic issues, and the management of this malignancy is different from that of other forms of extranodal NHL. Whole-brain radiation therapy (WBRT) alone is insufficient for durable tumor control. High-dose methotrexate (MTX) in combination with other chemotherapeutic agents followed by WBRT results in response rates approaching 100% and improved median survival times ranging between 30 and 60 months.

Primary central nervous system lymphoma (PCNSL) is the term applied to Non-Hodgkin's Lymphoma (NHL) arising in and confined to the central nervous system (CNS). This tumor has been known by many other names, including Reticulum Cell Sarcoma, Diffuse Histiocytic Lymphoma, and Microglioma, but its lymphocytic origin, usually the B cell, is now well established.¹ How a lymphoma develops within the CNS, which lacks lymph nodes and lymphatics, remains an unanswered question; however, lymphocytes do traffic in and out of the CNS normally, and these lymphocytes are probably the source of PCNSL.

PCNSL arises from B lymphocytes, which are usually small, noncleaved, or immunoblastic or centroblast cells. Lymphoid clustering around small cerebral vessels - a vasocentric growth pattern — is typically seen. Studies of clonality have demonstrated that multifocal PCNSL lesions arise from a single neoplastic clone. A study of adhesion molecules revealed an identical pattern of expression for PCNSL and systemic lymphomas. The Bcl-1 and Bcl-2 rearrangements have not been detected in PCNSL, and no unique molecular marker has been identified that discriminates PCNSL from its systemic counterparts. However, a recent study suggests that Bcl-6 expression was associated with longer survival in patients treated with high-dose methotrexate. Further search continues for the

identification of additional prognostic markers.²

PCNSL was once a rare tumor, accounting for only 0.5% to 1.2% of intracranial neoplasms, and usually associated with immunodeficiency states. PCNSL incidence has risen dramatically over the past 10-15 years. A U.S. epidemiologic study using the Surveillance, Epidemiology, and End Results registry (SEER) revealed an incidence in immunocompetent patients of approximately 51 per 10,000,000 per year.³ PCNSL has been reported in 6-20% of HIV-infected patients, and this proportion is expected to rise as patients with low CD4+ counts survive longer.

We have reviewed 577 patients covering a 17-year period (1988 through 2004) of diffuse large B-cell lymphoma (DLBCL) for clinico-pathologic characteristics, treatment outcome, and prognostic factors affecting overall survival. Of these, less than 3% were PCNSL.⁴

CLINICAL ASPECTS

By definition, if lymphoma is found outside of the CNS using abdominal, pelvic, and chest computed tomography scans, body positron emission tomography, or bone marrow biopsy in patients suspected with PCNSL, the

diagnosis is considered not to be PCNSL but rather NHL that is metastatic to the nervous system.

Brain

The frontal lobe is the most frequently involved region of the brain and multiple lesions are often seen. Changes in personality and level of alertness are more common presenting symptoms in PCNSL than in other brain tumors. Headaches and symptoms of increased intracranial pressure are also seen frequently. Because PCNSL affects deep brain structures rather than the cerebral cortex, seizures occur in only 10% of patients as a presenting sign. PCNSL also generally grows more rapidly than glioma, and thus symptoms are usually present for only weeks to a few months before a diagnosis is made.

PCNSL is multifocal in 40% of immunocompetent patients and almost 100% of AIDS patients, causing diagnostic confusion with brain metastases.⁵ Furthermore, PCNSL widely infiltrates brain parenchyma, and at autopsy, disease is usually seen microscopically in areas where magnetic resonance images were completely normal. At least 42% of patients have demonstrable leptomeningeal seeding on the basis of a positive CSF cytologic examination.^{6,7}

Eye

Ocular lymphoma can present with blurred vision or floaters, or it may be clinically silent.⁸ A cellular infiltrate of the vitreous can be visualized only by slit-lamp examination; choroidal or retinal lesions often require indirect ophthalmoscopy.⁹

Leptomeninges

Patients can present with progressive leg weakness, urinary incontinence or retention, cranial neuropathies, increased intracranial pressure, confusion, or a combination of these symptoms. Diagnosis is established by demonstration of malignant lymphocytes in the CSF or on meningeal biopsy. Gadolinium magnetic resonance imaging scan of the head or spine reveals meningeal enhancement, hydrocephalus but no brain tumors, or multiple intradural nodules.¹⁰

Spinal Cord

Primary spinal cord lymphoma patients present with painless bilateral limb weakness, usually involving the legs; sensory symptoms and signs may initially follow a radicular pattern, but eventually a sensory level may be found. CSF may be normal or have a mildly elevated protein concentration with a few lymphocytes. Prognosis has been poor with patients surviving only a few months from the

onset of symptoms, but this is often due to the fact that the diagnosis was not made until autopsy and no appropriate therapy was administered.¹¹

DIAGNOSTIC WORK-UP

The following should be done in an immunocompetent patient whose CT/MRI scan suggests PCNSL:

- Withhold corticosteroids as their use may complicate diagnosis
- Chest x-ray to rule out metastatic disease
- Complete blood count with differential
- HIV testing
- Slit-lamp examination for vitreous lymphoma
- Lumbar puncture for cells, glucose, protein, and cytology in CSF

In an HIV-infected or other immunocompromised patient whose CT/MRI scan suggests PCNSL, the above are followed, plus:

- Toxoplasmosis gondii serology
- Lumbar puncture for cells, syphilis testing, and cryptococcal antigen

Imaging Studies

• MRI of the brain usually reveals a hypointense lesion or lesions on long TR-weighted images, which enhance densely and homogeneously after contrast administration. Lesions are multifocal in 50% of patients with AIDS, whereas only 25% of immunocompetent patients have multifocal disease at presentation. MRI also gives information about leptomeningeal enhancement, hydrocephalus, and concurrent alternative diagnoses, such as infections in patients with AIDS.¹²

• Magnetic resonance spectroscopy may provide additional diagnostic information; PCNSL has marked elevation of lipid content and a much higher choline/creatine ratio than all grades of astrocytoma. This magnetic resonance spectroscopy pattern may suggest the diagnosis of PCNSL.¹³

• MRI of the spine with contrast should be performed in patients with focal, spinal, or root symptoms, as they may require radiation to localize the deposits of lymphoma.

• Thallium-201 single-photon emission computed tomography (SPECT) scanning is appropriate in patients with AIDS to help distinguish between infectious processes and PCNSL. Positron emission tomography or single photon emission computed tomography can differentiate between PCNSL and CNS infection with a high degree of

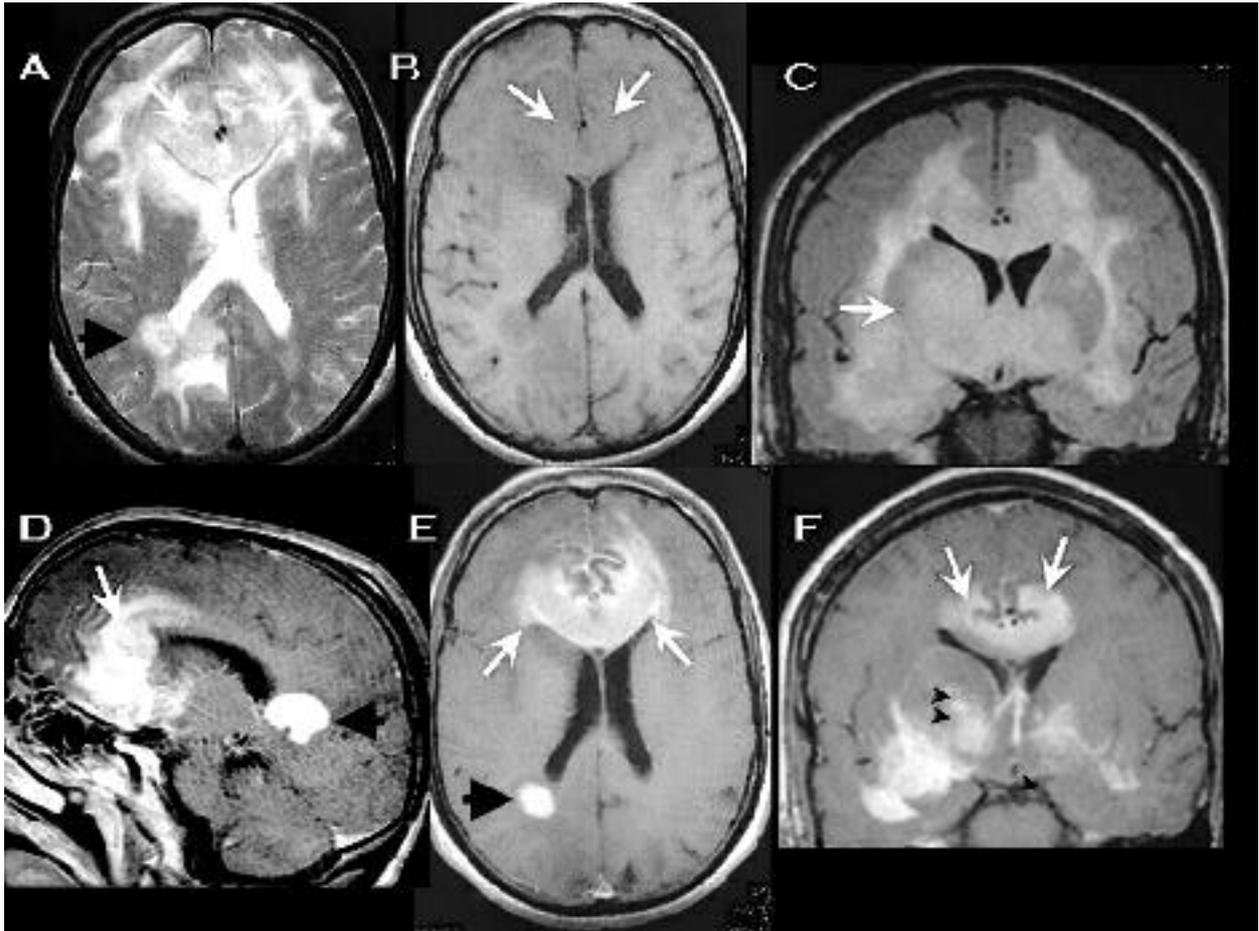


Figure 1
MR scan of the brain in a 50 year-old male with progressive left-sided weakness and personality changes who was eventually diagnosed with primary CNS lymphoma. A: T2-weighted axial image. There is a hyperintense T2 signal lesion occupying the anterior corpus callosum extending into both frontal lobes (white arrows). Further focal signal abnormality posteriorly in the periventricular white matter (black arrowhead). B: T1 axial scan. The lesions seen on T2-weighted images (white arrows) are largely isointense to neural tissue on T1-weighted images. C: FLAIR coronal image. The lesion infiltrates the basal ganglia (white arrow) and extends into the temporal lobe on the right side. D, E, F: Post-contrast sagittal, axial and coronal T1-weighted images. The lesions show bright enhancement on post-contrast images. Anterior corpus callosum lesion (white arrows) and the periventricular lesions (large black arrowhead) show uniform contrast uptake. Apparent infiltration of basal ganglia is demonstrated to be largely confined to white matter (small black arrowheads). Radiological diagnosis: Primary multifocal cerebral lymphoma; confirmed on histology.

(Figure and accompanying text courtesy of Dr. Zafar Sajjad)

reliability. PCNSL is hypermetabolic in comparison to infection, which is usually hypometabolic. Patients with AIDS may have a cystic, ring-enhancing lesion with PCNSL instead of the homogeneously enhancing abnormalities seen in immunocompetent patients. The presence of single or multiple ring-enhancing lesions in patients with AIDS raises suspicion of toxoplasmosis, *Nocardia asteroides* infection, or neurosyphilis.¹⁴

- Chest and abdominal CT scans should be performed for the establishment of a definitive diagnosis of PCNSL.

Procedures

- Slit-lamp examination and possible vitrectomy: Although fewer than 10% have vitreous involvement at

initial presentation, all patients should undergo slit-lamp examination. Vitrectomy may establish the diagnosis, sparing brain biopsy in these patients.^{8,9}

- Stereotactic brain biopsy: Since the disease is diffusely infiltrative, craniotomy and debulking of lesions have no role in PCNSL.⁷ Open brain biopsy may be necessary in those patients who have lesions located in areas of the brain that are difficult to access (e.g., brainstem). If possible, the procedure should be performed before corticosteroids have been administered.

Lumbar Puncture

A lumbar puncture should be part of the diagnostic evaluation of every patient with suspected PCNSL. Protein

concentration is elevated in 85% of patients, although rarely above 150 mg/dl. Glucose concentration is usually normal but can be low when florid leptomeningeal tumor is present.¹⁵ Tumor markers, such as β_2 -microglobulin, lactate dehydrogenase isoenzymes, and β -glucuronidase can, when the level is elevated, provide circumstantial evidence for tumor invasion of the leptomeninges. Occasionally, immunohistochemical stains of CSF demonstrate a monoclonal population of cells establishing the neoplastic nature of the pleocytosis even if the cells appear cytologically benign. Detecting a monoclonal population of lymphocytes in the CSF by polymerase chain reaction of immunoglobulin gene rearrangements may also prove useful.¹⁶

Other Tests

- Liver function tests: As the mainstay of treatment for many patients is high-dose methotrexate, hepatic function must be evaluated. Tests should include serum bilirubin (total/direct), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase.
- Twenty-four-hour urine collection for creatinine clearance: Patients being considered for methotrexate chemotherapy must have a glomerular filtration rate (GFR) of greater than 100 ml/min because inadequate renal clearance enhances methotrexate toxicity.

TREATMENT

The goal of treatment is eradication of both contrast-enhancing mass lesions and microscopic infiltration of brain, spine, leptomeninges, and vitreous. Successful therapy in immunocompetent patients achieves a complete (100%) response rate. Despite the highly responsive nature of PCNSL to cranial radiotherapy, median survival is only 12 to 18 months with a 3% to 4% 5-year survival rate. This short survival is due to tumor recurrence. Optimal treatment for PCNSL has not been established. The following recommendations are based on an ongoing protocol at the authors' and several other institutions, and observation.¹⁷

Prognostic factors

Regardless of treatment, recent studies clearly indicate the importance of prognostic factors. Age and performance status are the strongest factors, observed in almost all studies. Each can have a profound impact on outcome, particularly in patients aged 60 or older or with a Karnofsky performance status of 70 or less.¹⁸

Poor prognostic factors include the following:

- Age older than 60 years.
- Performance status over 1.
- Elevated serum level of lactate dehydrogenase.
- Elevated cerebrospinal fluid protein concentration.
- Involvement of nonhemispheric areas of the brain (periventricular, basal ganglia, brainstem, cerebellum).

Therapeutic strategies are the same for both immunologically competent as well immunocompromised patients, although in general treatment is less effective and more toxic in the presence of immunodeficiency.¹⁹

Corticosteroids

A unique feature of PCNSL in comparison to other brain tumors is its exquisite sensitivity to corticosteroids. At least 40% of patients have significant shrinkage or disappearance of tumor masses on magnetic resonance imaging scan after administration of corticosteroids. Regardless of apparent tumor regression, steroid-induced remission is short-lived in most patients and is not definitive treatment.

Surgery

Surgery is important to confirm the histologic diagnosis but has no therapeutic role. The mean survival of patients with PCNSL with supportive care alone is 1 to 3 months. Surgical resection adds little, prolonging the average survival to only 3 to 5 months. Stereotactic biopsy is the diagnostic method of choice that also allows for biopsy of deep lesions that cannot be approached safely by conventional surgery. If craniotomy has been undertaken without PCNSL being a preoperative consideration, an intraoperative frozen section can often establish the diagnosis of PCNSL; the procedure should be terminated, as further resection is unnecessary.

Radiotherapy

Whole brain radiotherapy (WBRT) combined with corticosteroids has been the conventional treatment for PCNSL, yielding median survivals of 12 to 18 months. The Radiation Therapy Oncology Group (RTOG) conducted a prospective study of PCNSL patients treated with 4000 cGy WBRT plus a 2000 cGy boost to the involved area to assess whether dose intensification improved outcome. Median survival was only 12.2 months, and most recurrences were in the boosted field.¹⁶

Because of the risk of late neurotoxicity when WBRT is combined with chemotherapy, attempts have been made

to reduce the dose or volume of radiation therapy (RT). The RTOG recently reported a study using a high-dose methotrexate-based regimen in combination with 4500 cGy WBRT.²¹ During the trial, the protocol was changed such that only 3600 cGy WBRT in a hyperfractionated schedule was given to patients who achieved a complete response with the pre-RT chemotherapy. Survival and disease control were identical regardless of WBRT dose, although the neurotoxicity was not reduced, suggesting that even lower doses of RT are necessary to decrease the risk of leukoencephalopathy. These data are in contrast to those reported by Bessell et al., who used a pre-RT regimen of cyclophosphamide, doxorubicin, and vincristine with dexamethasone plus carmustine, vincristine, and cytarabine to reduce the dose of WBRT from 4500 cGy to 3060 cGy in patients who achieved a complete response.²² No difference in outcome was observed for older patients, but in patients younger than 60 years, survival was significantly better (3-year overall survival 92% vs. 60%, $p = .04$) if the full dose of WBRT was used.

The primary treatment of ocular disease is 3500 to 4500 cGy RT over 4 to 5 weeks to the globe.⁷ Because ocular lymphoma is predominately a binocular process, both eyes should be irradiated even when only monocular disease can be detected on slit-lamp examination. This may increase with improved survival because many of the complications are delayed. Conjunctivitis, retinal atrophy, vitreous hemorrhage, and cataract formation have all been reported in PCNSL patients after ocular RT.

Chemotherapy

Accumulated data from multiple phase II studies clearly document the chemosensitivity of PCNSL to systemic chemotherapy and superior outcomes with combined modality therapy.

High-dose methotrexate is the single most important agent for the treatment of PCNSL. Originally chosen because of its ability to penetrate the blood-brain barrier and its known activity against lymphoma, methotrexate is now the cornerstone of PCNSL therapy despite the small role it plays in the treatment of comparable systemic lymphomas. Sensitivity to methotrexate may indicate a fundamental biologic difference between PCNSL and NHL.

Methotrexate has been used as a single agent as well as in combination with other drugs. Doses have ranged from 1 g/m² to 8 mg/m², without a clear indication that more is necessarily better. However, doses of 3 g/m² or more penetrate into the CNS more reliably than lower doses. Several phase II trials using a high-dose methotrexate-based regimen in combination with WBRT have all shown improved survival (median of 33 to 60 months) over

WBRT alone. The first multicenter trial, Radiation Therapy Oncology Group Study 93-10, was done in 102 newly diagnosed immunocompetent patients with PCNSL who received high-dose methotrexate combined with WBRT. Patients first received five cycles of methotrexate 2.5 g/m², vincristine, procarbazine, and intraventricular methotrexate (12 mg). Whole-brain radiotherapy was administered to a total dose of 45 Gy and all patients received high-dose cytarabine after RT. Median progression-free survival was 24.0 months and overall survival was 36.9 months, which was better than previous reports of RT alone.²¹

To date, the best results have been achieved combining high-dose methotrexate with vincristine and procarbazine before WBRT, giving a median survival of 60 months.²⁶ A large multicenter phase II trial based on this regimen was completed by the RTOG and median survival was 37 months, less than seen in the single institution experience. Part of this difference may have been the reduction in methotrexate dose from 3.5 g/m² to 2.5 g/m², but other factors, such as unfamiliarity in the administration of high-dose methotrexate, undoubtedly contributed to the decreased outcome observed when the regimen was used in the multicenter setting.

All methotrexate-based regimens, when combined with WBRT, carry a significant risk of severe, irreversible neurotoxicity characterized by dementia, ataxia, and incontinence.²⁷ There has been recent interest using single-agent methotrexate at a dose of 8 g/m² as sole therapy over a protracted maintenance period. A recent report on 25 patients achieved a median progression-free survival of 12.8 months, and median overall survival was not reached at 23 months.²⁸ However, an identical regimen was used in a prospective multicenter trial in Germany that had to be closed early because only 29.7% of patients achieved a complete response and 37.8% progressed on treatment.²⁹ These data suggest that single-agent methotrexate has limited efficacy and rarely produces sustained disease control.

There is a recent report using high-dose methotrexate as an induction regimen followed by high-dose chemotherapy with carmustine (BCNU), etoposide, cytarabine, and melphalan and autologous stem cell rescue without cranial RT.³⁰ Fourteen of the 28 patients had an objective response to induction and proceeded to transplant. Overall event-free survival was only 5.6 months for all patients and 9.3 for the transplanted patients; however, overall survival was not reached, with a median follow-up of 28 months. Six of the 14 transplanted patients (43%) remain free of disease at last follow-up. These data suggest that a high-dose chemotherapy approach may be useful in some patients.

It is important to recognize that regimens used for systemic NHL, including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and similar regimens, have no role in the treatment of PCNSL. There have now been two multicenter phase II studies and one prospective randomized phase III trial that definitively establish the poor efficacy and high toxicity of CHOP for PCNSL. The RTOG conducted a study in which patients received three cycles of CHOP followed by cranial irradiation.²³ The median survival was only 12.8 months for the 51 patients treated. A separate multi-institutional trial of preradiation CHOP had 46 evaluable patients, with an estimated median survival of approximately 9.5 months.²⁴ There was no difference in survival or failure-free survival in patients treated with WBRT alone compared with WBRT and CHOP.²⁵ Therefore, CHOP or similar regimens should not be used in PCNSL; these agents should have excellent activity against PCNSL tumor cells, but they are unable to penetrate an intact blood-brain barrier.

CONCLUSION

In summary, PCNSL, a rare form of extranodal Non-Hodgkin's lymphoma, is typically a DLBCL that is confined to the nervous system and eyes. The diagnosis of PCNSL is supported by CT and MRI studies as well as CSF testing, but is ultimately confirmed on the basis of stereotactic biopsy in most patients. Methotrexate-based, multiagent chemotherapy with WBRT currently is the treatment of choice. Future studies should address the modifications of the chemotherapy regimen that may improve disease control and outcome for all patients.

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