ECRONICON OPEN ACCESS

EC DENTAL SCIENCE
Commentary

The Elementary Encephalon-Primary Central Nervous System Lymphoma

Anubha Bajaj*

Department of Histopathology, Panjab University, A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University, A.B. Diagnostics, India.

Received: January 06, 2023; **Published:** January 25, 2023

Primary central nervous system lymphoma (PCNSL) is an uncommon variant of brain tumour devoid of concurrent systemic disease upon initial disease discernment, thereby demarcating the condition from central nervous system incriminated with secondary, systemic lymphoma.

Majority (> 90%) of the exceptional, aggressive primary central nervous system lymphomas arise as B cell lymphomas, especially diffuse large B cell lymphoma and high grade Burkitt-like B cell lymphoma. Malignant cells preferentially circumscribe and infiltrate vascular articulations. Low grade neoplasms emerge as T cell lymphoma or low grade B cell lymphoma.

Previously denominated as reticulum cell sarcoma, diffuse histiocytic lymphoma or lymphomatosis cerebri, primary diffuse large B cell central nervous system lymphoma preponderantly implicates the brain, ocular parenchyma, spinal cord or leptomeninges. Generally, systemic involvement is uncommon and immunodeficiency is absent.

Primary diffuse large B cell central nervous system lymphoma predominantly arises within elderly individuals. In contrast to systemic diffuse large B cell lymphoma, prognostic outcomes are inferior. The lymphoma is composed of enlarged, atypical, basophilic lymphocytes immune reactive to CD45, B cell markers, BCL6, MUM1 or BCL2 and demonstrate a distinct perivascular cuffing. Necrotic foci are frequently exemplified [1,2].

In contrast to CNS lymphomas associated with immunodeficiency due to diverse contributory factors as human immune deficiency virus (HIV) infection, primary CNS lymphoma occurring within immunocompetent subjects is a sporadic event and appears non concurrent with Epstein Barr virus infection [1,2].

High grade tumours are associated with inferior prognostic outcomes in spite of cogent therapy. Singular surgical resection is associated with mortality within months. Adoption of high dose chemotherapy aids in significantly decimating the neoplasm. However, tumour reappearance is commonly encountered and associated with median survival of ~30 months. Neoplasms occurring within immunocompromised subjects delineate significantly inferior outcomes [1,2].

Contingent to cell of origin and histological features, World Health Organization (WHO) classifies central nervous system lymphomas into diverse subtypes designated as:

- Immunodeficiency associated central nervous system lymphoma
- AIDS related diffuse large B cell lymphoma

- EBV+ diffuse large B cell lymphoma not otherwise specified (NOS)
- Lymphomatoid granulomatosis
- Primary CNS post-transplant lymphoproliferative disorder
- Intravascular lymphoma
- MALT lymphoma of the dura [1,2].

Primary central nervous system lymphoma configures < 1% of non-Hodgkin's lymphoma and ~3% of central nervous system neoplasms. Disease emergence is common within elderly subjects wherein clinical symptoms may evolve within few months.

Immunocompetent, HIV non infected, non transplant recipients demonstrate median age of disease discernment at 67 years. An equivalent gender predisposition or a male predominance with male to female proportion of ~2:1 may be encountered.

Majority of neoplasms arise within supra-tentorial space whereas posterior fossa and spinal cord are infrequently involved [1,2].

Generally, a singular tumour is exemplified although multiple lesions may be discerned. Around 20% subjects depict concurrent intraocular lesions. Extra-neural dissemination is exceptional although a propensity for tumour dissemination into testis is encountered.

Solitary (~70%) or multiple (~30%), preponderantly supra-tentorial lesions of primary central nervous system lymphoma delineate a predilection for periventricular white matter although cortex or deep grey matter may be implicated, especially within low grade lesions [1,2].

Of obscure pathophysiology, primary central nervous system lymphoma may demonstrate distinct genetic and phenotypic features which safeguards the neoplasm from perpetual immune surveillance. Neoplastic cells may arise from lymphocytes which are normal constituents of immune privileged milieu of central nervous system.

Alternatively, lymphocytes which metamorphose into a malignant cellular clone away from central nervous system with subsequent homing into the central nervous system and circumvention of normal immune regulation within immune privileged sites may engender the lymphoma.

Of obscure aetiology, primary central nervous system lymphoma arises within immunocompetent subjects. Viral incrimination as with Epstein Barr virus is unknown. Elderly population as with human immune deficiency (HIV) non infected or non-transplant recipients demonstrate enhanced possible disease occurrence, possibly due to immunosuppressive agents employed for treating autoimmune conditions of elderly [1,2].

Clinical symptoms pertain to site of incrimination within central nervous system. Commonly, cognitive or behavioural alterations, focal neurologic deficits and symptoms of increased intracranial pressure may ensue.

Seizures are infrequent. Typically, B symptoms as fever, night sweats or > 10% loss of body weight are absent.

Ocular manifestations as decreased visual acuity, blurry vision or floaters may be encountered. Upon autopsy, tumours depict a variable macroscopic appearance with varying demarcation from circumscribing brain parenchyma [1,2].

Frozen section demonstrates histological features akin to permanent sections.

Intraoperative cytology may be beneficially adopted to evaluate the lymphoma.

Touch preparations are comprised of dis-cohesive, enlarged, atypical, immature, lymphoblast-like or basophilic cells delineating enlarged nuclei with elevated nucleo-cytoplasmic ratio and open chromatin. Post therapy neoplasms appear composed of necrotic cells or reactive T lymphocytes.

Cytological examination exhibits dispersed neoplastic lymphocytes circulating within cerebrospinal fluid. Enlarged tumour cells frequently display irregular nuclear contours, abnormal chromatin and prominent nucleoli and appear admixed with reactive lymphocytes. Preponderantly dis-cohesive clusters of monomorphic, intermediate to enlarged, basophilic lymphoid cells demonstrate prominent smearing artefact and appear admixed with reactive glial cells [1,2].

Upon gross examination, lesions may appear as firm, homogenous, brownish, grey, tan or yellow with areas of haemorrhage and centric necrosis.

Macroscopically, primary central nervous system lymphoma delineates a variable picture with an indistinguishable lesion confined to normal brain, well circumscribed tumefaction or a heterogeneous, poorly defined, haemorrhagic or necrotic neoplasm [1,2].

Upon microscopy, the lymphoma enunciates a characteristic angiocentric pattern of tumour configuration. Neoplastic lymphocytes appear to circumscribe and infiltrate vascular articulations.

Miniature clusters or singular neoplastic lymphocytes appear to diffusely infiltrate brain parenchyma. Focal necrosis is commonly discerned. Neoplastic infiltration is accompanied by activation of astrocytes and microglia along with a reactive inflammatory infiltrate. Neoplastic B cells appear as intermediate to enlarged cells imbued with vesicular chromatin and prominent nucleoli [1,2].

Primary central nervous system lymphoma is constituted of significant quantities of neoplastic lymphocytes lacking a specific pattern of tumour evolution. Nevertheless, a predilection for perivascular tumour dissemination and vascular infiltration is encountered. Foci of necrosis are encountered in lesions appearing within immuno-deficient subjects.

Administration of corticosteroids prior to surgical tissue sampling may induce significant shrinkage of the neoplasm along with elevated quantifiable macrophages and cellular debris [1,2].

Diffuse large B cell primary central nervous system lymphoma is immune reactive to B cell markers as PAX5, CD19, CD20, CD22, CD79a, BCL6, MUM1/IRF4, BCL2 or MYC.

Primary central nervous system lymphoma is immune non reactive to plasma cell markers as CD38, CD138, CD10, CD30, ALK1 or HHV8. Flow cytometry of stereotactic needle core tissue samples may be challenging to discern on account of paucity of tissue [3,4].

Flow cytometry of cerebrospinal fluid can aid appropriate disease discernment or evaluation of leptomeningeal disease, especially where core needle tissue samples are inadequate.

Immuno-phenotyping of samples with flow cytometry may identify abnormal B cell population associated with light chain restriction. Primary central nervous system lymphoma frequently depicts genetic rearrangements of BCL6 gene whereas genetic rearrangements of MYC or BCL2 are uncommon.

Oncogenic gain of function mutations confined to MYD88 (MYD88- L265P) are frequently observed [3,4].

Primary central nervous system lymphoma necessitates segregation from neoplasms such as systemic malignant lymphoma or diffuse large B cell lymphoma associated with human immune deficiency virus (HIV) infection, high grade glioma, toxoplasmosis, cerebral

abscess, metastatic melanoma, metastatic carcinoma, demyelinating lesions of central nervous system or cerebral infarct. Histological demarcation is required from neoplasms such as gliomas, metastases from various primaries, toxoplasmosis, sarcoidosis, histiocytic lesions, progressive multifocal leukoencephalopathy, multiple sclerosis or inflammatory disorders as vasculitis [3,4].

Distinction upon computerized tomography (CT) and magnetic resonance imaging (MRI) is necessitated from secondary central nervous system lymphoma, cerebral toxoplasmosis, butterfly glioma or glioblastoma multiforme, tumefactive multiple sclerosis or acute disseminated encephalomyelitis (MS/ADEM), cerebral abscess or neuro-sarcoidosis.

Contrast enhanced magnetic resonance imaging (MRI) of brain is an optimal neuroimaging modality adopted to detect primary central nervous system lymphoma. Nevertheless, confirmation with surgical tissue sampling or assessment of cerebrospinal fluid is necessitated. Stereotactic needle biopsy is recommended for diagnosis and classification of primary central nervous system lymphoma.

Cerebrospinal fluid (CSF) cytology and flow cytometry is employed where surgical tissue samples are challenging to obtain or to evaluate leptomeningeal involvement. Cerebrospinal fluid (CSF) demonstrates elevated protein and decimated glucose. Neoplastic cells are uncommonly (~25%) discerned upon cytology. Lymphoma arising within immunocompromised individuals appears immune reactive to Epstein Barr viral DNA [3,4].

Glucocorticoids as dexamethasone or prednisolone demonstrate a transient, profound response upon central nervous system lymphoma, employed for treating intracranial mass effect arising due to tumour or intracranial oedema. Following administration of steroids, central nervous system lymphoma diminishes significantly due to combined effect of cytotoxic steroid agent which decimates neoplastic B cell population and anti oedema agent with consequently decimated capillary permeability through various mechanisms.

Nevertheless, it is posited that steroid administration prior to surgical tissue sampling may circumvent appropriate disease discernment (~50%). Thus, prevention of steroid administration prior to surgical sampling is recommended in order to maximize accrual of diagnostic tissue [3,4].

Generally, imaging features of diverse subtypes of central nervous system lymphomas are identical. Lesions appearing within immunocompetent subjects are devoid of haemorrhage, calcification, necrosis or ring enhancement. Solitary lesions appear within deep white matter and periventricular region.

Typically, supra-tentorial primary central nervous system lymphoma occurs as a singular or multiple masses adhering to subarachnoid or ependymal surfaces. Corpus callosum may frequently be traversed. CT and MRI display significantly enhanced, homogeneous lesions. Enlarged lesions depict minimal mass effect and circumscribing vasogenic oedema [3,4].

Upon computerized tomography (CT), primary central nervous system lymphoma emerging within untreated, non immunocompromised subjects classically depicts hyper-dense, avidly enhancing tumefaction with minimal centric necrosis or vasogenic oedema.

Primary central nervous system lymphomas arising within immunocompromised, post-transplant recipients or subjects infected with HIV appear as heterogeneous neoplasms with centric non enhancement, necrosis and haemorrhage.

In contrast to high grade primary central nervous system lymphoma, low grade central nervous system tumours emerge as:

- Deep seated tumours with frequent incrimination of spinal cord
- Absent, irregular or mild tumour enhancement is observed upon administration of contrast. High grade primary central nervous lymphoma uncommonly delineates disseminated meningeal or intraventricular disease [3,4].

Upon computerized tomography, primary central nervous system lymphomas occur as hyper-attenuating, enhancing, supra-tentorial lesions (70%). Haemorrhage is infrequent. Subjects with HIV infection frequently display multiple lesions.

Upon magnetic resonance imaging (MRI) primary CNS lymphoma demonstrates:

- Typically hypo-intense lesion to grey matter upon T1 weighted imaging
- Upon administration of gadolinium contrast, high grade tumours depict an intense, homogeneous enhancement whereas low grade neoplasms display an absent to moderate enhancement
- Immunocompromised subjects with HIV exhibit peripheral ring enhancement or a notch sign
- A variable, isointense to hypo-intense to grey matter signal intensity upon T2 weighted imaging.

Lesions with necrosis may be hyper-intense.

Administration of gadolinium contrast enunciates vivid, homogenous, enhancing lesions with restricted diffusion along with sub-ependymal extension and bridging of corpus callosum.

Magnetic resonance (MR) spectroscopy exhibits a significant choline peak, lactate peak, reversal of choline/creatinine ratio and significantly decreased N-acetyl aspartate (NAA) levels.

Magnetic resonance (MR) perfusion displays a moderate enhancement of relative cerebral blood volume (rCBV).

Upon thallium-201 scintigraphy, fluorine-18 fluorodeoxy glucose (FDG PET) or carbon-11 methionine positron emission tomography, primary central nervous system lymphoma enunciates an enhanced uptake.

Diffusion weighted imaging exhibits restricted diffusion. Neoplasms with apparent diffusion coefficient (ADC) values below normal brain demonstrate an inferior therapeutic response and elevated proportionate tumour reoccurrence [3,4].

Primary central nervous system lymphoma is predominantly treated with steroids which can significantly shrivel the neoplasm due to anti-oedema and cytotoxic effects. Besides, methotrexate based chemotherapy appears efficacious.

Whole brain irradiation can be employed for treating high grade or recurrent tumours.

Uncommonly discerned low grade neoplasms are subjected to localized surgical eradication and radiotherapy, manoeuvers which are associated with long term survival.

Primary central nervous system lymphoma treated with high dose intravenous methotrexate regimen is adopted as an optimal induction therapy.

Consolidation therapy is comprised of conventional chemotherapy, radiotherapy, high dose chemotherapy with autologous stem cell transplantation or combinations of aforesaid therapies [3,4].

In contrast to systemic diffuse large B cell lymphoma, primary central nervous system lymphoma demonstrates an inferior prognostic outcome wherein age and performance status of incriminated subjects are significant prognostic factors. Subjects managed with methotrexate based regimens may demonstrate BCL6 expression as a predictor of meliorated progression free survival.

Prognostic outcomes and risk stratification may be assessed with

- International Extra-nodal Lymphoma Study Group (IELSG) score comprised of
- Eastern Cooperative Oncology Group (ECOG) performance score
- Age of incriminated subject
- Protein concentration of cerebrospinal fluid
- Serum lactate dehydrogenase (LDH) levels
- Deep seated involvement of brain.

Two year proportionate survival rate is contingent to aforesaid risk factors assessed as

- 0 to 1 adverse factor - 80% proportionate survival
- 2 to 3 adverse factors - 48% proportionate survival
- 4 to 5 adverse factors - 15% proportionate survival.

Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic score designates distinctive prognostic subgroups contingent to

- Age ≤ 50 associated with median overall survival of 8.5 years
- Age > 50 and Karnofsky performance status(KPS) ≥ 70 delineating median overall survival of 3.2 years
- Age > 50 and Karnofsky performance status (KPS) < 70 enunciating median overall survival of 1.1 years.

With ameliorated disease detection and therapeutic strategies, median overall survival appears enhanced, especially in incriminated subjects < 70 years. Prognostic outcomes of refractory or relapsed primary central nervous system lymphoma is adverse with survival < 6 months [3,4].

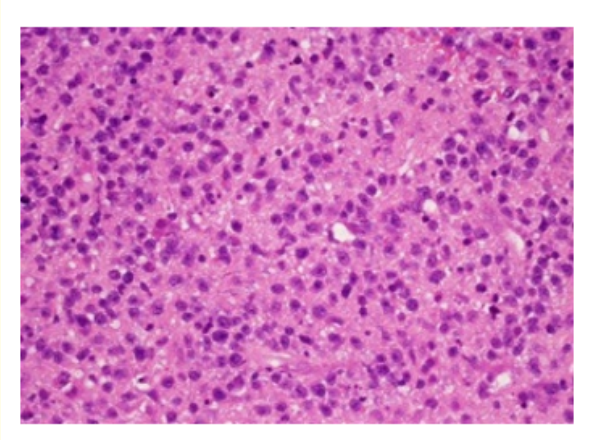

Figure 1: *Primary central nervous system lymphoma depicting intermediate to enlarged neoplastic lymphocytes with abundant cytoplasm, vesicular nuclei with conspicuous nucleoli [5].*

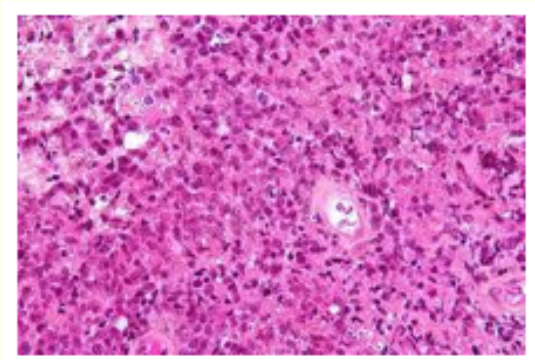

Figure 2: *Primary central nervous system lymphoma depicting randomly disseminated neoplastic lymphocytes with circumscription and invasion of vascular articulations [6].*

Bibliography

1. Green K and Hogg JP. "Central Nervous System Lymphoma". Stat Pearls International, Treasure Island, Florida (2022).
2. Mo SS., *et al*. "Primary CNS lymphoma: update on molecular pathogenesis and therapy". *Leukemia and Lymphoma* (2022): 1-9.
3. Schaff LR and Grommes C. "Primary central nervous system lymphoma". *Blood* 140.9 (2022): 971-979.
4. Kaulen LD and Baehring JM. "Treatment Options for Recurrent Primary CNS Lymphoma". *Current Treatment Options in Oncology* 23.11 (2022): 1548-1565.
5. Image 1 Courtesy: Radiopaedia.com.
6. Image 2 Courtesy: Wikimedia commons.com.

Volume 22 Issue 2 February 2023