Primary CNS Lymphoma – current barriers to improving prognosis and predicting outcome

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Primary CNS lymphoma (PCNSL) is a rare high grade non-Hodgkin's lymphoma representing around 5% of all primary brain tumours [1,3]. Patients typically present in their 50's or 60's with clinical features of an expanding intracranial mass lesion. There also appears to be a slight male predominance in presentation. For the overwhelming majority of patients, overall survival remains poor, partly due to often poor performance status at diagnosis and difficulties tolerating the neurotoxic effects of chemoradiotherapy, with median survival rates around 10-20 months [2]. Unlike systemic diffuse large B cell lymphoma (DLBCL), the pathophysiology of PCNSL is poorly understood. In this article we discuss the clinicopathological features of PCNSL, the limitations in current management and the emergence of potential prognostic markers similar to those routinely assessed in systemic DLBCL.

Changing incidence and risk factors

Until the late 1990's, the incidence of PCNSL had been steadily increasing over the preceding 20 years [3]. The reasons for this still remain unclear, with the steady rise now no longer so evident and current incidence rates stable around 2.7-2.8 per million population in the immune competent [4]. Immunosuppression is well-recognised as a major risk factor in the aetiology of PCNSL, and prior to the introduction of highly active antiretroviral therapy (HAART), the incidence rate of PCNSL in the HIV positive population was several thousand fold higher than in the general population, probably accounting for some of this observed increase. Since HAART however, these rates have fallen considerably [5]. Widespread use of immunosuppressant drugs in autoimmune diseases and for post-transplant immunosuppression has also been implicated in this rise in PCNSL [6]. Of note, whilst the majority of cases of PCNSL are Ebstein-Barr virus (EBV) negative, in the immune compromised EBV may be found.

Clinical features

Given the aggressive nature of the disease there is usually a short interval between onset of symptoms and diagnosis with the specific clinical features encountered depending on the regions of CNS involvement. The majority of cases present with a focal neurological deficit (70%); sequelae of raised intracranial pressure (33%) and seizures (14%) are also common at presentation [7]. In those patients with ocular disease, only half present with visual symptoms such as floaters, blurred vision or reduced visual acuity, therefore specific examination of the eye is a requirement of full staging of the disease. In addition, diagnosis can be delayed as ocular disease can often mimic other more common conditions such as posterior uveitis.

Table 1: A summary of the staging investigations recommended by BNOS [10].

STAGING INVESTIGATIONS FOR PCNSL
HIV serology
Examination of eyes (slit lamp, ophthalmoscopy +/- biopsy)
CSF for protein/glucose/cytology/molecular studies
Bone marrow aspirate and trephine
CT chest/abdomen/pelvis
Testicular ultrasound – elderly males

The typical radiological appearance of PCNSL is a deep enhancing periventricular or subependymal mass with homogenous enhancement and without central necrosis. On MR, these often appear as isointense or hypointense lesions on T2 weighted imaging, with the frontal lobes as the most commonly involved region along with corpus callosum and basal ganglia. Lesions are typically solitary but can be multifocal, particularly in end stage disease or in immunocompromised patients. 10% of cases present with leptomeningeal involvement, which is an unusual feature and often reflects a late stage in the course of the disease. This can mimic other more common meningeal lesions such as meningiomas. Whilst the radiological appearances can be distinctive, PCNSL lesions can mimic other diagnoses, including high grade glioma, metastases or infective/inflammatory lesions. Therefore, a stereotactic or image guided open biopsy with intraoperative neuropathological assessment is required to histologically confirm the diagnosis. Resection is not advocated as it is well established that it does not alter overall survival [2].

Corticosteroids are usually the first line therapy following diagnosis as they significantly reduce symptoms related to raised intracranial pressure and mass effect by reducing oedema and inducing apoptosis of tumour cells. Because of this, they can potentially induce 'radiological' tumour regression (the 'disappearing tumour') and affect the quality of histological material for assessment. The general advice is therefore to avoid giving steroids prior to biopsy unless there is an urgent clinical need. However, a recent study of 109 patients by Porter et al showed similar rates of repeat biopsy in patients who received pre-operative steroids compared to those who did not [8], suggesting this may not be as severe a problem as previously thought. In our experience the diagnostic yield is usually high regardless of prior treatment.

Once histological diagnosis is established, a number of staging investigations are recommended by the International PCNSL Collaboration Group [9],

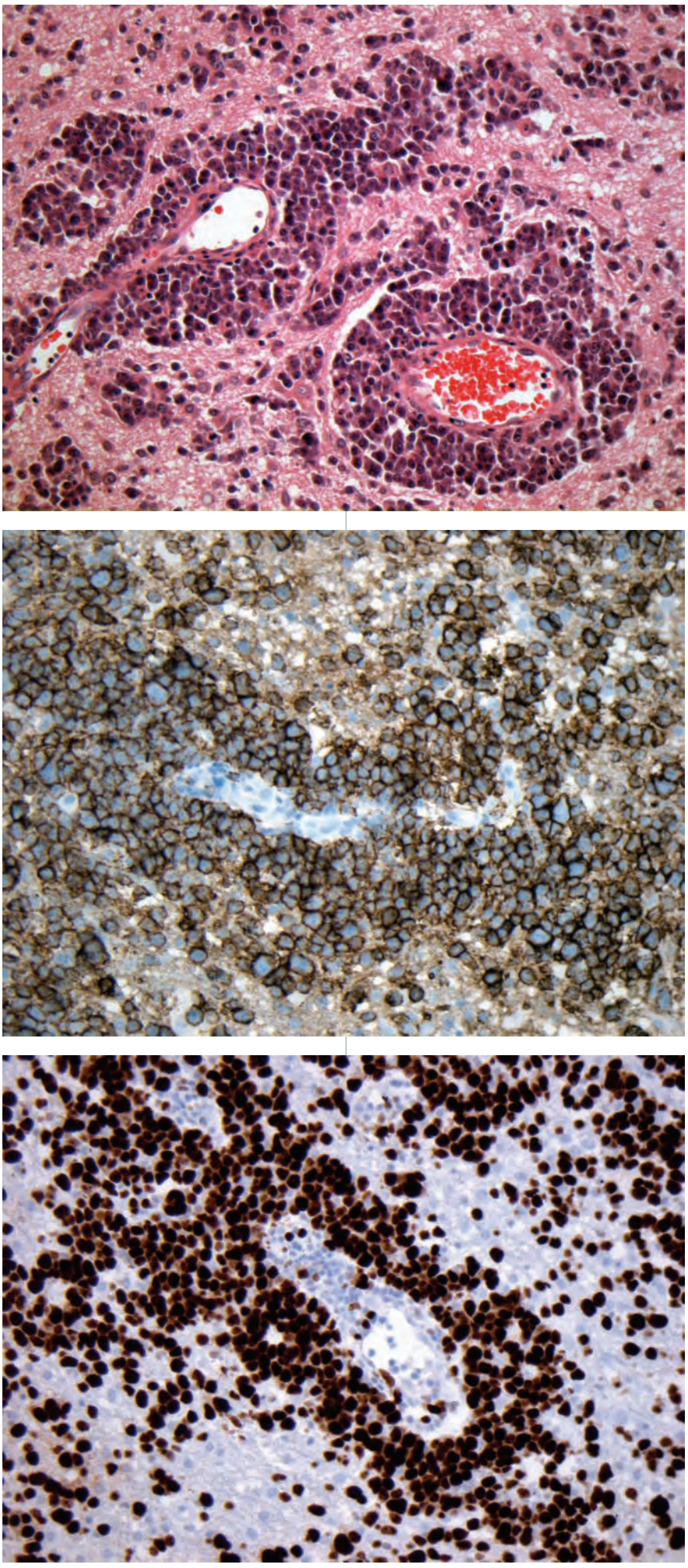

Figure 1: Shows medium to large tumour cells with rounded irregular nuclei and limited cytoplasm infiltrating neural tissue and showing characteristic perivascular 'cuffing' (a; H&E x20). Immunocytochemistry shows positivity for the pan-B cell marker CD20 (b; x20) and a high proliferation index (c; Ki67 x20).

all of which have been highlighted in the recent British Neuro-oncology Society (BNOS) Rare Brain/ CNS Tumour Guidelines on Primary CNS Lymphoma. These investigations are summarised in Table 1 and are aimed at excluding systemic disease and fully assessing the extent of CNS involvement. A CT chest, abdomen and pelvis should be carried out along with bone marrow examination to exclude CNS spread of systemic lymphoma. Given the potential for synchronous ocular or leptomeningeal involvement, eye examination and CSF assessment is recommended. Testicular ultrasound should be performed in elderly males due to the high propensity for testicular lymphomas to spread to the CNS. As HIV infection is a risk factor for the development of PCNSL, an HIV test should also be carried out in all patients following informed consent. Although FDG-PET is well-established in the management of systemic lymphoma, its exact role in PCNSL is yet to be established. Up to 12% of cases initially thought to be confined to the CNS are found to have synchronous systemic involvement on subsequent investigations [11].

Histopathological features

The overwhelming majority (over 95%) of PCNSL are high grade B cell lymphomas of diffuse large B cell type (DLBCL). Low grade lymphomas, such as lympho-plasmacytic lymphoma and marginal zone lymphoma, rarely present in the CNS. Approximately 2% of PCNSLs are of T cell lineage and show a predilection for the posterior fossa. The remainder of lymphomas presenting in the CNS are extremely rare, such as Burkitt lymphoma, anaplastic large cell lymphoma, lymphoid granulomatosis and Hodgkin's lymphoma, which often presents as leptomeningeal lesions late in the course of the disease (i.e. secondary spread).

Macroscopically, PCNSLs are space occupying lesions with an ill-defined boundary and greyish/yellow cut surface. Histologically, medium to large tumour cells with rounded nuclei and limited cytoplasm diffusely infiltrate the parenchyma and show an angiocentric pattern of spread, forming a characteristic perivascular 'cuff' of tumour cells (Figure 1). The tumour cells are associated with occasional reactive T cells, reactive astrocytes and microglia with stains for reticulin revealing increased perivascular

deposition. Necrosis is often present, particularly following steroid treatment. As the majority of PCNSLs are of B cell origin, they stain positively with pan-B cell markers CD20 and CD79a. The majority of PCNSLs are also positive for BCL2, BCL6 and MUM-1. The proliferation rate is usually high, with around 70-90% of tumour cells positive for the proliferation marker Ki67.

PCNSL – a distinct entity from systemic lymphoma?

PCNSL cells are postulated to recapitulate late/post germinal centre B cells however the exact origin of this neoplastic clonal population remains unclear. At a morphological level, the neoplastic cells of PCNSL are indistinguishable from those of systemic DLBCL. However, PCNSL is an extremely infiltrative tumour with a characteristic angiocentric pattern of growth; a pattern not normally found in other organs involved by DLBCL. There is high expression of growth factors such as IL-4 and XBP-1 within endothelial cells of tumour associated vessels which may be responsible for the angiocentric pattern of growth observed in PCNSL [12].

Diagnostic molecular pathology plays a major role in the diagnosis and prognostication of systemic lymphomas, however the same is not yet so for PCNSL. The role of oncogenes and transcription factors in the molecular pathogenesis of PCNSL is poorly understood, however there is growing evidence that PCNSL may have a molecular profile distinct to systemic DLBCL. The commonest aberrations observed are deletions or hypermethylation of CDKN2A which expresses p14ARF [13]. Array Comparative Genomic Hybridisation studies have also shown that loss of heterozygosity of 6q may be associated with poorer outcome in PCNSL, similar to outcomes in other systemic lymphomas [14]. IgH gene rearrangements may also be more frequent in PCNSL than in other lymphomas. Further studies characterising this disease at a molecular and cytogenetic level and correlation with clinical outcome are urgently required.

Following validation in a number of studies, systemic DLBCL is now routinely subtyped into two broad prognostic groups according to their positivity for the immunocytochemical markers CD10, BCL6 and MUM-1 (Figure 2) [15]. There is also a third group ('type 3') which is less well defined. Systemic DLBCL's which show a 'germinal centre' (GC: CD10+, BCL6+, MUM1+/-) phenotype have improved five-year survival rates when compared to 'non-germinal centre' (NGC: CD10-, BCL6+/-, MUM1+) phenotypes. Furthermore, BCL2 is known to confer a poorer survival in patients with NGC

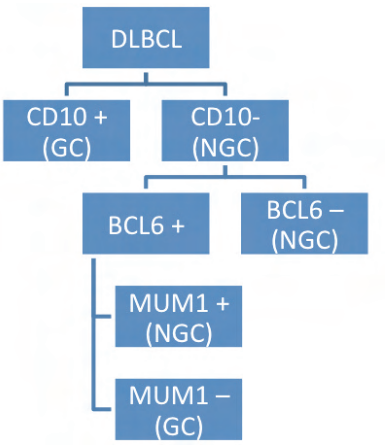

Figure 2: DLBCL's are subtyped into Germinal centre (GC) and Non germinal centre (NGC) phenotypes according to their positivity for CD10, MUM-1 and BCL6. (Adapted from Hans et al [15]).

phenotype. To date, the evidence for similar prognostic groups in PCNSL is somewhat limited. Some studies suggest a prognostic advantage in GC subgroups similar to DLBCL [16], however other studies have failed to show this benefit. One explanation is that the majority of PCNSLs appear to have a NGC phenotype with higher BCL2 and MUM1 expression when compared to DLBCL and therefore comparison to GC groups in small studies is flawed. There is also some evidence that BCL-6 is associated with a more favourable outcome in PCNSL [17]. Again, further work is required in a larger cohort of patients independently to assess these subtypes in PCNSL and correlate with clinical outcome.

Current management and potential barriers to improving outcomes

Similar to most other forms of lymphoma, PCNSL is sensitive to both radiotherapy and chemotherapy. Radiotherapy alone increases survival from around two months (untreated) to 11-18 months [18,19]. The most effective chemotherapeutic agent is methotrexate, improving survival to over 30 months [20,21], with high doses required to achieve adequate penetration of the blood brain barrier. Over the last decade optimal treatment has been regarded as methotrexate-based combination chemotherapy followed by radiotherapy [22,23], though this carries significant morbidity, including age-related dementia, limiting this aggressive approach to only the fittest patients, generally those less than 60 years old. This severe neurocognitive toxicity has prompted the investigation of the possibility of deferring radiation in those responding well to primary chemotherapy, which appears to be a successful approach with no detriment to survival [24].

Because of many factors including the advanced age of many patients and levels of fitness / comorbidity, the individual management of PCNSL varies significantly and population survival statistics remain poor. Unifying management strategies across different centres and countries is an important but difficult goal to achieve in this rare disease. Three main factors can be identified as potential barriers. Firstly, the CNS is a unique site to treat with problems related to poor blood brain barrier penetration of potentially active drugs and the neurotoxicity associated with both chemotherapy and radiotherapy. Secondly, because of this rarity, clinical trials are often underpowered, and cross-trial comparisons limited by heterogeneity. Steps have been taken to ameliorate this, as in the last twelve months guidelines on standardising investigation, management and outcome measures have been released by both the British Neuro-Oncology Society and the International PCNSL Collaborative Group [9] which will hopefully aid in the design of future studies. Finally the pathophysiology of PCNSL is yet to be fully defined both in terms of pathological subtyping and the development of useful prognostic molecular markers.

Given the rarity of the diagnosis and the poor but heterogeneous survival outlined above, identifying prognostic factors to tailor treatment is an important ambition. A number of prognostic models have previously been proposed incorporating combinations of age, performance status, serum lactate dehydrogenase (LDH) level, CSF protein concentration, and involvement of deep brain regions (periventricular regions, basal ganglia, brainstem, cerebellum), multifocal, or meningeal disease. In addition to individualising care through consideration of these factors, treatment decisions must also be multi-disciplinary.

Conclusions

In conclusion, PCNSL is a rare, aggressive B cell lymphoma with outcomes remaining poor for the majority of patients. PCNSL remains a challenge to treat oncologically due to the balance between disease control and minimising neurotoxicity. Current research efforts include a need to focus on improving our understanding of the pathology of PCNSL, in particular identifying specific molecular features which may aid in diagnosis and predicting prognosis. Furthermore, the initiation of large, multicentre and ideally multinational clinical trials should help to standardise optimal management. ■

References

1. Rubenstein J, Ferreri AJ, Pittaluga S. *Primary lymphoma of the central nervous system: Epidemiology, pathology and current approaches to diagnosis, prognosis and treatment.* Leuk Lymphoma 2008;49(1):43-51.
2. Reni M, Ferreri AJM, Garancini MP and Villa E. *Therapeutic management of primary central nervous system lymphoma in immunocompetent patients: results of a critical review of the literature.* Annals of Oncology 1997;8:227-34.
3. 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 [Internet]. 2002;95(7):1504–10.
4. Hoffman S, Propp JM, McCarthy BJ. *Temporal trends in incidence of primary brain tumors in the United States, 1985-1999.* Neuro-oncology 2006;8(1):27-37.
5. Besson C. *Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy.* Blood 2001;98(8):2339-44.
6. Schabet M. *Epidemiology of Primary CNS Lymphoma.* Journal of Neuro-Oncology. 1999;43(3):199-201.
7. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. *Primary intracerebral malignant lymphoma: report of 248 cases.* Journal of Neurosurgery. 2000;92(2):261–6.
8. Porter A, Giannini C, Kaufmann T, Lucchinetti CF, Wu W, Decker PA, Atkinson JLD, O'Neil BP. *Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma.* Annals of Neurology 2008;62:662-7.
9. Abrey LE, Batchelor TT, Ferreri AJM et al. *Report of an international workshop to standardize baseline evaluation and response criteria for primary central nervous system lymphoma.* J Clin Oncol 2005;23:5034-43.
10. BNOS Rare Brain and CNS Tumours Guidelines. In collaboration with the National Cancer Action Team. *Guidelines on the diagnosis a nd management of primary CNS and intra-ocular Lymphoma.* [Internet]. Available from: www.bnos.org.uk
11. Ferreri AJ, Reni M, Zoldon MC, Terreni MR, Villa E. *Importance of complete staging in non hodgkins lymphoma presenting as a cerebral mass lesion.* Cancer 1996;77(5):827-33.
12. 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.
13. Kadock C, Treseler P. *Molecular Pathogenesis of Primary CNS Lymphoma.* Neurosurg focus 2006;21(5):61-7.
14. Nakamura M, Shimada K, Ishida E, Konishi N: *Histopathology, pathogenesis and molecular genetics in primary central nervous system lymphomas.* Histol Histopathol 2004;19:211–9.
15. Hans CP, Weisenburger DD, Greiner TC et al. *Confirmation of molecular classification of diffuse large B cell lymphoma by immunohistochemistry using tissue microarray.* Blood 2004; 103(1): 275-82.
16. 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(9):3716–23.
17. Braaten KM, Betensky RA, Leval LD, Okada Y, Hochberg FH, Louis DN, et al. *BCL-6 Expression Predicts Improved Survival in Patients with Primary Central Nervous System Lymphoma BCL-6 Expression Predicts Improved Survival in Patients with Primary Central Nervous System Lymphoma 1.* Clinical Cancer Research. 2003;3:1063–9.
18. Nelson D, Martz K, Bonner H, Nelson J, Newall J, Kerman H, et al. *Non-Hodgkin's lymphoma of the brain: Can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315.* . Int J Radiat Oncol Biol Phys. 1992;23:9–17.
19. Shibamoto Y, Ogino H, Hasegawa M, Suzuki K, Nishio M et al. *Results of radiation monotherapy for primary central nervous system lymphoma in the 1990s.* International Journal of Radiation Oncology Biology Physics. 2005;62(3):809–13.
20. Glass J, Gruber ML, Cher L, Hochberg FH. *Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome.* Journal of Neurosurgery. 1994;81(2):188–95.
21. O'Brien P, Roos D, Pratt G, Liew K, Barton M, Poulsen M, et al. *Phase II Multicenter Study of Brief Single-Agent Methotrexate Followed by Irradiation in Primary CNS Lymphoma.* J. Clin. Oncol 2000;18(3):519.
22. Laack NN, O'Neill BP, Ballman KV, O'Fallon JR, Carrero XW, Kurtin PJ, et al. *CHOD/BVAM Chemotherapy and Whole-Brain Radiotherapy for Newly Diagnosed Primary Central Nervous System Lymphoma.* International journal of radiation oncology, biology, physics. 2011;81(2):476–82.
23. Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, et al. *High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial.* The lancet oncology. 2010;11(11):1036–47.
24. Correa D, DeAngelis L, Shi W, Thaler H et al. *Cognitive functions in survivors of Primary CNS Lymphoma.* Neurology 2004;62:548-55.