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# Primary central nervous system lymphoma presenting as isolated oculomotor nerve palsy☆

Terence Tan, MBBS*, Cesar Salinas-La Rosa, MD, FRCPA, MAACB, Tiew F. Han, MBBS, FRACS

*Department of Neurosurgery, St. Vincent's Hospital Melbourne, Victoria, Australia*

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ABSTRACT

The authors report an unusual case of primary central nervous system lymphoma presenting with isolated pupil-involved oculomotor nerve palsy. Magnetic resonance imaging demonstrated leptomeningeal involvement of the midbrain and interpeduncular cistern, a single hypothalamic lesion, and intraventricular involvement. Diffuse large B-cell lymphoma was confirmed by stereotactic intraventricular biopsy. Combination chemotherapy with methotrexate, vincristine, procarbazine and rituximab was instituted with resolution of oculomotor nerve palsy and complete disease remission. An interdisciplinary approach involving neurosurgeons, neuroradiologists, neuropathologists and neurologists is crucial in the management of primary central nervous system lymphoma.



## Introduction

Primary central nervous system lymphoma (PCNSL) is a rare, extra-nodal form of non-Hodgkin lymphoma accounting for 2.4% of all primary brain tumours. In immunocompetent patients, PCNSL commonly presents with a solitary lesion in the cerebral hemispheres, basal ganglia, or periventricular region. Focal neurological deficits (70%), neuropsychiatric symptoms (43%) and symptoms of increased intracranial pressure (33%) are the commonest forms of presentation [1]. We present the rare case of a patient with PCNSL presenting with isolated oculomotor nerve palsy (ONP). Combination chemotherapy and intrathecal methotrexate was instituted with complete disease remission and resolution of ONP. Third nerve palsy as a presenting symptom should be considered by clinicians in PCNSL, especially given its increasing incidence. Additionally, we perform a review of the current literature pertaining to this unusual presentation.

## Case report

### *History and examination*

This 42 year-old male presented with sudden obscuration of his vision due to an inability to lift his right eyelid. On manual elevation of the right eyelid, his partner noticed that his right pupil was significantly larger than the left, a previously absent finding. The patient also complained of double vision. This was on a background of intermittent headaches, nausea and vomiting over the preceding two months. He denied any preceding trauma and any upper or lower limb neurological symptoms. He had no significant past medical history and did not take any regular medications. On examination, his right eyelid was partially ptosed. The right pupil was dilated (8 mm) compared to the left (5 mm). Direct and consensual pupillary light reflexes were sluggish on the right compared to the left. Adduction, elevation and depression of the right eye were impaired, while abduction and intorsion was intact. Visual acuity was 6/6 bilaterally and there were no abnormalities seen on fundoscopy and perimetry testing for visual field defects. The remainder of the cranial nerve and neurological exam was unremarkable. There was no palpable lymphadenopathy.

### *Investigation and diagnosis*

Given the pupil-involved ONP, contrast-enhanced computed tomography (CT) and computed tomography angiogram (CTA) of the brain were performed. No saccular aneurysms were identified on CTA. On contrast-enhanced CT and subsequent magnetic resonance imaging (MRI), a leptomeningeal nodular and irregular enhancement encasing the midbrain involving the interpeduncular cistern was demonstrated. Additionally, a T1-isointense, T2-isointense hypothalamic lesion measuring 12 mm × 11 mm × 11 mm was noted. This lesion was homogeneously-enhancing with intravenous gadolinium contrast. A further intraventricular lesion centred on the septum

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* Corresponding author at: Victorian Brain and Spine Centre, PO Box 2900, Fitzroy, Victoria 3065, Australia. Tel.: +61 3 9288 3650; fax: +61 3 9288 3350.
*E-mail address:* Terence.TAN@svhm.org.au (T. Tan).

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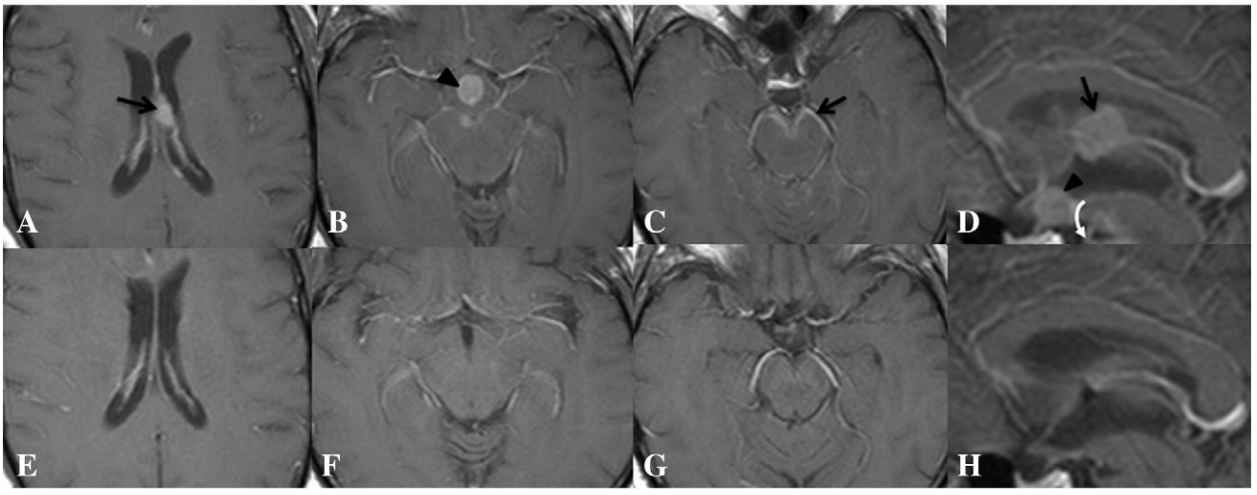


**Fig. 1.** Axial (A to C, E–G) and sagittal (D, H) contrast-enhanced, T1-weighted, magnetic resonance imaging pre-chemotherapy (A–D) and post-chemotherapy (E–H). Interval disease remission demonstrated by resolution of the nodular, homogeneously-enhancing lesion centred in the septum pellucidum (A, arrow & D, arrow) and hypothalamus (B, arrowhead & D, arrowhead). Leptomeningeal enhancement encasing midbrain and interpeduncular cistern (C, arrow & D, curved arrow) is similarly resolved post-chemotherapy. Note that there is no appreciable hydrocephalus.

pellucidum with similar MRI characteristics was identified together with widespread irregular ependymal enhancement of the fourth ventricle and bilateral foramen of Luschka (Fig. 1). There was no hydrocephalus and contrast-enhanced MRI of the spine was normal without leptomeningeal or intramedullary involvement. A working diagnosis of CNS lymphoma was made and the haematology department at the institution was consulted.

Further investigations were conducted to confirm and determine the extent of PCNSL. Cerebrospinal fluid (CSF) analysis via lumbar puncture revealed a cell count of $2 \times 10^6$/L erythrocytes and $93 \times 10^6$/L leukocytes comprising 86% lymphocytes and 14% polymorphs. CSF protein was elevated (1.22 g/L) and glucose concentration was at the lower range of normal (2.7 mmol/L). CSF cytology and flow cytometry was not suggestive of lymphoma. The serum full blood and white cell differential count, human immunodeficiency virus (HIV) antigen/antibody test, hormonal panel, serum lactate dehydrogenase and testicular ultrasound were normal. CT of the chest, abdomen and pelvis did not demonstrate lymphadenopathy. Bone marrow aspirate and trephine (BMAT) did not reveal lymphomatous infiltration.

An image-guided, endoscopic intraventricular biopsy was undertaken via a left frontal burrhole. At operation, extensive grey-white tumour lining the lateral ventricles bilaterally across the septum pellucidum was visualized and biopsied. Histopathological examination revealed sheets of atypical cells with hyperchromatic nuclei and scant cytoplasm of lymphoid origin. Immunohistochemistry was strongly positive for CD20 and mildly positive for CD3 (Fig. 2). A definitive diagnosis of PCNSL (diffuse large B-cell lymphoma subtype) was made. Post histopathological diagnosis, an Ommaya reservoir was inserted.

*Management and clinical progress*

The patient recovered well postoperatively and was commenced on combination chemotherapy by the haematology department. The protocol consisted of five 14-day cycles of R-MPV (Rituximab, Methotrexate, Procarbazine, Vincristine) with intra-Ommaya methotrexate between cycles [2]. The patient completed chemotherapy without major side effects, with resolution of his ONP. Post-chemotherapy brain MRI three months post-diagnosis demonstrated complete disease remission (Fig. 1). Given the patient's relatively young age and good performance status, whole-brain radiotherapy (WBRT) followed by high-dose cytarabine will be instituted with curative intent.

## Discussion

This is an unusual case of PCNSL presenting in the form of isolated ONP. ONP was most likely secondary to leptomeningeal lymphoma causing extrinsic compression of the OcN as it exited the midbrain via the interpeduncular cistern. This is reflected as irregular contrast enhancement of the interpeduncular cistern encasing the midbrain on contrast-enhanced MRI of the brain. A systematic review of the current literature revealed six previous cases of PCNSL presenting as isolated ONP [3–8]. In 1967, Braverman et al. [4] reported the case of a 59 year-old female with autopsy evidence of PCNSL in the basal leptomeninges and septum pellucidum with contiguous extension to the corpus callosum superiorly and hypothalamus caudally. The cause of ONP and distribution of intracranial lymphoma is very similar to the present case and is consistent with the predilection of intracranial lymphoma to involve the periventricular white matter and basal ganglia. In cases where diagnostic imaging was performed [3,5–8], all but one [6] revealed abnormalities of the cisternal or cavernous OcN accounting for ONP. Given advances in MRI of the OcN, and the near-universal enhancement of PCNSL post-contrast administration, contrast-enhanced MRI is a sensitive modality for demonstrating OcN involvement in cases of PCNSL presenting with isolated ONP.

Diagnostic evaluation of PCNSL focuses on histopathological assessment and confirmation of the absence of systemic involvement. The latter is crucial in therapy and prognostics as secondary central nervous system lymphoma is an aggressive, terminal form of non-Hodgkin lymphoma with a median survival of six months. As presented in the current case, thorough evaluation of suspected PCNSL with laboratory tests and diagnostic imaging in accordance with the International PCNSL Collaborative Group [9] is required, especially given reports of occult systemic disease in cases misdiagnosed as PCNSL. Prompt referral to the haematologists and oncologists, together with an interdisciplinary approach to diagnosis and treatment provides the best possible patient outcome.

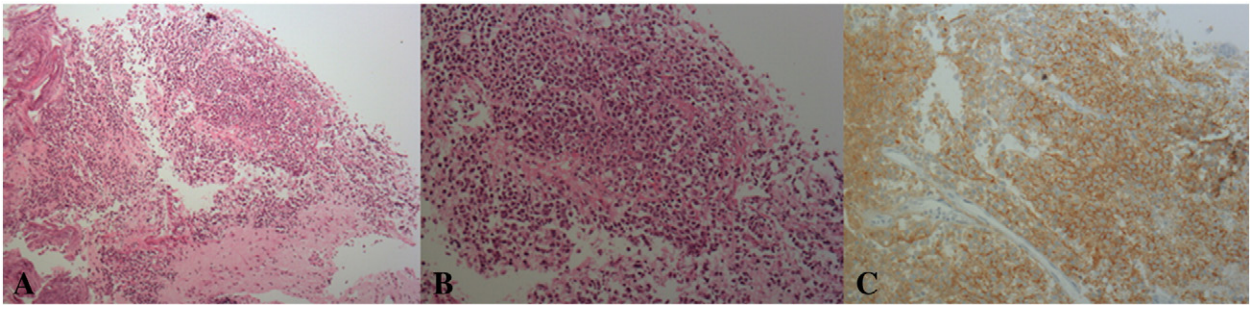


**Fig. 2.** Neoplastic cells comprising of sheets of atypical cells, hyperchromatic nuclei and scant cytoplasm. Frequent apoptotic debris, mitotic figures and focal necrosis noted (haematoxylin and eosin; original magnification ×10 [A] and ×20 [B]). Neoplastic cells are positive-staining for CD20 (C; Immunohistochemistry with haematoxylin and eosin counterstain; original magnification ×20).

The treatment of PCNSL is an area of active research with multiple on-going phase II trials. High incidences of neurotoxicity, especially in the elderly, have resulted in a shift away from WBRT as primary treatment towards regimens of combination chemotherapy with methotrexate as an anchor chemotherapeutic agent. Importantly, WBRT administered after combination chemotherapy does not extend overall survival in newly-diagnosed PCNSL [10] and there is a contemporary tendency to reserve WBRT to non/partial-responders to chemotherapy or relapses of PCNSL. An example is the protocol established by Morris et al. [2] and applied to the currently presented case. In this protocol induction chemotherapy with R-MPV followed by reduced or standard WBRT and consolidation cytarabine achieved a two-year progression free survival of 77%. Overall survival was not reached at a median of 5.9 years follow up. The use of intrathecal methotrexate remains an area of controversy, as retrospective studies have not shown a survival benefit [11], and the use of systemic high-dose methotrexate-based regimens likely result in attainment of therapeutic methotrexate levels in the CSF [12]. There are currently no prospective randomized trials specifically investigating the use of intrathecal methotrexate. Of note, leptomeningeal dissemination in PCNSL is not a negative prognostic factor in terms of overall survival and progression-free survival [13]. Neurosurgical intervention for PCNSL has traditionally been recommended in the form of tissue biopsy and the management of neurosurgical emergencies. However, in a secondary analysis of a phase III trial, Weller et al. [14] demonstrated improved overall and progression-free survival in patients undergoing subtotal or gross total resection as compared to those undergoing biopsy. Therefore, cytoreductive surgery for PCNSL, especially in cases where solitary lesions can be safely resected, should be considered in the management of PCNSL.

## Conclusion

In conclusion, isolated ONP is a rare presentation of PCNSL that neurosurgeons should be aware of. An interdisciplinary approach involving neurosurgeons, neuroradiologists, neuropathologists and neurologists is crucial, and thorough diagnostic evaluation including contrast-enhanced MRI and exclusion of systemic disease is paramount for disease management and prognostication.

## References

[1] Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. Primary intracerebral malignant lymphoma: report of 248 cases. J Neurosurg 2000;92(2):261–6.
[2] Curry RC, Correa D, Raizer JJ, Grimm SA, Lai R, Schiff D, et al. Consolidation reduced dose whole brain radiotherapy (rdWBRT) following methotrexate, rituximab, procarbazine, vincristine, cytarabine (R-MPV-A) for newly diagnosed primary CNS lymphoma (PCNSL): Final results and long-term outcome. J Clin Oncol 2012;30(15).
[3] Manabe Y, Kurokawa K, Kashihara K, Abe K. Isolated oculomotor nerve palsy in lymphoma. Neurol Res 2000;22(4):347–8.
[4] Braverman S. Reticulum cell sarcoma of septum pellucidum. Unusual case of third nerve paralysis presenting to the ophthalmologist. Arch Ophthalmol 1967;78(6):738–9.
[5] Galetta SL, Sergott RC, Wells GB, Atlas SW, Bird SJ. Spontaneous remission of a third-nerve palsy in meningeal lymphoma. Ann Neurol 1992;32(1):100–2.
[6] Berger JR, Flaster M, Schatz N, Droller D, Benedetto P, Poblete R, et al. Cranial neuropathy heralding otherwise occult AIDS-related large cell lymphoma. J Clin Neuroophthalmol 1993;13(2):113–8.
[7] Bhatti MT, Schmalfuss IM, Eskin TA. Isolated cranial nerve III palsy as the presenting manifestation of HIV-related large B-cell lymphoma: clinical, radiological and postmortem observations: report of a case and review of the literature. Surv Ophthalmol 2005;50(6):598–606.
[8] Park YM, Cho JH, Cho JY, Huh JS, Ahn JY. Non-Hodgkin's lymphoma of the sphenoid sinus presenting as isolated oculomotor nerve palsy. World J Surg Oncol 2007;5:86.
[9] Abrey LE, Batchelor TT, Ferreri AJM, Gospodarowicz M, Pulczynski EJ, Zucca E, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005;23(22):5034–43.
[10] 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. Lancet Oncol 2010;11(11):1036–47.
[11] Khan RB, Shi W, Thaler HT, DeAngelis LM, Abrey LE. Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? J Neuro-Oncol 2002;58(2):175–8.
[12] Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. J Clin Oncol 2000;18(17):3144–50.
[13] Korfel A, Weller M, Martus P, Roth P, Klasen HA, Roeth A, et al. Prognostic impact of meningeal dissemination in primary CNS lymphoma (PCNSL): experience from the G-PCNSL-SG1 trial. Ann Oncol 2012;23(9):2374–80.
[14] Weller M, Martus P, Roth P, Thiel E, Korfel A, German PSG. Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro-Oncology 2012;14(12):1481–4.