Multiple Cranial Nerve Involvement as the Initial Manifestation of Primary Central Nervous System Lymphoma

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Background: Primary central nervous system lymphoma (PCNSL) which mostly consists of B-cell lymphomas can be described as extranodal high-grade non-Hodgkin lymphoma that is limited to the central nervous system

Case presentation: We report a case of a newly-diagnosed retroviral-positive patient who first presented with multiple cranial nerve palsy, started with left facial asymmetry for three weeks and subsequently developed symptoms involving multiple neurological foci and eye manifestations. Blood investigations revealed a markedly elevated level of lactate dehydrogenase (LDH) and cerebrospinal fluid analysis showed the presence of Oligoclonal bands. Magnetic Resonance Imaging (MRI) of the brain and orbit revealed multiple brain hyperintense T2 lesions, enlarged extraocular muscle and perineural enhancement of the optic nerve. Diagnosis of central nervous system (CNS) lymphoma was eventually confirmed by biopsy of globus pallidus that showed diffuse large B-cell lymphoma however no specific treatment was initiated due to patient succumbed to death post biopsy.

Conclusion: Diagnosing PCNSL presents a diagnostic challenge due to its diverse clinical manifestation. It requires a high level of suspicion in immunocompromised patients presented with non-specific neurological and ophthalmic symptoms. Ideally, brain biopsy should not be delayed to establish a final diagnosis and initiate treatment.

Conflict of interest: None to declare.

Keywords: primary central nervous system lymphoma, B-cells lymphoma, immunocompromised, non-Hodgkin lymphoma, ocular lymphoma.

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Background

Primary central nervous system lymphoma (PCNSL) is a rare type of lymphoma with immunosuppression being the most important risk factor, although few immunocompetent individuals are also affected.[1,2] Primary central nervous system lymphoma (PCNSL) which mostly consists of B-cell lymphomas can be described as extranodal high-grade non-Hodgkin lymphoma that is limited to the central nervous system. It can affect any part of neuroaxis which includes the brain, spinal cord, meninges, cranial nerves, and eyes.[2,3] Despite recent advances, it is difficult to establish a prompt diagnosis

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of this disease owing to its rarity. In addition, the clinical features are often nonspecific thus definite diagnosis relies on advanced imaging techniques together with cytology and molecular study. These will result in delayed diagnosis as well as treatment. PCNSL that causing cranial or peripheral nerve infiltration is rare and account for about 3% of non-Hodgkin lymphoma.[4] A previous case-based review report stated that the PCNSL presented with multiple cranial nerves involvement carried difficulties in diagnosis and biopsy, routine CSF study and CSF flow cytometry were the common techniques used to confirm the diagnosis.[5] In this case report, we presented a case of multiple cranial nerve palsy as initial presentation of PCNSL preceded eye and systemic neurological signs and difficulties faced in establishing the diagnosis.

Case Presentation

A 42-year-old female with no known medical illness presented with sudden onset of right partially ptosis, double vision and right-sided headache for two months. Three weeks prior to presentation, she experienced left facial asymmetry and was diagnosed with left Bells palsy but defaulted treatment and follow up. There was no history of blurring of vision, systemic infective or malignancy symptoms or head trauma.

Eye examination revealed visual acuity of 6/6 in both eyes with a negative relative afferent pupillary defect (RAPD). Fundus examination was unremarkable. Intraocular pressure was normal at 14 and 14 in the right and left eye respectively. Cranial nerve examination showed right pupil sparing 3rd nerve palsy and left lower motor neuron (LMN) 7th cranial nerve palsy. The other cranial nerves were not involved. Systemic and other neurological examinations were normal. At this point, a diagnosis of multiple cranial nerves neuropathies to rule out brainstem lesions was made. Investigation on causes such as infective cause, myelinating disease and malignancies were done. Posterior communicating artery aneurysm was also suspected in view of 3rd cranial nerve palsy involvement.

Blood investigations revealed a markedly elevated level of lactate dehydrogenase (LDH) with a value of 800 IU/L(normal value <280 IU/L) and tested positive for human immunodeficiency virus, HIV. However, tuberculosis, syphilis, and toxoplasmosis tests were negative. Cerebrospinal fluid analysis showed the presence of Oligoclonal bands. Other parameters such as cell count, glucose and protein levels were within normal limits.

CT contrast of the brain and orbit showed no focal brain lesion or intracranial haemorrhages. The ventricles, CSF, cerebellum, brainstem and orbit were normal. CT brain angiography showed no evidence of aneurysm or arteriovenous malformation. An emergency MRI was planned but not done as the patient requested to be discharged. She also refused to be started on HIV treatment for the time being although being counselled to. Patient then did not showed up for her follow-up.

Two months later the patient presented with worsening of diplopia together with right upper and lower limb weakness for the past two weeks. Other symptoms were headaches and nausea. Cranial nerves examination showed right 3rd, 4th and 6th cranial nerve palsy signified by frozen eye, complete ptosis, along with fixed and dilated pupil. She also had bilateral LMN 7th nerve palsy and left 6th cranial nerve palsy. Other cranial nerve examinations were normal. The rest of the ocular examination was similar to the previous admission. However on the third day of admission, the patient developed a swollen left optic disc with multiple discrete chorio-retinal lesions in the nasal retina (Figure 1). At this point, a provisional diagnosis of primary CNS lymphoma was made.

Brain MRI showed multiple abnormal T2-hyperintense lesions at the body and splenium of corpus callosum, right superior cerebellar peduncle and right globus pallidus (Figure 2a). The lesions at the right globus pallidus are enhanced post IV Gadolinium while the rest of the lesions are not enhanced. No restricted diffusion on DWI images. No perilesional oedema, midline shift or mass effect seen. Lesions on brainstem might explained the present of facial nerve palsy although there was no obvious thickening of the VII nerve found in the MRI. Orbit MRI showed bulky left extraocular muscles (EOM) with reduced enhancement suggestive of oedema or inflammation. Her left optic nerve was bulky with perineural enhancement correlates with her swollen left optic disc. Right orbit and right EOM were unremarkable despite patient had total

ophthalmoplegia of the right eye (Figure 2b).

The patient then underwent an Image-Guided biopsy over the right globus pallidus lesion for definite diagnosis purpose as others investigation were inconclusive. The biopsy result showed glial tissue infiltrated by neoplastic lymphoid cells of high-grade B-cell lymphoma suggestive of diffuse large B-cell lymphoma (DLBCL) (Figure 3). Unfortunately, the patient succumbed to death 10 days after the procedure due to progression of the disease.

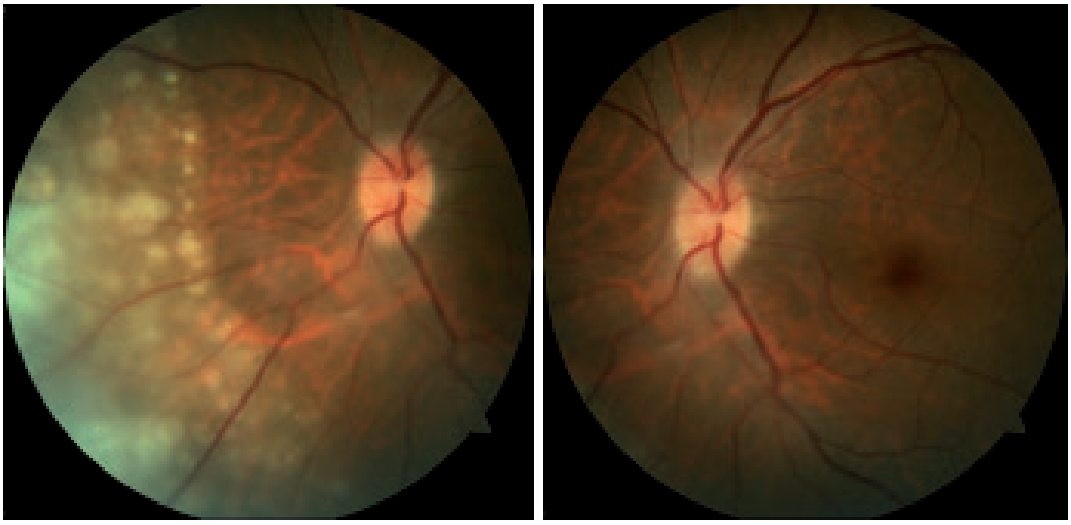
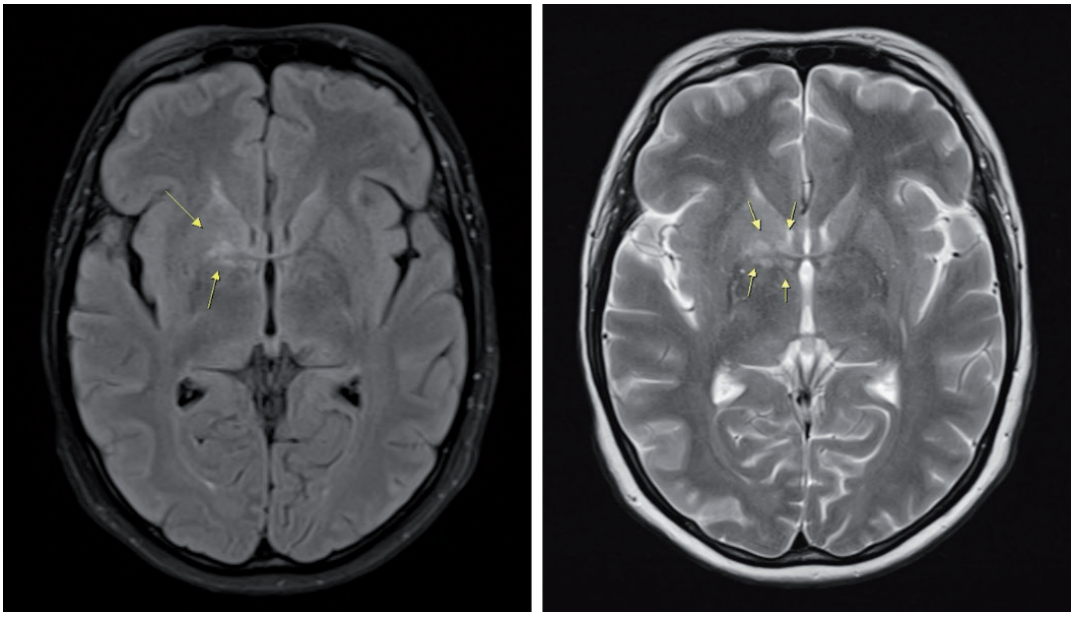


Figure 1: Fundus photo of the left eye showed swollen optic disc with multiple discrete choroidal retinal lesion (left picture : nasal part, right picture: macula region).



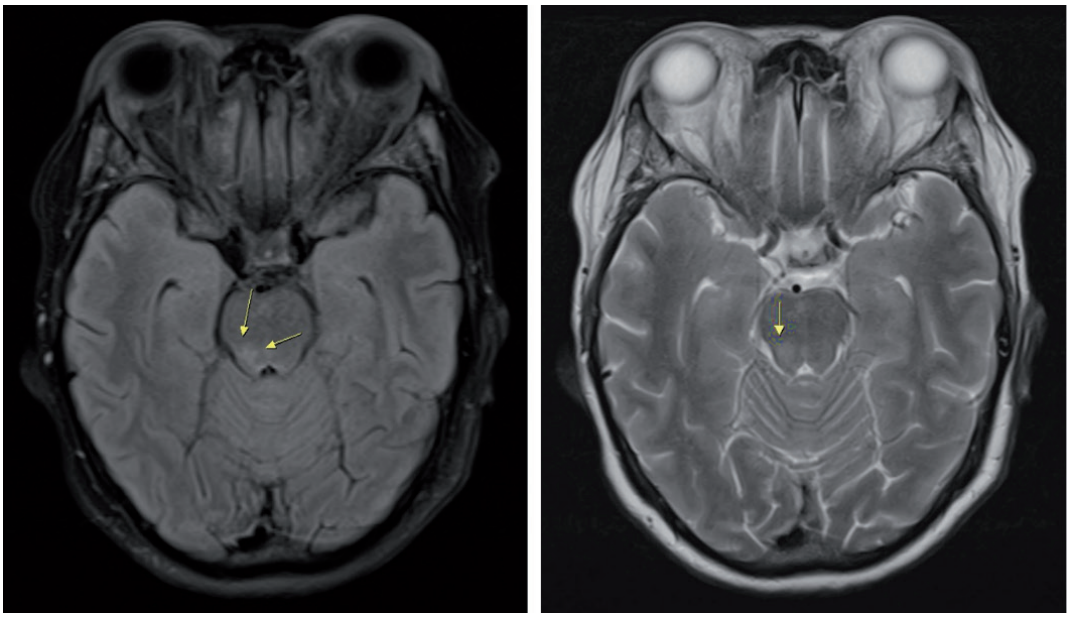


Figure 2a (left): Arrow showed multiple abnormal T2-hyperintense lesions at the body and splenium of corpus callosum and right globus pallidus(above) and , right superior cerebellar peduncle (below). Flair image (left) as comparison.

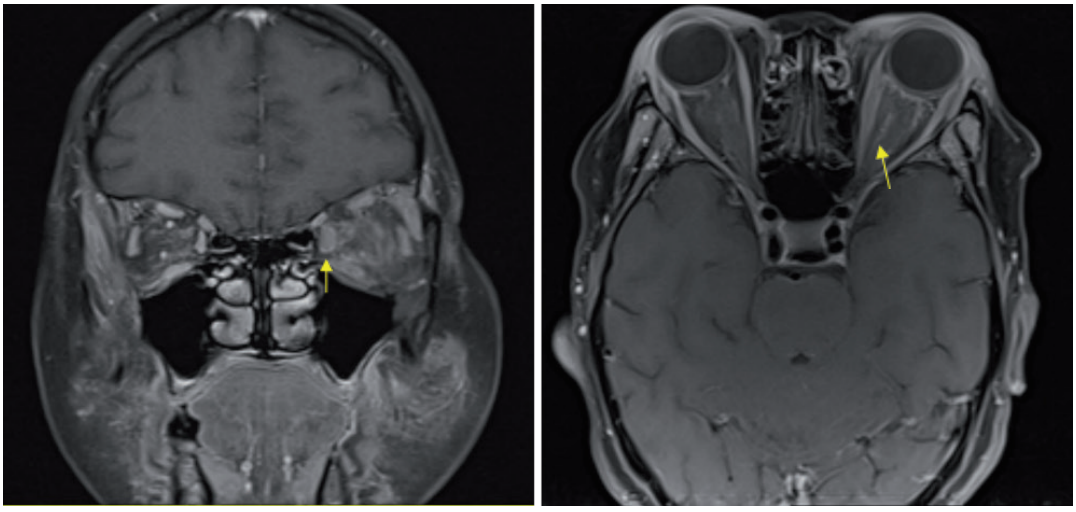


Figure 2b (right): Noted left bulky EOM and optic nerve compare to right EOM in MRI orbit

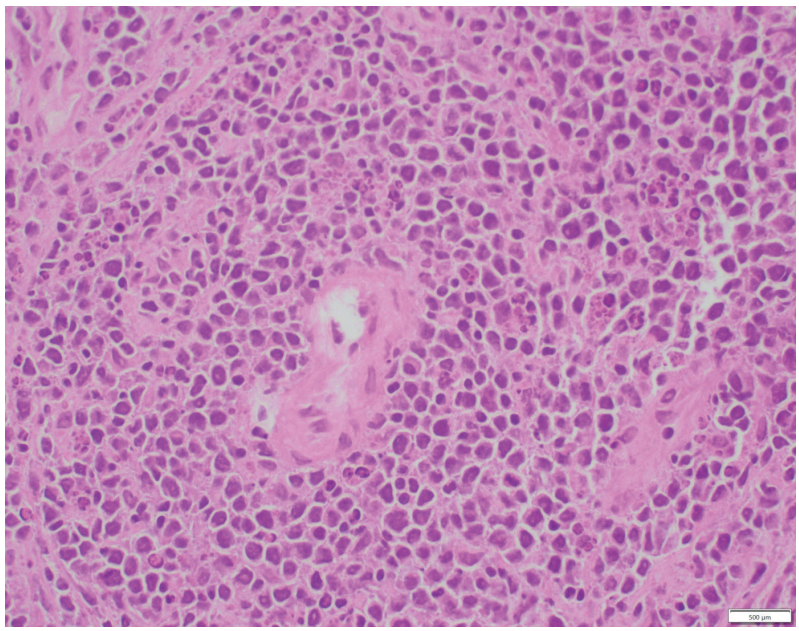


Figure 3: Histopathology image showed large B-cells lymphoma - glial tissue infiltrate by medium-large neoplastic lymphoid cells in diffuse cohesive manners

Discussion

Primary CNS lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma that comprises 0.8% to 6.6% of all primary CNS tumours, accounting for up to 1% of all lymphoma cases.[1,2] Diagnosing this disease often presents extra challenges due to the unspecific clinical presentation and neuroimaging characteristics. Patients may have symptoms that imitate other progressive neurologic disorders, such as primary brain tumour, demyelinating disease, paraneoplastic autoimmune disorders (PAD), or CNS infection. Thus, concrete diagnosis can only be made by biopsy.[3]

PCNSL has a variable clinical presentation depending on which part of the CNS is initially involved such as the brain, meninges, spinal cord, eyes or peripheral nerves. Initial presentation of multiple cranial nerve palsy is uncommon in PCNSL (around 3%), meanwhile, ocular involvement is present in 15-25% of patients with PCNSL at some point of the disease.[4 - 6] A case-based review and few case reports showed that all patient that had cranial nerve palsy as the presentation of PCNSL presented with facial nerve palsy and most of them presented with diplopia.[6-8] Our patient initially presented with multiple cranial nerve palsy; facial nerve palsy then diplopia, followed by focal neurologic manifestation, and lastly ocular manifestation.

There are no specific diagnostic serological studies for CNSL. However, elevation of LDH indicates the aggressiveness of this disease and it is a predictor of poor prognosis in non-Hodgkin lymphoma.[9] As immunocompromised patients are more likely to get PCNSL, early determination of HIV status is crucial.[5,10] While the presence of Oligoclonal bands in CSF fluid is routinely used for the evaluation of multiple sclerosis, it is also can be used for diagnosing paraneoplastic syndrome in the presence of abnormal cell count and protein levels.[11,12]

In immunocompromised patients, brain imaging findings of PCNSL will show multifocal abnormalities and peripheral enhancement, contrary to immunocompetent CNS lymphoma patients who have a homogenous enhancement pattern. Most cases (56-71%) present with multiple lesions as shown in our patient's MRI.[5,11-13] One of the lesson that can be learned from this case was if earlier MRI was done to this patient will result in a prompt higher suspicion of lymphoma hence an earlier biopsy could be done. About 95% of histology reports of PCNSL display diffuse large B cells (DLBC), while the remaining are low-grade B cell lymphoma, T cell lymphoma, and Burkitt lymphoma.[13-15]

Conclusion

Establishing the diagnosis of PCNSL could be very challenging due to its diverse clinical manifestation. It is vital to have a high degree of suspicion in immunocompromised patients presented with non-specific neurological and ophthalmic symptoms, including an urgent biopsy in the diagnostic plan. This will ensure a prompt diagnosis followed by adequate treatment for patients.

Declaration

Consent for publication

Due to the patient's untimely death after brain biopsy, the authors were unable to seek consent for publication. However, all details contained in this article have been sufficiently anonymized to protect the patient's identity.

Conflict of interest

None to declare.

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