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BILATERAL INFILTRATIVE OPTIC NEUROPATHY IN RELAPSED LYMPHORETICULAR MALIGNANCIES - A CASE SERIES

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ABSTRACT

Background: Leukaemic or lymphomatous infiltration of the optic nerve is a rare, but severe neuro-ophthalmology condition. Its diagnosis is often confused with either optic neuropathy due to infection, inflammation, optic nerve compression or side effect of chemotherapy or radiotherapy itself.

Case Series: In our series, there were four cases with bilateral infiltrative optic neuropathy secondary to lymphoreticular malignancies. Their ages ranged from 17 to 49 years of age. Two were male and two were female. Two patients had non-Hodgkin lymphoma, one had Hodgkin lymphoma (HL) and one had B-cell acute lymphoblastic leukaemia (B-ALL). All patients presented with acute reduced vision. Three cases also had diplopia and symptoms of increased intracranial pressure symptoms. Visual acuity upon presentation ranged from 6/6 to counting fingers. All cases had bilateral optic nerve swelling. Computed tomography (CT) scan in all patients showed optic nerve involvement. Two patients had obvious intracranial lesions, one patient with hydrocephalus only, while one patient had intraorbital lesion, with no intracranial involvement. All patients received chemotherapy. Three patients with central nervous system lymphoma had poor outcome. One patient with intraorbital involvement, survived.

Conclusion: Optic nerve infiltrations by lymphoreticular malignancies are rare. During disease recurrence or relapse, optic nerve involvement may be the first or only presenting feature. Thus, a high index of suspicion and early neuroimaging studies are important to assist in the diagnosis. In our review, optic nerve infiltration with CNS involvement has poor prognosis.

Keywords: Infiltrative optic neuropathy, lymphoreticular malignancy

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1.0 Introduction

Optic nerve (ON) infiltration by lymphoreticular malignancies is rare. It can be the only presenting feature in cases of relapse or recurrence of tumour. Identifying infiltrative optic neuropathy from other myriad causes of optic disc swelling like optic neuritis, infection increased intracranial pressure, ischemic optic neuropathy or treatment-related neuropathy is important in management of patient. We report four different clinical presentations of lymphoreticular malignancy with central nervous system (CNS) relapse.

2.0 Methods

This was a retrospective review of medical records of patients with bilateral infiltrative optic neuropathy secondary to relapsed lymphoreticular malignancies treated in the Ophthalmology Clinic of Hospital University Sains Malaysia between 2014 and 2018. Four patients were identified from the hospital records. Data collected included age at presentation, initial eye symptoms, investigations, treatment and outcome.

3.0 Case Series

3.1 Case 1

A 39-year-old lady with treated B-cell acute lymphoblastic leukaemia (ALL) in remission for the past one year presented with acute onset of mild progressive blurring of vision in both eyes for one week. It was associated with lethargy and significant loss of weight (more than 13 kg). Visual acuity was 6/6 bilaterally with normal anterior segments and intraocular pressure. Both pupils were sluggish. There was no relative afferent pupillary defect (RAPD) detected. Colour vision was impaired bilaterally. Extraocular eye movement showed restriction in right eye abduction. Humphrey visual field testing demonstrated enlarged blind spots in both eyes. Fundoscopy revealed bilateral optic disc swelling with disc haemorrhage, and tortuous dilated veins (***Figure 1a***). Computed tomography (CT) scan of brain was normal and cerebrospinal fluid (CSF) cytology examination showed no malignant cells. Patient was diagnosed to have bilateral infiltrative optic neuropathy secondary to CNS relapse B-cell ALL. A short course of systemic corticosteroids was given. However, the symptoms persisted. Additionally, she developed a right eye exotropia, right ear tinnitus and right facial weakness within that same month. Repeated CT (***Figure 1b***) scan revealed a heterogenous lesion at right temporal lobe with bone extension to the right parapharyngeal, right middle and external ear. The mass was biopsied and histopathology examination (HPE) showed malignant infiltration suggestive of recurrent CNS lymphoma. Patient was commenced on another course of systemic chemotherapy. However, patient succumbed to her disease after six months of CNS relapse due to sepsis.

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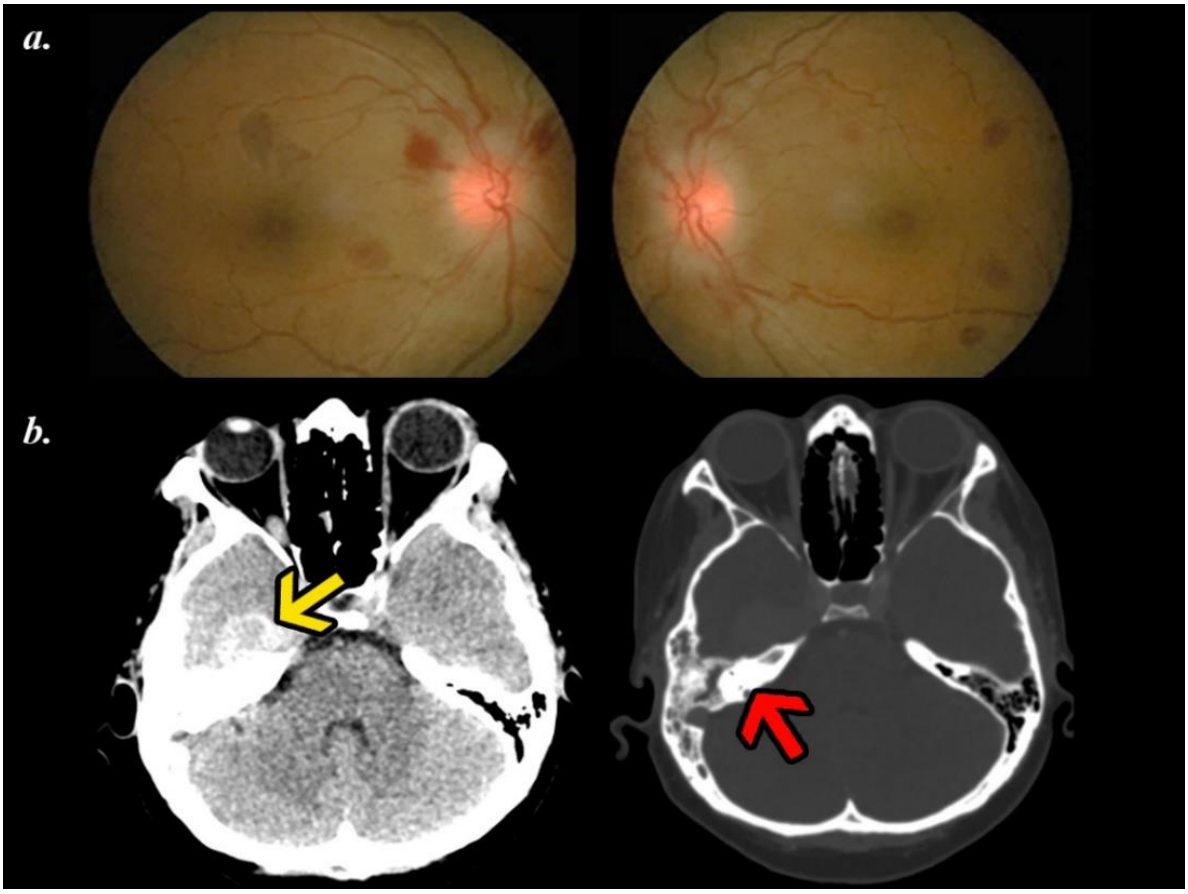

***Figure 1* – a.** *Bilateral optic disc swelling with disc haemorrhage and tortuous dilated veins.* **b.** *Contrasted CT axial revealed heterogenous lesion at right temporal lobe (yellow arrow) with bone extension to the right parapharyngeal, right middle and external ear (red arrow).*

3.2 Case 2

A 17-year-old boy with underlying Hodgkin lymphoma in remission for two years presented with sudden onset of blurring of vision in both eyes. Over the next two weeks, he also developed diplopia associated with an inwardly deviated right eye, right sensorineural hearing loss. On examination, he had right esotropia. There was no proptosis. The visual acuity was 6/6 bilaterally and the pupillary reflexes normal, with no RAPD. Colour vision was impaired and Humphrey visual field testing in both eyes showed enlarged blind spot. Fundoscopy showed bilateral optic disc swelling with disc haemorrhages (***Figure 2a***). The remainder of the posterior segment examination was normal. CT scan of the brain revealed presence of hydrocephalus (***Figure 2b***). Cerebrospinal fluid (CSF) cytology showed presence of monoclonal B cells (CSF flow cytometry). Patient was diagnosed to have bilateral optic nerve infiltration secondary to CNS relapse of Hodgkin lymphoma. Systemic chemotherapy was commenced. Unfortunately, he passed away within two months due to progression of disease with concurrent cryptococcal meningitis.

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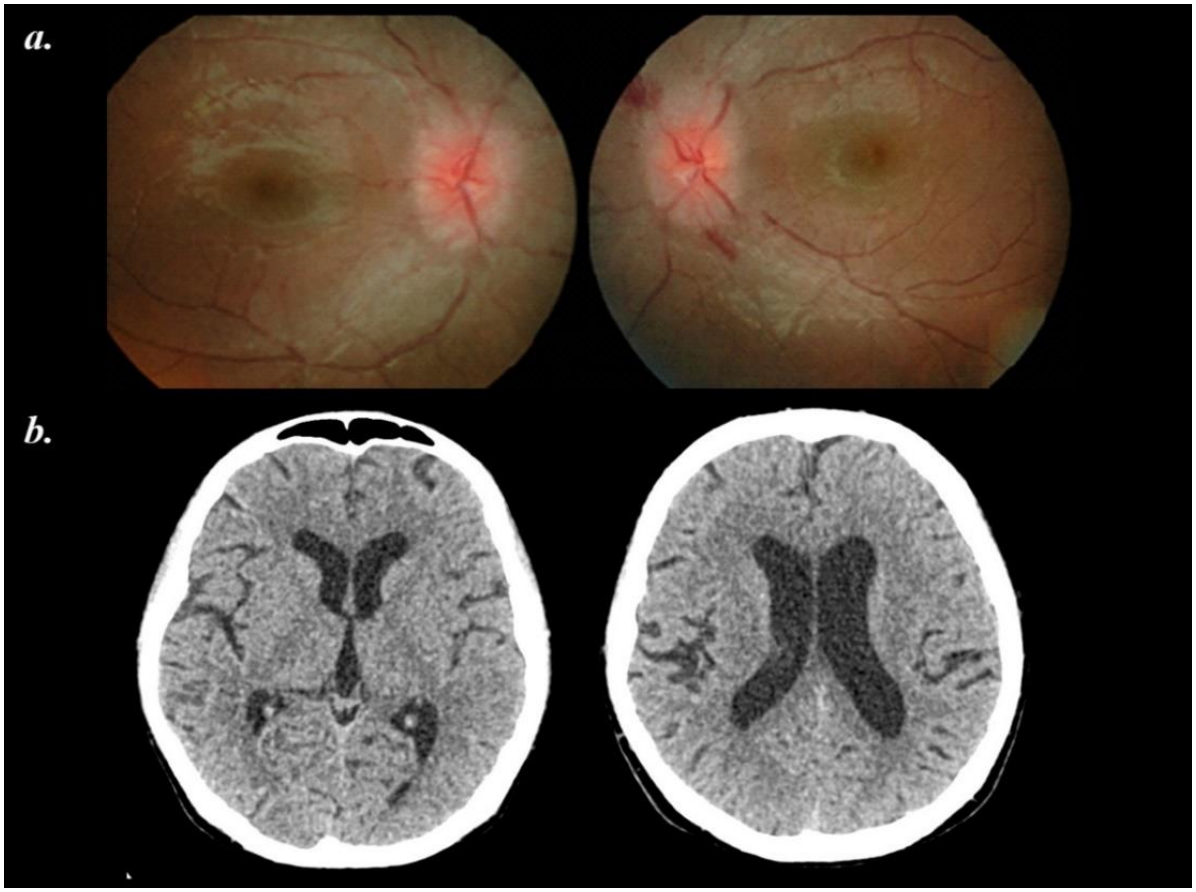

Figure 2 - a. *Bilateral optic disc swelling with flame shaped haemorrhage.* ***b.*** *Axial view CT brain showed hydrocephalus.*

3.3 Case 3

A 19-year-old female with primary mediastinal B-cell lymphoma diagnosed in 2014, presented a year later with bilateral blurring of vision for one week. She was on chemotherapy but defaulted treatment. She also presented with high intracranial pressure symptoms like headache, nausea and vomiting. Visual acuity in both eyes was 6/9. Pupillary reaction was normal with no RAPD. Anterior segment in both eyes was normal. Fundoscopy revealed bilateral optic disc swelling with disc haemorrhages and flame shaped retinal haemorrhages (***Figure 3a***). There were otherwise no vitritis or chorioretinitis. MRI of brain showed features suggestive of of cerebellar infiltration of lymphoma with generalised oedema and obstructive hydrocephalus (***Figure 3b***). Patient was diagnosed to have bilateral optic nerve infiltration secondary to CNS relapse B-cell lymphoma. She was restarted on a high dose chemotherapy. However, patient developed septicaemia and multi-organ failure after two months.

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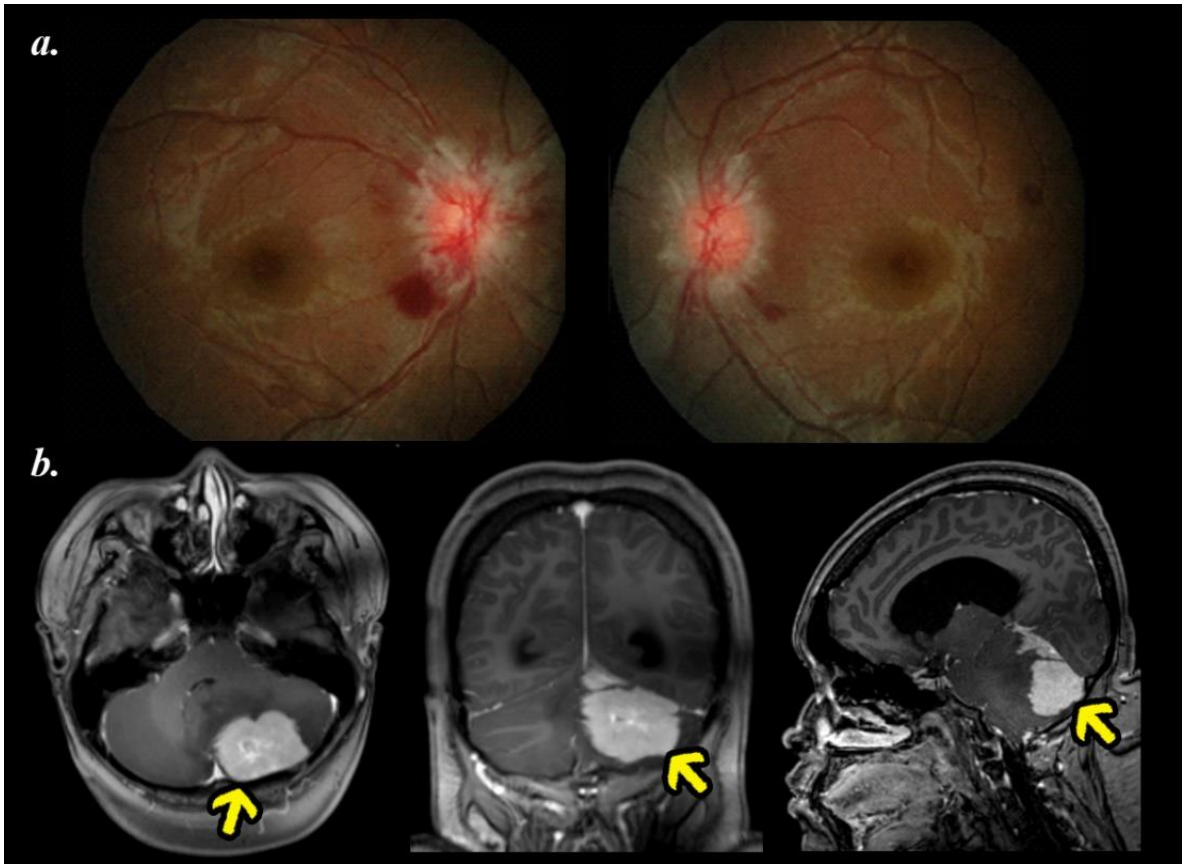

Figure 3 - a. *Bilateral optic disc swelling with flame shaped haemorrhage at disc and peripapillary region.* ***b.*** *MRI post contrast of brain showed lobulated heterogenous left cerebellar infiltration (arrows) with surrounding oedema with obstructive hydrocephalus.*

3.4 Case 4

A 49-year-old gentleman was diagnosed with non-Hodgkin lymphoma in 2010 when he was presented with left upper lid swelling. Biopsy was performed and HPE revealed left orbital lymphoma. Chemotherapy and local radiotherapy were commenced. After four years of remission, patient presented again in 2016 with sudden onset of right eye blurred vision. Visual acuity in the right eye were 6/120 and CF in the left eye. Bilateral anterior segment was unremarkable. Fundoscopy of the right eye ***(Figure 4a)*** showed swollen disc, macula oedema, dilated tortuous vein and pre-retinal haemorrhages. The left fundus view was impaired due to mature cataract ***(Figure 4b)***, attributed to previous local radiotherapy. B-scan of left eye suggestive of swollen optic disc. CT Scan of brain and orbit revealed relapse of left orbital lymphoma with bilateral optic nerve infiltration (***Figure 4c***). However no intracranial involvement. After completing three cycles of chemotherapy, patient achieve remission, and the right visual acuity improved to 6/36 with resolution of disc oedema.

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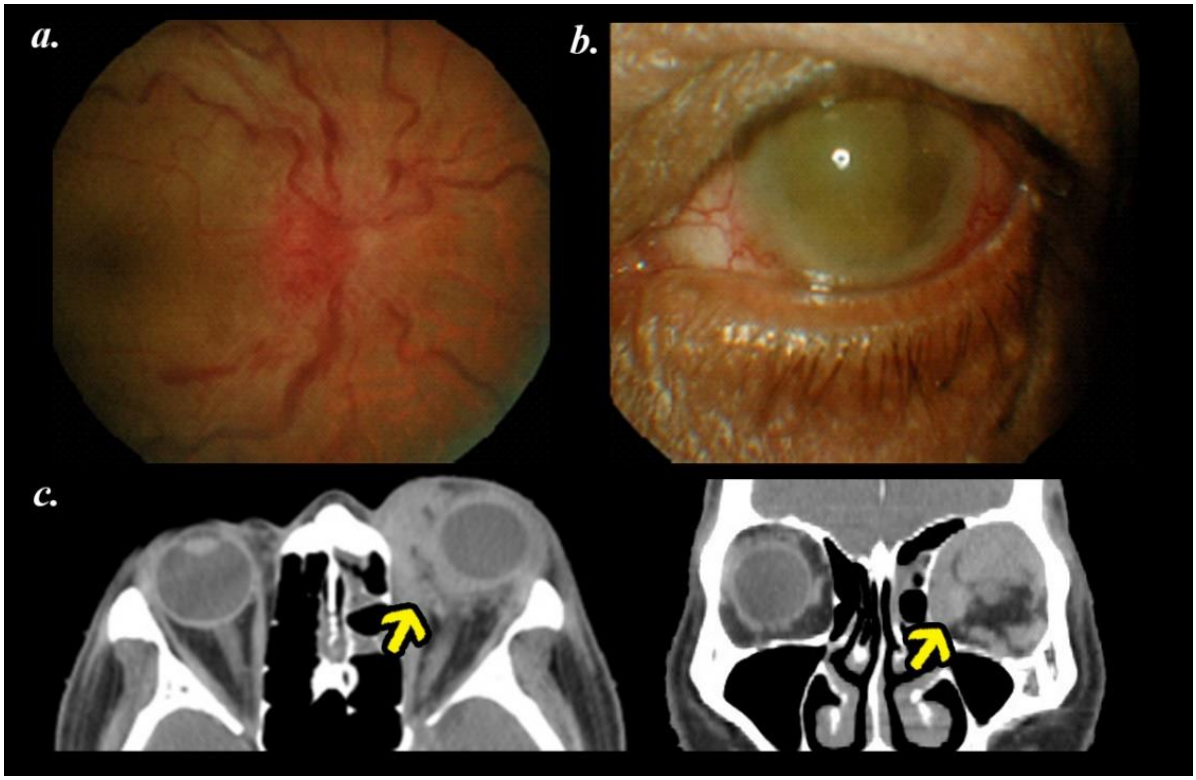

Figure 4 - a. *right eye showed swollen disc, macula oedema, dilated tortuous vein and pre-retinal haemorrhage.* ***b.*** *Left eye mature cataract.* ***c.*** *CT orbit revealed evidence of relapsed left orbital lymphoma (yellow arrow) with enhanced right optic nerve.*

4.0 Discussion

Reports of optic nerve infiltration as CNS relapse in context of systemic leukaemia and lymphoma was reviewed. 12 cases of leukaemia and 10 cases of lymphoma with CNS relapse published in PubMed from 1988 to 2017 were identified. ***Table 1*** and ***Table 2*** showed a summary of lymphoreticular disease type, laterality of presentation, investigation, treatment received and outcome.

In our review, all four patients range between 17 to 49 years old. Two were males and two were females. Two were diagnosed with Non-Hodgkin lymphoma, one with Hodgkin lymphoma and the other one was acute lymphoblastic leukaemia. All patients presented with an acute reduced vision and three cases had diplopia due to increased intracranial pressure. Visual acuity on presentation ranged from 6/6 to CF. Three cases had bilateral optic nerve swelling and one had unilateral involvement. Radio imaging study in all patients showed involvement of optic nerve with two patients had various brain lesions and hydrocephalus. One patient had a lesion at the temporal bone that extended to the parapharyngeal area. One patient had no involvement of the brain. All patients received specific regime of chemotherapy. Three patients with bilateral ON infiltration that presented as central nervous system relapse had poor outcome. One patient with sole intraorbital optic nerve involvement was survived.

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***Table 1*:** CNS relapse with optic nerve infiltration in leukaemia

Author (year)	Disease type	Laterality	CT/MRI	CSF	Treatment			Outcome
					Systemic chemo	Intrathecal chemo	Radio-therapy	
Nikaido (1988)	ALL	Unilateral	Swollen ON	Malignant cells	-	/	/	Optic atrophy and remission
	AML	Unilateral	Normal	normal	/	-	-	Passed away
	AML	Unilateral	Swollen ON	No CSF	/	/	/	Optic atrophy and remission
Fadhilah S. (2001)	ALL	Unilateral	Swollen ON	Proteins	-	-	/	Optic atrophy and remission
Mulvihill (2004)	AML	Unilateral	Swollen ON	Normal	/	-	/	Passed away
	ALL	Unilateral	Swollen ON	Normal	/	/	-	Passed away
	ALL	Bilateral	Swollen ON	-	-	-	/ & PBCT	Remission, VA improved
Hsuen F.L. (2005)	ALL	Unilateral	Swollen ON	Malignant cell	/	/	/	Passed away
Mateo (2007)	ALL	Bilateral	Normal	Normal	/	/	-	Passed away
Shah P (2011)	ALL	Bilateral	Swollen ON	Malignant cells	/	/	-	Remission, VA improved
Salazar (2014)	ALL	Unilateral	Swollen ON	Malignant cells	-	-	/	Passed away
Mbekaeni (2016)	CML	Unilateral	Swollen ON	Malignant cells	/	/	/	Remission, VA improved

AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia; CML = chronic myeloid leukaemia; PBCT = peripheral blood cell transplant Chemo = chemotherapy.

Lymphoreticular malignancies involving optic nerve is rare and account for 1% of all intracranial tumours and less than 1% of all intraocular tumour (Johnson et al., 2015). Review by Kenneth et al. (2017), ON infiltration by lymphoreticular malignancies are mainly by ALL (53%) and B-cell type NHL (67%) as compared to other leukaemia and lymphoma subtypes including acute myeloid leukaemia (AML), chronic lymphoblastic leukaemia (CLL), chronic myeloid leukaemia (CML), T-cell NHL and HL (Myers et al., 2016).

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***Table 2*:** CNS relapse with optic nerve infiltration in lymphoma

Author (year)	Disease type	Laterality	CT/MRI	CSF	Treatment			Outcome
					Systemic chemo	Intrathecal chemo	Radio-therapy	
Shunji K. (2000)	B-cell NHL	Bilateral	Swollen ON	Normal	-	-	/	Optic atrophy and remission
Kim U.R. (2010)	B-cell NHL	Unilateral	Optic nerve lesion	Normal	/	/	/	Regression of lesion. Final outcome NR
Finke E. (2012)	NHL	Unilateral	Infiltrated optic nerve	Malignant cell	-	/	/	Improved VA, but passed away
Ahle G. (2017)	7 cases of PCNSL	5 unilateral 2 bilateral	3 swollen ON 7 enhanced optic nerve	2 malignant cells 5 normal	/	-	-	2 partial recovery 5 blindness

NHL = Non-Hodgkin Lymphoma; CMSL = Primary central nervous system lymphomas; NR = not reported; Chemo = chemotherapy.

Optic nerve as sole initial presentation of CNS relapse is rare as 56-85% will have other CNS involvement during relapse or recurrence presentation (Aronow et al., 2015)(Coupland et al., 2004) including brain parenchyma, leptomeninges and spinal cord. CNS relapse rate in leukaemia and lymphoma patients is relatively rare with only 20-30% and 5-27%% respectively, especially in patients without any CNS prophylaxis treatment (Matoto, 2005; Jacoline, 2016). Isolated CNS relapse without systemic involvement only occur in less than 1% of patients with systemic NHL (Doolittle et al., 2008). Although previously thought to be rare, the incidence rate of CNS relapse is reported increasingly. This could be attributed to advancement in treatment therapy causing improved survival rate.

Optic nerve involvement is due to extension of CNS involvement, either by direct infiltration of the nerve head or by passive swelling secondary to increased intracranial pressure or obstructed cerebrospinal fluid (CSF) flow. Presence of associated parenchymal CNS lesion or lymphomatous meningitis will support the diagnosis of optic nerve infiltration (Ahle et al., 2017). Optic nerve is particularly susceptible to lymphoreticular malignancy relapse as optic nerve is believed to be the pharmacology sanctuary for disease that is relatively unaffected by systemic chemotherapy. Malignant cell may act as a mechanical blockage to CSF flow of systemic chemotherapy treatment. Thus, act as reservoirs for malignant cells (Leal et al., 2011).

Therefore, it is essential to have a high index of suspicion, as CNS disease involving ON infiltration is commonly confused with other aetiology namely inflammatory, autoimmune disease, infection, ischemic neuropathy or toxic effect of therapeutic drugs (Girmenia et al., 2006;Myers et al., 2016). Cytotoxic drug including vincristine, cyclosporin A, cytarabine,

deferoxamine, dasatinib and interferon alpha-2A has been reported to cause optic neuropathy, with both imatinib and methotrexate reported to cause disc oedema (Myers et al., 2016).

The most frequent symptom that might indicate CNS involvement include altered mental status (42%), headache (29%) and cranial nerve palsy (29-54.5%) (Doolittle et al., 2008). Tariq et al., (2008) reported only 6.5% patient presented with blurred vision as an initial complaint due CNS relapse (Al-Shujairi, 2008). Other symptoms reported include eye redness, pain and epiphora (Hsuen F., 2015). In a review by Kenneth et al. (2016), disc oedema with or without haemorrhage was the common findings with only four cases reported normal fundus at time of visual symptoms onset (Myers et al., 2016). In our case review, all our cases came with vague blurred vision that preceded other neurological complaints during CNS relapse. Three cases came with minimal visual loss of 6/6 to 6/7.5 with only one case came with vision of 6/120. However, all three cases showed exaggerated colour vision reduction which was disproportionate with vision loss accompanied with enlarged blind spot. In three out of four cases initial radiology assessment and CSF evaluation came back as normal, which delayed the recognition of the CNS relapse. This is consistent with review by Kenneth et al., (2016), that reported CT/MRI was normal in 43% of leukemic CNS relapse while most of lymphomatous CNS relapse had positive neuroimaging findings (Myers et al., 2016). Only two cases of CNS relapse in NHL were reported normal.

Examination of cerebrospinal fluids (CSF) for presence of malignant cells may help clinician to confirm diagnosis of CNS relapse. However, negative finding does not necessarily rule out the presence of direct optic nerve infiltrations. It has been reported that CSF analysis was found to be negative in 36% and 58% of leukaemia and lymphoma during CNS relapse respectively.
Thus, it is important for treating clinician to have a high index of suspicion. Patients with known history of lymphoreticular malignancies ought to have a prompt and thorough eye examination at onset of eye complaints. In an event of obvious ON infiltrations, treatment can be started early including orbital irradiation or intrathecal chemotherapy that may improve survival rate thus future prevent complications related to ON infiltration including central retinal vein obstruction (CRVO), central retinal artery occlusion (CRAO), neovascular glaucoma (NVG), and sequential retinal detachment (RD) (Kuo, 2014).

The diagnosis of ON infiltration is elusive and often delayed. This proved to be a challenge for treating physician in terms of accurate timely diagnosis and choice of treatment. CNS relapse that occur during disease progression or after recurrent of systemic disease, proves as an indicator of disease that will be refractory to therapy with bleak prognosis. Median CNS relapse duration was reported to be 1.8 year from time of initial diagnosis with range of 0.25-15.9 years (Doolittle et al., 2008). Survival rate is generally poor in CNS relapse. Padmantan et al., (2017) and Shah P et al. (2011) reported leukemic patients CNS relapsed with overall survival (OS) rate of six months to less than one year and projected five years OS of zero. Meanwhile, for CNS relapse in NHL, survival rate at one year and five years to be <10 % and <5% respectively (Gill and Jampol, 2001;Jacoline, 2013; Doolittle et al., 2008).

Review of 113 patients by Doolittle et al. (2007) reported 74% of patient deaths are mainly due to disease progression, while 15% is due to treatment related toxicity including dementia, leukoencephalopathy, septic shock, liver failure and pancytopenia. Thus, due to the grave

prognosis of patients with optic nerve infiltration with CNS relapse, early detection and tailored treatment strategies is crucial to increase survival rate (Doolittle et al., 2008).

5.0 Conclusion and recommendation

Sudden vision disturbance in a patient with underlying lymphoreticular malignancy should be followed by prompt and thorough ophthalmology assessment even in remission state. Subtle eye symptoms can be the only presenting symptoms of CNS relapse. Thus, early initiation of more aggressive chemoradiotherapy should be considered in CNS relapse as delayed treatment may lead to a grave prognosis.

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Declaration

The authors declare no conflict of interests. The authors are responsible for the content and writing of the paper.

Authors contribution

Author 1: Wrote the manuscript with consultation from author 4 and 5.
Author 2: Wrote the manuscript with consultation from author 4 and 5.
Author 3: Wrote the manuscript with consultation from author 4 and 5.
Author 4: Provided critical feedback.
Author 5: Provided critical feedback and supervised the whole process.

References

Ahle, G., Touitou, V., Cassoux, N., Bouyon, M., Humbrecht, C., Oesterlé, H., … Gaultier, C. (2017). Optic nerve infiltration in primary central nervous system lymphoma. *JAMA Neurology*, **74**(**11**), 1368–1373.

Al-Shujairi, T. A. (2008). Central Nervous System Relapse in acute Lymphoblastic Leukemia: Prognostic Factors and the Outcome. *Iraqi Academic Scientific Journal*, **7**(**4**), 339–346.

Aronow, M. E., Shen, D., Hochman, J., & Chan, C.-C. (2015). Intraocular lymphoma models. *Ocular Oncology and Pathology*, **1**(**3**), 214–222.

Coupland, S. E., Heimann, H., & Bechrakis, N. E. (2004). Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **242**(**11**), 901–913.

Doolittle, N. D., Abrey, L. E., Shenkier, T. N., Tali, S., Bromberg, J. E. C., Neuwelt, E. A., … Illerhaus, G. (2008). Brain parenchyma involvement as isolated central nervous system relapse of systemic non-Hodgkin lymphoma: an International Primary CNS Lymphoma Collaborative Group report. *Blood*, **111**(**3**), 1085–1093.

Finke, E., Hage, R., Donnio, A., Bomahou, C., Guyomarch, J., Sutter, C., … Merle, H. (2012). Retrobulbar optic neuropathy and non-Hodgkin lymphoma. *Journal Francais d'ophtalmologie*, **35**(**2**), 124-e1.

Gill, M. K., & Jampol, L. M. (2001). Variations in the presentation of primary intraocular lymphoma: case reports and a review. *Survey of Ophthalmology*, **45**(**6**), 463–471.

Girmenia, C., Pizzarelli, G., Cristini, F., Barchiesi, F., Spreghini, E., Scalise, G., & Martino, P. (2006). Candida guilliermondii fungemia in patients with hematologic malignancies. *Journal of Clinical Microbiology*, **44**(**7**), 2458–2464.

Johnson, J. S., Lopez, J. S., Kavanaugh, A. S., Liang, C., & Mata, D. A. (2015). A 25-year-old man with exudative retinal detachments and infiltrates without hematological or neurological findings found to have relapsed precursor T-cell acute lymphoblastic leukemia. *Case Reports in Ophthalmology*, **6**(**3**), 321–327.

Leal, T., E Chang, J., Mehta, M., & Ian Robins, H. (2011). Leptomeningeal metastasis: challenges in diagnosis and treatment. *Current Cancer Therapy Reviews*, **7**(**4**), 319–327.

Myers, K. A., Nikolic, A., Romanchuk, K., Weis, E., Brundler, M.-A., Lafay-Cousin, L., & Costello, F. (2016). Optic neuropathy in the context of leukemia or lymphoma: diagnostic approach to a neuro-oncologic emergency. *Neuro-Oncology Practice*, **4**(**1**), 60–66. doi:10.1093/nop/npw006

Chan, C.-C., & Wallace, D. J. (2004). Intraocular Lymphoma: *Update on Diagnosis and Management. Cancer Control, 11*(5), 285–295. doi:10.1177/107327480401100502

DeSouza, P. J., Hooten, C. G., Lack, C. M., John, V. J., & Martin, T. J. (2017). Bilateral Central Retinal Artery Occlusion Associated with Bilateral Lymphoproliferative Infiltrative Optic Neuropathy. *Ocular Oncology and Pathology*, *3*(3), 229–234. doi:10.1159/000458414

Hedayatfar, A., & Chee, S. (2012). Presumptive primary intraocular lymphoma presented as an intraocular mass involving the optic nerve head. *Journal of Ophthalmic Inflammation and Infection*, *2*(1), 49–51. doi:10.1007/s12348-011-0045-7

Kincaid, M. C., & Green, W. R. (1983). Ocular and orbital involvement in leukemia. *Survey of Ophthalmology*, *27*(4), 211–232. doi:10.1016/0039-6257(83)90123-6

Kuro, M., Matsuyama, K., Matsuoka, M., Kosaki, R., Shikata, N., Nishimura, T., & Takahashi, K. (2015). Case of Primary Intraocular Lymphoma with Extraocular Extension. *Ocular Oncology and Pathology*, *2*(2), 66–70. doi:10.1159/000439053

Palme, C., Bechrakis, N. E., Stattin, M., Haas, G., & Zehetner, C. (2016). Decreased Vision as Initial Presenting Symptom of Acute Lymphoblastic Leukemia: A Case Report. *Case Reports in Ophthalmology*, *7*(2), 377–383. doi:10.1159/000447994

Reports, C. (1988). Leukemic Involvement of the Optic Nerve, 294–298. doi:10.1016/0002-9394(88)90013-X

Sáenz-Francés San Baldomero, F. C., & Romea, J. (2007). Bilateral Papilledema Secondary to Chronic Lymphocytic Leukaemia. *Arch Soc Esp Oftalmol*, *82*, 303–306. Retrieved from http://www.oftalmo.com/seo/archivos/maquetas/E/2E883EBC-4B92-D0C9-AB8A-00001B5BEEFE/articulo.pdf

Sagoo, M. S., Mehta, H., Swampillai, A. J., Cohen, V. M. L., Amin, S. Z., Plowman, P. N., & Lightman, S. (2014). Primary intraocular lymphoma. *Survey of Ophthalmology*, *59*(5), 503–16. doi:10.1016/j.survophthal.2013.12.001

Yang, Q. T., Zhang, G. H., Liu, X., Ye, J., & Li, Y. (2012). The therapeutic efficacy of endoscopic optic nerve decompression and its effects on the prognoses of 96 cases of traumatic optic neuropathy. *Journal of Trauma and Acute Care Surgery*, *72*(5), 1350–1355.