

## **Bilateral Combined Retinal Vascular Occlusion: An Ocular Presentation in Central Nervous System Re-relapse of Non-Hodgkins Lymphoma**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author AC wrote the first draft of the manuscript. Authors AC and PS managed the literature searches, and author JC edited the final draft. All authors read and approved the final manuscript.*

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**Case Study**

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### **ABSTRACT**

**Aim:** We describe an atypical case of central nervous system (CNS) involvement in non-Hodgkins lymphoma (NHL), presenting with ocular manifestations.

**Presentation:** Here we present an extremely rare case of a 63 year old male with past history of relapsed NHL in remission with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, primarily presenting with bilateral sequential acute loss of vision without any systemic manifestations of relapse. On ophthalmological evaluation, he was found to have mixed central retinal artery and central retinal vein obstruction (CRAO & CRVO). CSF (cerebro-spinal fluid) evaluation revealed large B cell lymphoma cells. Management was initiated with triple intrathecal chemotherapy.

**Discussion:** NHL is the commonest type of ocular lymphoma, which is often the first manifestation of systemic relapse in cases of previous therapy. However, CRVO secondary to NHL is extremely rare. To the best of our knowledge, there are no previous reports of bilateral CRVO as a result of re-relapse of DLBCL presenting with features of ophthalmoplegia.

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**Conclusion:** Re-relapse as isolated CNS lymphoma at second remission in a patient with systemic NHL is quite rare. Although unlikely, bilateral combined CRAO & CRVO may be the first manifestation of relapsed CNS lymphoma. Hence, clinicians should have a raised index of suspicion in cases of NHL presenting primarily with sudden, total loss of vision.

**Keywords:** *Bilateral central retinal artery occlusion; central retinal venous occlusion; non hodgkin lymphoma; diffuse large B cell lymphoma; central nervous system; ocular lymphoma.*

## 1. INTRODUCTION

CNS involvement of systemic NHL may occur either primarily or as secondary spread of systemic disease, with the incidence varying from 1.6 to 22%, depending on the grade of malignancy [1]. Presentation may be varied, however, CNS re-relapse of NHL, presenting primarily with ocular manifestations is extremely rare. Although combined CRAO & CRVO secondary to systemic NHL has been reported [2], extensive literature review shows no previous reported cases of bilateral combined CRAO & CRVO in CNS relapse of NHL.

Spread of lymphomas to the CNS may occur through blood brain dissemination from the retroperitoneal glands or bone marrow to the leptomeninges, possibly through the intervertebral venous plexus [1,3]. It is essential to accurately diagnose such cases in order to initiate timely and appropriate management. CSF cytology is considered the gold standard investigation [4]. Other diagnostic modalities include immunocytology for cell surface antigen detection [5] and magnetic resonance imaging (MRI), which is highly sensitive for detection of meningeal pathology [6]. Flowcytometry and polymerase chain reaction (PCR) are other important diagnostic aids. Potential risk factors for CNS involvement of NHL during or after first line therapy include clinical parameters such as age, size of tumor, Eastern cooperation oncology group (ECOG) performance status of the patient, international prognostic index (IPI), laboratory parameters, lymph node involvement and extranodal involvement [1].

In primary intraocular lymphoma (PIOL), tumor cells are present only in the eyes without involvement of any other parts of the CNS [7] in cases of primary CNS lymphoma (PCNSL). Ocular involvement occurs in 15-25% cases of PCNSL and visual symptoms have been reported in only 8-10% cases [7]. Although our case involves CNS relapse of systemic NHL, and not PCNSL, the presenting features are comparable, which usually include floaters and decreased vision, red eye, features of uveitis.

Ophthalmic examination findings may reveal keratic precipitates, inflammatory deposits on the posterior cornea, cellular reaction in anterior chamber and vitreous strands. Retinal findings commonly seen include scattered punctuate retinal lesions, subretinal infiltrates, focal haemorrhages, retinal pigment epithelium perturbations and detachments [7,8,9].

Treatment includes radiation, combined radiation and chemotherapy or chemotherapy only regimens with intravenous or intrathecal agents using high dose methotrexate [7]. However, prognosis remains poor with CNS involvement of NHL [1,10].

## 2. CASE PRESENTATION

A 63 year old gentleman presented to casualty with acute loss of right eye vision. He had a four day history of headache with rapid loss of right eye vision while the left eye vision was unaffected. A previous medical history of NHL, being in remission following R-CHOP chemotherapy and a history of Parkinson's disease were noted. There was no obvious lymphadenopathy or hepatosplenomegaly. A normal computed tomography (CT) scan of the brain excluded cerebral haemorrhage, infarction or any space occupying lesion. Normal inflammatory blood serum markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) ruled out conditions such as giant cell arteritis.

The following day, he developed pain on moving the right eye. Visual acuity evaluation was done, which revealed no light perception (NPL) in the right eye and unaided 6/6 vision in the left eye. A right relative afferent papillary defect (RAPD) was detected along with mild restriction of movements in the right eye in all directions of gaze. He was also noted to have a 1 mm ptosis and 2 mm exophthalmos. Subsequent Fundoscopy of the right eye revealed a swollen right disc, four quadrant flame haemorrhages, a pale macula with cherry-red spot and 'cattle trucking' of the major vessels (Fig. 1). Left eye examination was entirely normal.



**Fig. 1. Fundoscopy right eye showing swollen optic disc, four quadrant flame haemorrhages and pale macula with cherry-red spot**

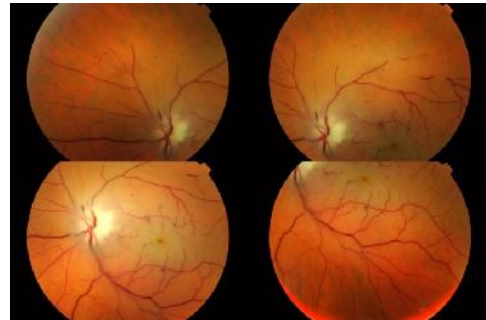
Right eye features were compatible with a generalised vascular stasis, with mixed CRAO & CRVO. A working diagnosis of right orbital apex syndrome (OAS) was made. However, scleritis and CNS involvement of NHL were considered as differentials. Subsequently, fine cut CT of orbits, with contrast was performed, which did not reveal any abnormality.

Treatment with high dose steroids was contemplated, however, in view of the patient having a history of two separate episodes of neutropenic sepsis following R-CHOP chemotherapy, lack of radiological evidence suggesting optic nerve compression and normal inflammatory serum markers, steroidal therapy was deferred till further haematological work-up to exclude recurrence of NHL although there were no systemic manifestations suggestive of recurrence or relapse of NHL.

The following day, the patient developed loss of vision in his previously unaffected left eye. Following haematological evaluation, he was administered with 1 gm of intravenous methylprednisolone. Visual acuity was that of bilateral NPL, with a complete right ptosis and gross bilateral ophthalmoplegia. However, the right fundus was unchanged in appearance, while the left fundus that earlier showed significant findings, appeared normal surprisingly.

CNS relapse of NHL was strongly suspected, with the possible explanation of cortical blindness due to occipital lobe involvement and non-arteritic anterior ischaemic optic neuropathy (NA-AION) secondary to R-CHOP toxicity. Repeat fine cut CT of orbits was normal. The following day, after the second dose of methylprednisolone, ophthalmological review showed bilateral NPL with dilated unresponsive

pupils. Fundoscopic features included bilateral swollen optic discs (Figs. 1 and 2). MRI was done and was suggestive of bilateral optic neuritis with possible optic atrophy. No compression or evidence of lymphoma was evident. Subsequent fundus fluorescein angiogram showed total absence of perfusion of the retinal vasculature, with only a slight flush of fluorescein at the cup of the optic discs after 6 minutes (Fig. 3). Choroidal perfusion was not patchy or delayed.

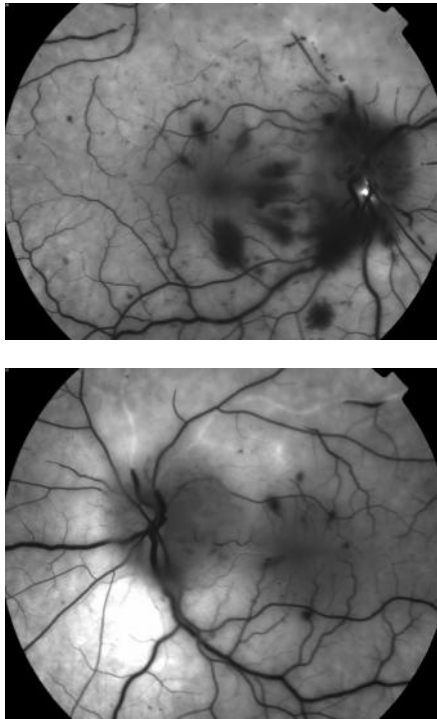


**Fig. 2. Fundoscopy left eye showing swollen optic disc, retinal haemorrhage and pale macula with cherry-red spot**

Cerebro-spinal fluid (CSF) evaluation revealed large B-cell lymphoma cells, hence confirming CNS involvement of lymphoma. This was followed by intrathecal chemotherapy with high dose methotrexate (7.6 gm), cytarabine 50 mg and hydrocortisone 50 mg. Eventually the patient developed pancytopenia with neutropenic sepsis, and unfortunately died two weeks after his initial presentation of vision loss.

### 3. DISCUSSION

Ocular involvement of NHL constitutes about 15-25% cases of PCNSL with only 8-10% cases presenting with primary ocular manifestations [7]. Although ocular involvement in cases of systemic NHL has been reported [2], primary ophthalmic presentation in cases of CNS relapse of NHL is an extremely rare entity. We did not come across any such previously reported cases after extensive literature review. Lymphomas constitute a heterogenous group of malignancies of the lymphoid system. The World Health Organization (WHO) has classified them into B cell and T cell types, with mature B cell neoplasms accounting for more than 85% cases [11]. Intraocular lymphomas are usually B cell type, and can be intraocular, orbital or adnexal, depending on the site of involvement [2].



**Fig. 3. Fluorescein angiogram of (a) Right eye and (b) Left eye demonstrating choroidal filling and lack of filling along arterioles and venules at 8 minutes**

An important pathogenetic feature of PIOL and CNL lymphoma is its localization within the neuraxis and eyes and their mechanism of spread within them. Systemic lymphoma cells may gain access to the CNS due to acquired selective homing receptors where they cannot be destroyed by the immune system; or may be derived from polyclonal inflammatory proliferations in the CNS [7,12].

In the present case, the patient initially presented with lymphadenopathy that was diagnosed as a low grade systemic marginal zone B-cell lymphoma and treated with six with cycles of rituximab, cyclophosphamide, vincristine and prednisone (R-CVP) regimen. Unfortunately, The lymphoma transformed into the more aggressive DLBCL, which was then treated with R-CHOP chemotherapy. Following the fourth cycle, the patient was noted to be in remission both clinically and radiologically. However, he subsequently presented with ocular manifestations and visual loss four weeks later.

Ocular lymphoma is often the first manifestation of systemic relapse in previously treated NHL [13], though, optic nerve and chiasmal disease is

unusual. The literature reports several cases of optic disc swelling secondary to lymphomatous infiltration of the optic nerves [14,15], but combined vascular occlusion secondary to NHL is extremely rare. Literature review shows four previous case reports with combined vascular occlusion secondary to NHL, with three cases describing unilateral combined vascular occlusion [16,17,18] and one case of mixed cell lymphoma with bilateral involvement [2]. We are unaware of any previous reports of bilateral combined vascular occlusion secondary to DLBCL with CNS relapse, associated with ophthalmoplegia.

The pattern of infiltration in ocular lymphoma may be suggestive of the source of infiltration. Ocular lymphoma associated with systemic disease often presents with involvement of the anterior segment or with uveal masses due to presumed haematological spread through the choroidal circulation. In contrast, CNS lymphomas tend to present with retinal masses, vitritis or with optic nerve and/or retinal vascular infiltration. Hollender et al. [1], in their study show that high grade NHLs are more likely to spread to the CNS, with only 2.8% patients with low grade NHL having CNS recurrence as opposed to 4.3% of high grade NHL with CNS recurrence. Hollender et al. further state that patients with high grade disease should receive CNS prophylaxis.

Treatment strategies include ocular radiation, combined chemotherapy and radiotherapy or chemotherapy alone with high dose methotrexate [7]. Ocular radiation may induce a variety of late complications such as radiation retinopathy, optic neuropathy, dry eyes, corneal epithelial defects, limbal stem cell loss, cataract, glaucoma and a high incidence of recurrence. Combined chemo-radiotherapy is used for majority cases; however, disease recurrence is quite frequent [7].

#### **4. CONCLUSION**

Sudden, dramatic loss of vision from 6/6 to beyond to NPL is very unusual for both arteritic and non-arteritic AION. Primary presentation with ocular manifestations and vision loss in known NHL warrants a raised index of suspicion for CNS involvement. Such cases should be thoroughly investigated in order to ensure proper and timely intervention, though the prognosis remains dismal.

#### **CONSENT**

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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