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*Original Article*

# Epidemiology and clinical features of intraocular lymphoma in Singapore

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## Abstract

**Introduction:** Intraocular lymphoma is rare. There are very few studies on intraocular lymphoma published from Asian countries.
**Objective:** To report our case series of intraocular lymphoma patients from a tertiary eye centre in Singapore.
**Subjects and methods:** Nine patients with intraocular lymphoma managed between January 2005 and December 2014 were identified from Ocular Autoimmune Systemic Inflammatory Infectious Study (OASIS) database. Demographic characteristics, clinical presentation, investigations performed and outcomes recorded.
**Results:** There were almost equal distribution between males (four patients) and females (five patients) with mean age of presentation was 60.3 years. Five patients had bilateral involvement and vitreo-retina was the most common site of infiltration. All of our patients had central nervous system involvement although four of them had presented with ocular manifestations initially. Anterior chamber fluid cytology, as a less invasive alternative to vitreous analysis was proven to be useful. The time from ocular presentation to diagnosis of ocular lymphoma was variable; from one day to 18 months. Mortality in our study group was 55% with death occurring 1 month to 8 years from diagnosis of intraocular lymphoma.
**Conclusion:** Intraocular lymphoma is a masquerade syndrome that mimics chronic uveitis and poses a diagnostic challenge. The diagnosis is often delayed and despite the eventual diagnosis, the disease prognosis is poor even with aggressive treatment.

**Key words:** intraocular lymphoma, uveitis, masquerade syndrome

## Introduction

Intraocular lymphoma is a rare malignancy that invades intraocular tissues; the retina, vitreous, and/or optic nerve. Intraocular lymphoma can be classified as primary which can be primarily ocular or oculo-central nervous system (PCNSL); and secondary when it spreads to the eye from a systemic malignancy (Augsburger and Greatrex, 1989). Primary intraocular lymphoma can also be classified based on the location in the eye that is affected; into primary vitreoretinal lymphoma (PVRL) and primary uveal lymphoma. The most common form of PVRL are of B-cell origin and associated with primary CNS non-Hodgkin's lymphoma. T-cell

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origin occur rarely. Primary uveal lymphoma usually present with localized uveal mass with extraocular extension, typically extranodal marginal zone lymphoma (mucosa-associated lymphoid tissue B-cell lymphomas) type(Tang, Gu and Zhang, 2017).PVRL is highly associated with PCNSL and studies have shown that approximately 80% of PVRL patients eventually develop PCNSL and approximately 20% of PCNSL patients present with PVRL (Hong *et al*., 2011).

There are very few studies on intraocular lymphoma published from Asian countries, although recently there were a few reports from Japan and Korea(Lee *et al*., 2015;Kimura, Usui and Goto, 2012). We aim to report our case series of intraocular lymphoma patients from Singapore.

## Subjects and Methods

A retrospective study was done on all patients diagnosed with intraocular lymphoma seen at a uveitis subspecialty clinic at a tertiary referral eye care centre in Singapore from January 2005 to December 2014. Ethics approval was obtained from the local institutional review board and the study was conducted as per tenets of declaration of Helsinki.

A total of nine patients with intraocular lymphoma were identified from the OASIS database (Ocular Autoimmune Systemic Inflammatory Infectious Study database from 2004 -2015). Their medical records were reviewed for demographics; which included gender, race, age and co-morbidities on presentation. Comorbidities assessed included any systemic lymphoma diagnosis, HIV status, and if the patients were undergoing any immunosuppression therapies such as chemotherapy, radiation or steroids.

Clinical information collected included presenting symptoms (e.g. floaters, pain, redness or proptosis) and visual acuity on presentation. Ocular and systemic manifestations were recorded. All patients had ophthalmic history taken and examination at the time of presentation consisting of Snellen visual acuity (VA), slit-lamp examination, Goldmann applanation tonometry (GAT) and fundus biomicroscopy. The primary site of inflammation was classified using the Standardization of Uveitis Nomenclature (SUN) working group anatomic classification of uveitis. Ancillary ocular investigations, such as fundus fluorescein angiography, indocyanine green angiography, optical coherence tomography, auto-fluorescence and ultrasonography scan, were performed as clinically indicated.

Patients were co-managed with neurologists, oncologists and haematologists as clinically indicated. All nine patients had contrasted cranial magnetic resonance imagining (MRI) and/or computed tomography (CT) to detect central nervous system (CNS) lesions. Further investigations such as lumbar puncture, lymph nodes or bone marrow biopsies, if performed were recorded in the database. Treatment modalities performed as well as their progress on follow-up visits were reviewed.

## Results

Nine patients were found to have diagnosis of intraocular lymphoma from the OASIS database; a total of 2015 patients with uveitis condition at the time of writing. Table 1 shows the demographic characteristics and clinical information of the patients enrolled in this study. There was a slight preponderance of female patients at 56%; with mean age of 60.3 (Range: 41-75) years at presentation.

The most frequent presenting complaint was blurring of vision and floaters (six patients). This was followed by redness (four patients) and pain in the eye(one patient). The visual acuity on presentation ranged from 6/6 to hand movement vision. Five patientspresented with bilateral involvement with vitreo-retina being the most common site of infiltration.

**Table 1: Nine patients included in the study with their demographics, ocular symptoms and presentations, visual acuity at presentation, systemic organs involved, sequence of ocular/ systemic involvement, positive diagnostic test, duration from ocular presentation to diagnosis and treatment received**

| Patient | Gender/ Age | Ocular symptoms | Ocular presentation | VA at presentation | Systemic involvement | Sequence of Ocular/Systemic diagnosis | Positive Diagnostic test | Ocular presentation to diagnosis | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F/56 | BE redness and BOV | Bilateral AC cells and vitritis | BE hand movement | Left parieto-occipital lesion, scar epilepsy | Systemic→ocular | AC tap | 1 month | WBRT |
| 2 | F/70 | LE BOV and floaters | Unilateral AC cells and mutton-fat KP | LE 6/21 to 6/18 (ph) | Left parieto-occipital tumour | Ocular→systemic | Vitrectomy (positive on second attempt) Biopsy of left occipital tumour | 9 months | CMT IVT MTX |
| 3 | M/75 | BE BOV and floaters | Bilateral AC cells, vitritis, subretinal lesions and exudative RD | RE CF, LE 6/60 | Left frontal brain mass | Ocular→systemic | Vitrectomy | 2 months | Chemo IVT MTX |
| 4 | F/44 | LE floaters | Unilateral Vitritis | LE 6/6. | Multiple lesions in both cerebral hemispheres | Ocular→systemic | Vitreous tap biopsy of left frontal lobe lesion | 18 months | CMT |
| 5 | F/64 | BE BOV | Bilateral AC cells and choroidal lesions | RE 6/12, LE 6/24 | Liver, spleen, right kidney lesions | Concurrent ocular and systemic | Lymph node biopsy LP | Same day | CMT |
| 6 | M/41 | BE redness and BOV | Bilateral Subretinal lesions, bilateral discs swelling and exudative RDE | RE CF to 6/120 (ph), LE 6/120 to 6/45 (ph) | *HIV positive 6th and 7th nerve palsies Lung and bilateral kidney masses Stomach and small bowel thickening with nodularity in the greater omentum | Concurrent ocular and systemic | LP BMA OGD biopsy Skin biopsy | 6 days | Chemo |
| 7 | M/63 | LE redness and pain | Unilateral AC cells and pseudohypopyon | LE 6/9. | Tonsillar lymphoma, laryngeal cancer | Systemic→ocular | AC tap | 1 month | Chemo |
| 8 | M/67 | LE redness and floaters | Unilateral AC cells and pseudohypopyon | LE 6/9 to 6/6 (ph) | lymphoma of pleura, bone marrow, CNS and subcutaneous soft tissues | Systemic→ocular | AC tap LP BMA | 4 days | Chemo IVT MTX |
| 9 | F/63 | BE BOV and floaters | Bilateral vitritis | RE 6/9, LE 6/7.5-1 | Lung and spleen masses | Ocular→systemic | Vitrectomy | 5 months | CMT IVT MTX |

Abbreviations: F, female; M, male; AC, anterior chamber; BOV, blurring of vision; BE, both eyes; LE, left eye; RE, right eye; VA, visual acuity; ph, pinhole; RD, retinal detachment; OGD, oesophago-gastroduodenoscopy; WBRT, whole brain radiotherapy; KP, keratic precipitate; LP, lumbar puncture; CMT, combined modality therapy; Chemo, chemotherapy; BMA, bone marrow aspiration; IVT MTX, intravitreal methotrexate.

Interestingly, there was a predilection for the left eye in all the four patient that had unilateral presentation. Clinical presentations included anterior chamber inflammation (six patients), vitritis (five patients), subretinal lesions with exudative retinal detachment (two patients) (Figure 1), choroidal lesions (one patient) and optic nerve infiltration (one patient). Two patients presented with severe inflammation that caused pseudohypopyon and one patient had mutton-fat keratic precipitates. Five patients had central nervous system findings and seizure was the most common presentation, which was found in three patients; followed by alteration in cognitive function seen in two patients. None of the nine patients had hemiparesis or cerebellar signs.

Ocular presentation to diagnosis of ocular lymphoma ranged from one day to 18 months. Four of our patients presented with ocular

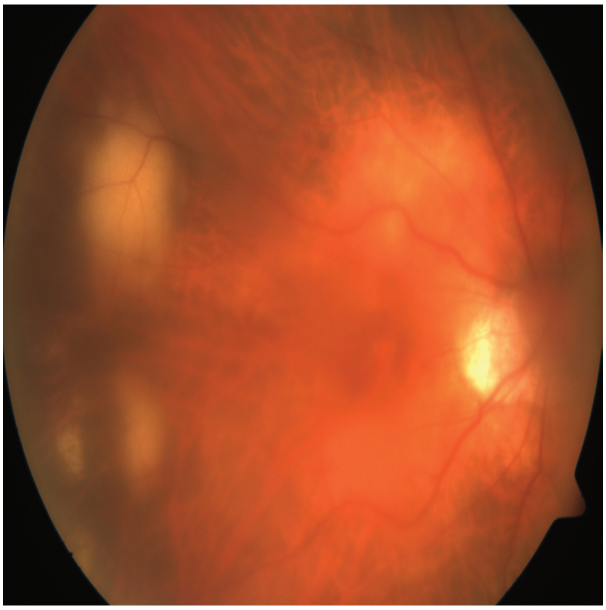

**Figure 1:** Right eye fundus photo of patient 3 showing hazy view due to vitritis and multiple subretinal lesions and exudative retinal detachment seen at temporal retina.

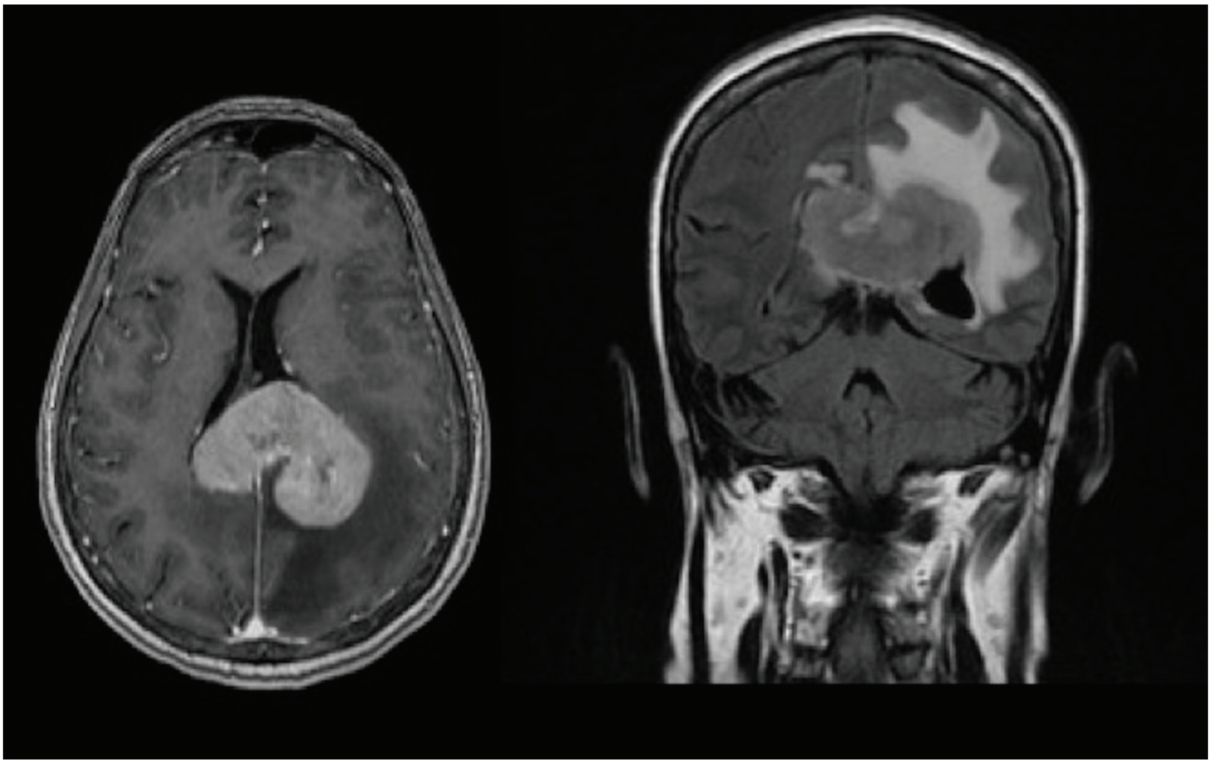

**Figure 2:** T1 Magnetic resonance imaging of the brain of patient 1 showing cerebral lymphoma infiltration in axial and coronal view of infiltrative lesion in splenium of corpus callosum with the bulk of the lesion in the left side of the midline.

symptoms first but were diagnosed with systemic lymphoma infiltration eventually. All of our patients had both ocular and systemic lymphoma involvement. Two patients presented with concurrent ocular and systemic symptoms, leading to earlier diagnosis of lymphoma. Eight patients were diagnosed with diffuse large B-cell lymphoma and one had skin biopsy and cerebrospinal fluid (CSF) cytology showing intermediate features between diffuse large B-cell lymphoma and Burkitt's lymphoma. Anterior chamber paracentesis was performed in four patients and three patients demonstrated atypical lymphoid cells by cytospin technique (Finger*et al.*, 2006).

Tissue biopsy of other sites were performed depending on their corresponding systemic involvement suspected. A total of four patients underwent bone marrow aspiration and two patients had bone marrow infiltration by lymphoma demonstrated (patient 6 and 8). Lymph node biopsy was performed and positive in one patient in our study. Two out of four of our patients had lymphoma findings in CSF when lumbar puncture was performed.

The imaging modality performed in these patients was tailored to their ocular and systemic findings. In our study group, fundus fluorescein, indocyanine green, optical coherent tomography and auto-fluorescence studies were not clinically useful due to the hazy media caused by the anterior chamber inflammation and vitritis and therefore performed only when there is a view of the fundus. Ultrasonography brightness scan (B-scan) was performed in four patients but mainly to determine that the retina was flat and to document the amount of vitreous opacities. All nine patients underwent cranial magnetic resonance imagining (MRI) to look for central nervous system involvement (Figure 2) and computed tomography (CT) of the thorax/abdomen/pelvis to look for systemic lymphoma infiltration.

The choice of therapy for our patients was made by the ophthalmologist, haematologist or/and oncologist based on the systemic involvement, severity and recurrence of the disease. The most common treatment modality was systemic chemotherapy (eight patients) and four of them also received radiotherapy (whole brain radiotherapy). Four patients had local intravitreal methotrexate. The low number of intravitreal methotrexate also likely due to patient's aversion to injection into the eye as the study period was in the era before the widespread use of intravitreal injections.Patient 1 only had whole brain radiotherapy without systemic chemotherapy as she was very ill and unable to tolerate systemic chemotherapy. The range of chemotherapy drugs used in our patients was wide which included intravenous rituximab, intravenous methotrexate, R-CHOP therapy (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin and Prednisolone), R-EPOCH therapy (Rituximab, Etoposide, Prednisolone, Oncovin, Cyclophosphamide and Hydroxydaunorubicin) and R- ESHAP therapy (Rituximab, Etoposide, Solu-medrol, Ara-Cytarabine and Platinol). The reason for the variation in treatment protocol was likely due to the lack of standard protocol for the treatment of intraocular lymphoma and difference in physicians' and patients' preferences. Prognosis is poor with mortality in our study group at 55% with death occurring 1 month to 8 years from diagnosis of ocular lymphoma.

**Discussion**

Intraocular lymphoma is rare and it accounts for <0.01% of ophthalmic disease (Chan *et al.*, 2011). This is reflected in our study as only nine patients (0.004%) out of 2015 patients were found to have diagnosis of intraocular lymphoma in our centre from January 2005 to December 2014.This low number, however, could be biased towards patients presented with mild ocular diseases and subsequently diagnosed with ocular lymphoma as the more severe lymphoma cases were mostly referred to the national cancer unit for management.

The mean age of presentation of 60.5 years old correlated with many other reports, suggesting that intraocular lymphoma typically occur in older patients in the range of 60s (Chan and Sen, 2013). There were seven Chinese and two Malay patients included in this study. It is not surprising to see more Chinese patients in our study group as the Chinese constituted the majority of the population in Singapore. A collaborative international study would be required to look for any significant difference between the races, although there appears to be no racial predilection of the disease reported in other studies Sagoo*et al.*, 2014). Most case series also suggested a gender bias with more women being affected than men, and this is also reflected in our study (Berenbom *et al.*, 2007) even with our small number of patients. Despite the possible attribution of Human Immunodeficiency Virus (HIV) (Mochizuki and Singh, 2009), only one of our nine patients was diagnosed to be HIV-positive (patient 6).

The higher suspicion for lymphoma especially when patient presenting with systemic symptoms concurrently (patient 5 and 6) led to earlier diagnosis of intraocular lymphoma. The rest of the patients, however, had extensive systemic investigations to rule out infection and other inflammatory disease which was a major cause for the delay in diagnosis. In contrary to most reports that anterior segment inflammatory findings are frequently absent, (Chan and Sen, 2013) our patients had significant anterior chamber inflammation with six patients presented with panuveitis and two patients had pseudohypopyon on presentation.

The gold standard for diagnosing PVRL involves the detection of malignant lymphoid cells in the retina, vitreous or optic nerve(Rajagopal *et al.*, 2011) . Vitreous analysis had good yield with positive results when performed in four of our patients (one via vitreous tap and three vitreous biopsies via vitrectomy). Pars plana vitrectomy is known to be beneficial to clear the vitreous debris therefore improving vision and maximizing the sample size. However, vitrectomy poses ocular as well as anaesthetic risks. Multiple vitreous biopsies may be required to reach a pathological diagnosis. There is also risk of extension of the lymphoma through the sclerotomy port to the epibulbar space following vitrectomy(Cursiefen*et al.*, 2000). Among our patients, only one patient (patient 2) required a repeated vitrectomy and had positive vitreous biopsy result from the second vitrectomy. There were no ocular or systemic complications reported in our patients.

Three out of four of our patients (patient 1,7 and 8) who presented with anterior chamber activity had lymphoma cells detected on cytology from the aqueous fluid tap. Although usually considered as an inferior diagnostic approach to vitreous analysis, anterior chamber paracentesis cytology (cytospin technique) was proven to be effective and less invasive alternative (Finger *et al.*, 2006). It is a cheaper, easier with relatively low risk procedure that could done in clinic setting as compared to vitrectomy. Based on this observation, we recommend performing anterior chamber tap as an early diagnostic test especially in patients with severe anterior chamber inflammation or pseudo-hypopyon. It is also important to remember that ocular fluids removed (via aqueous tap, vitreous diagnosis or diagnostic vitrectomy) need to be delivered quickly to the lab for analysis to prevent cell degeneration that can make diagnosis difficult(Tang*et al.*, 2017).

CSF for cytology and flow cytometry was performed in four of our patients (patient 5,6, 8 and 9) but only two patients (patient 6 and 8) had positive yield. Despite the low yield for lymphoma cells in the CSF, lumbar puncture is still recommended as it is important to rule out PCNSL in the presence of PVRL. Besides, the presence of lymphoma cells in the CSF will also support the diagnosis of PVRL when the diagnosis is unclear and it spares patient form further invasive diagnostic procedures such as diagnostic vitrectomy or retinal biopsy(Chan and Sen, 2013) that may be more invasive.

The diagnosis of intraocular lymphoma involves morphological assessment in conjunction with immunocytochemistry and molecular analysis (such as flow cytometry and polymerase chain reaction analysis)(Tang*et al.*, 2017). Morphologically, typical lymphoma cells are those with scanty cytoplasm, elevated nucleus : cytoplasm ratio, irregular shaped nuclei with coarse chromatin and prominent or multiple nuclei(Coupland *et al.*, 2003). Lymphoma cells can also be identified by staining positive with CD20 for B cells and CD3 for T cells. Flow cytometry is useful to demonstrate the monoclonal B-cell population. Molecular analysis showing an elevated IL-10:IL-6 ratio >1.0 is useful in lymphoma diagnosis as inflammatory conditions typically show elevated IL-6. All the biopsy samples from our patients had the morphological and flow cytometry performed but not the interleukin study as it was not available in our centre.

There is still no standard optimal therapy for intraocular lymphoma. The PSNSL Collaborative Group in 2011, recommendations for therapeutic regimens for uniocular lymphoma without CNS involvement include local ocular treatment with intravitreal methotrexate, intravitreal rituximab or ocular radiation with 30-35 Gy external beam(Chan *et al.*, 2011). In bilateral ocular involvement, the study recommended systemic treatment with local therapy, even in the absence of CNS lymphoma. If CNS involvement is present, systemic treatment should be administered. In our study, systemic chemotherapy was most commonly used due to the fact that all our patients had systemic involvement.

Currently, there is no particular study that could demonstrate the clear superiority of systemic treatment over local treatment or combined treatment in isolated PVRL without CNS involvement. The small number of patients in our study was too limited to evaluate these differences. In one study, Riemenset al demonstrated that the additional benefit of systemic chemotherapy could not be proven and was associated with a greater number of more severe adverse effects compared with local treatment (Riemens *et al., 2015)*.

Radiation therapy is useful but may cause potential severe side effects. Whole brain radiation with or without chemotherapy often induced a delayed neurotoxicity with decline in cognitive function, ataxia, urinary incontinence, dementia and even death(Rosenfeld and Pruitt, 2012). Prica*et al.*compared treatment between chemotherapy alone or a combined modality therapy (CMT) with high dose methotrexate and whole brain radiotherapy for PCNSL and found that the CMT had better response rates but higher neurotoxicity(Prica, Chan and Cheung, 2014). Their findings supported for chemotherapy alone for older PCNSL patients. Conversely, in younger patients, the optimal induction strategy appears to be CMT, which significantly maximizes life expectancy and quality-adjusted life-expectancy while minimizing costs.

Our study was limited with the retrospective nature of this study which had included a small group of patients diagnosed with ocular lymphoma over a wide time frame; with the earliest patient presented in 2006 to the latest presentation in year 2012. It would be useful to follow up on the remaining surviving patients to look at their morbidity and mortality outcomes.

## Conclusion

The diagnosis of intraocular lymphoma is very challenging and often delayed. Aqueous fluid cytology via anterior chamber tap could be useful for early diagnosis of intraocular lymphoma as compared to a more invasive vitreous biopsy. Our study also shows the variability of treatment for ocular lymphoma which highlights the importance of further studies and discussions to form a standard protocol in managing this disease for Asian population. This major step may be a solution to curb the current grave diagnosis of intraocular lymphoma.

**Compliance With Ethical Standards**

Potential conflict of interest : Nil

Funding : Nil

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants

Informed consent: This was a retrospective study that received a waiver of informed consent from the instutional research board (IRB).

This article does not contain any studies with animals performed by any of the authors.

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