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Intraocular Lymphoma – Lessons Learned by an Ophthalmologist

ABSTRACT

Introduction: Primary intraocular lymphoma can have various presentations; most commonly, it masquerades as an intermediate and/or posterior uveitis. It usually originates from vitreoretina, known as primary vitreoretinal lymphoma (PVRL) or from uveal tissue and the optic nerve. This gives the ophthalmologist an avenue to use the eye as a window to the brain or the body and suspect/diagnose disease before its spread. **Methods:** This study was retrospective chart review of patients with PVRL from January 2014 to December 2019. **Results:** In the study period, four patients (two females/two males) had PVRL. Two patients (both females) were 50 years; one was 53 and one was 65 years. Initial diagnoses were "tubercular subretinal abscess," "VKH Disease," "viral uveitis," and "Optic neuritis." With a high index of suspicion for PVRL based on clinical picture and inadequate response, an initial cytological analysis of the vitreous was done in three patients and was normal. Central nervous system (CNS) involvement occurred in all patients; in 10, 5, 35, and 9 months after initial vitreoretinal involvement. Histopathological diagnosis made in all patients after a brain biopsy, leading to chemotherapy. **Conclusion:** PVRL is increasingly presenting in younger age group and should be kept in mind in patients with atypical uveitis. The eye indeed is a window to the brain or the body for an ophthalmologist to suspect/diagnose intraocular lymphoma, a disorder masquerading as intraocular inflammation, before its CNS spread.

Key words: Intraocular lymphoma, Masquerade syndrome, Primary vitreoretinal lymphoma

INTRODUCTION

"Masquerade Syndrome" was a term coined in 1967 to describe a case of "conjunctival carcinoma" masquerading as "chronic conjunctivitis."[1] In masquerade syndromes, the detrimental nature of the disease necessitates early diagnosis and prompt treatment.

Intraocular lymphoma is a rare malignancy that accounts for 0.01% of ophthalmic conditions. It includes primary intraocular lymphoma (PIOL) with or without primary central nervous system lymphoma (PCNSL).[1] Majority of the patients with lymphoma are elderly individuals over 50 years of age.[2] The disease when untreated is obviously lethal, and hence, rapid and accurate diagnosis is crucial to increase the survival, especially if one is able to diagnose the disease before CNS involvement.[1,3]

PIOL can have various presentations; most commonly, it masquerades as an intermediate and/or posterior uveitis.[3] It usually originates from vitreoretina, known as primary vitreoretinal lymphoma (PVRL) or from uveal tissue and the optic nerve.[4] This gives the ophthalmologist an avenue to use the eye as a window to the brain or the body and suspect/diagnose disease before its spread.

METHODS

With this background, we undertook a retrospective chart review of patients with lymphoma who presented to our institute from January 2014 to December 2019. For the purpose of this study, we included those patients with intraocular symptoms and signs, preceding any CNS manifestations of the disease. Thus, patients who presented to ophthalmology services with symptoms of intraocular inflammation, with/without a clinical suspicion of lymphoma on examination (or review of old records) by the ophthalmologist, which later progressed to develop CNS Lymphoma were included in the study. Those patients with clear symptoms and signs of CNS disease at presentation itself were excluded from the study.

RESULTS

In the study period, four patients (two females/two males) had a primary ocular disease with no initial CNS manifestations

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[Tables 1 and 2]. Two patients (both females) were 50 years, one gentleman was 53 years and the other was 65 years. Initial diagnoses done elsewhere were "Tubercular subretinal abscess," "VKH disease," "Optic neuritis," and "Viral retinitis."

With a high index of suspicion for PVRL based on clinical picture and inadequate response to treatment, an initial cytological analysis of the vitreous was done in three of the four patients which was normal. An initial neuroimaging was also done in the same three patients, which was also normal.

CNS involvement occurred in all patients, in 1, 5, 9, and 35 months after initial vitreoretinal involvement, respectively. Histopathological diagnosis was possible in all patients, only after a brain biopsy by the neurosurgeons, leading to treatment by the oncologists with chemotherapy. At the time of preparing this manuscript, two patients are doing well (7 years and 2 years follow-up since CNS involvement) and the other two have unfortunately succumbed to their disease. Individual cases are discussed here after the tables.

Patient 1: Lymphoma masquerading as tubercular subretinal abscess

A 50-year-old lady was extensively investigated (including magnetic resonance imaging [MRI] Brain and a vitreous biopsy) and was put on empirical treatment with antibiotics (anti-tubercular and anti-Toxoplasma treatment with an oral steroid cover) for a doubtful submacular abscess seen through excessive media haze [Figure 1]. She is a college professor by profession and was specifically counseled for a "atypicality" of her uveitis.

A month later, she developed CNS symptoms and was admitted and showed evolving cerebral lesions on repeat MRI brain, on which biopsy showed features of CNS lymphoma (non-Hodgkin's type). Her antibiotics were stopped and subsequent chemotherapy caused remission of CNS and ocular lesions.

Patient 2: Lymphoma masquerading as VKH disease

A 50-year-old lady with no other apparent illness presented elsewhere with bilateral asymmetrical decrease of vision since 5 months due to "multifocal choroiditis with panuveitis" which was investigated and treated elsewhere as VKH Disease [Figure 2].

Neuroimaging or a vitreous biopsy was not done as the initial treating ophthalmologist did not suspect lymphoma due to the age of the patient.

She presented to us after developing CNS symptoms which mandated ICU admission, where fundus showed typical retinochoroidal lesions suspicious of ocular lymphoma.

MRI brain was done and showed cerebral lesions which were neurosurgically biopsied and showed CNS lymphoma (Non-Hodgkin's type). She was put on chemotherapy with an initial response, but she finally succumbed to her CNS disease.

Patient 3: Lymphoma masquerading as optic neuritis

A 65-year-old gentleman came with decrease of vision in both eyes for 4 months.

The patient had been treated elsewhere as "Optic Neuritis," but due to the macular subretinal yellowish lesions [Figure 3], we suspected lymphoma. MRI brain was normal and vitreous biopsy was inconclusive. Cerebrospinal fluid (CSF) analysis was done which was also inconclusive. Oncologists were unable to treat due to no other evidence of malignancy, expect our clinical suspicion.

Local therapy in the form of intravitreal methotrexate was given awaiting oncology management. Two weeks later, there was an improvement in vision and hence patient chose to be continued locally on regular intravitreal methotrexate to maintain his vision. He did undergo repeated counseling for possibility of lymphoma until 5 months later, he was diagnosed with a right frontal lobe space-occupying lesion, after a repeat MRI brain for neurological symptoms, which was biopsied to show an atypical medium to large cell lymphoid infiltrate with

Table 1: Analysis of the patients diagnosed with PVRL

Patient	Age	Gender	Initial diagnosis	Initial magnetic resonance imaging	Clinical picture on presentation	Clinical suspicion	Vitreous biopsy
1	50	F	Tuberculosis	Negative	Subretinal Abscess	Present	Negative
2	50	F	VKH Disease	Not Done	Subretinal Exudation	Not present	Not done
3	65	M	Optic Neuritis	Negative	Subretinal yellow lesion	Present	Negative
4	53	M	Viral Retinitis	Negative	Vitritis with leopard skin lesions	Present	Negative

Table 2: Investigations and course of patients with PVRL

Patient	CNS symptoms after onset of eye symptoms (months)	Repeat magnetic resonance imaging	CNS Biopsy	Follow up
1	1	Positive	Positive	7 years
2	5	Positive	Positive	Succumbed to disease
3	9	Positive	Positive	2 years
4	35	Positive	Positive	Succumbed to disease

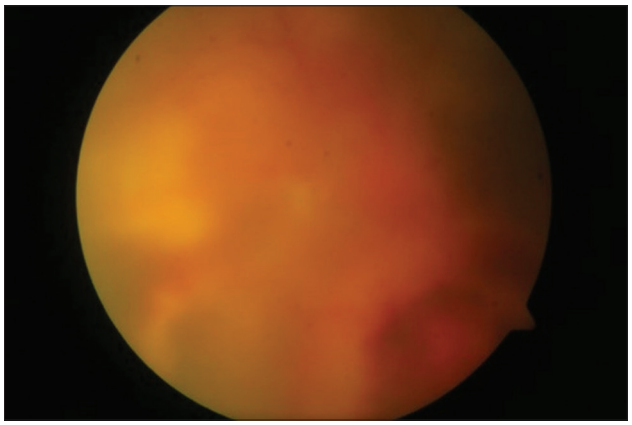

Figure 1: Fundus picture of a 50-year-old lady with the left eye showing dense vitritis with a lesion resembling a submacular abscess

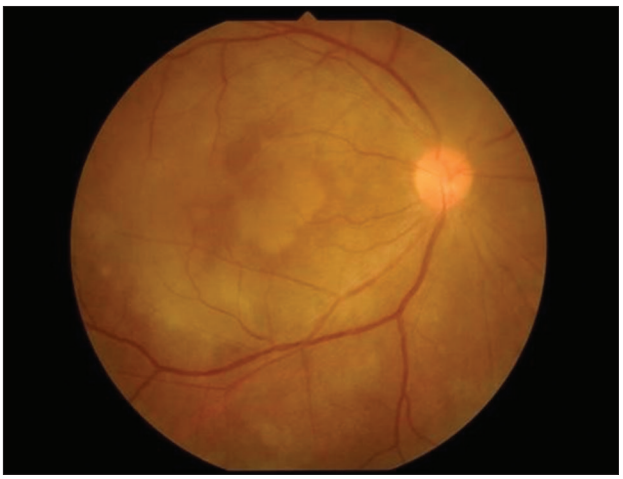

Figure 2: Fundus picture of a 50-year-old lady with the right eye showing ill-defined subretinal lesions diagnosed initially to be multifocal choroiditis with panuveitis

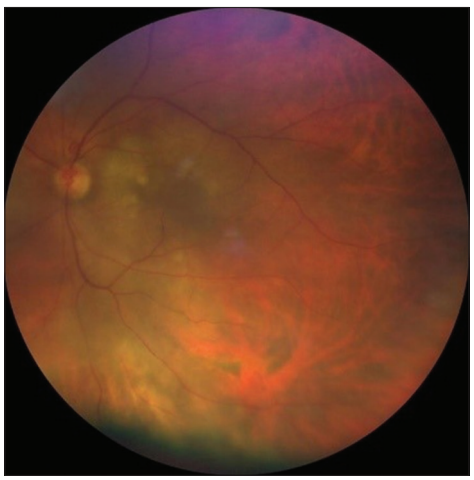

Figure 3: Fundus picture of a 65-year-old gentleman with the left eye showing ill-defined macular subretinal yellowish lesions

increased mitoses and apoptosis, suggestive of high grade non-Hodgkin's Lymphoma.

Patient 4: Lymphoma masquerading as viral retinitis

A 53-year-old gentleman presented with gradual painless diminution of vision in both eyes for 2 months had been diagnosed as viral uveitis. Fundus examination of the eyes revealed vitritis, which was marked in the right eye with glaucomatous disc in both eyes. His raised IOP responded to steroids, but there was very minimal improvement in vitreous haze with vision remaining poor in both eyes. In view of persistent vitritis, a decision for vitrectomy was taken but cytology and PCR from undiluted vitreous aspirate were inconclusive on two occasions. MRI brain and orbit were normal and did not show any evidence of CNS involvement.

Thirty-five months from the onset of first ocular symptoms, the patient was admitted to our neurology unit with vomiting and difficulty in walking associated with speech disturbance. MRI brain was suspicious of CNS Lymphoma [Figure 4]. CSF examination including Gene Xpert mycobacterium tuberculosis, whole body positron emission tomography – computed tomography, serum neuromyelitis optica, and myelin oligodendrocyte glycoprotein antibodies were all inconclusive.

Fundus examination, now, revealed a hazily seen glaucomatous disk through 3+ vitritis in right eye and leopard skin areas in the left eye. A repeat vitreous biopsy from the right eye showed occasional mature lymphocytes with normal cell morphology; again, inconclusive of any ocular lymphoma.

Frozen section from specimens of the right frontal corona radiata lesions obtained through brain biopsy indicated a round cell tumor – non-Hodgkin lymphoma leading to treatment, 35 years after an initial ophthalmologist suspicion of lymphoma.

DISCUSSION

PIOL is a fatal disease, with an especially worse prognosis and a high mortality when the CNS is involved.[5] Therefore, an accurate and timely diagnosis for an effective therapy are of great significance before involvement of the CNS.

PIOL usually masquerades as uveitis or other intraocular inflammations due to a wide variety of manifestations with a great potential for misdiagnosis.[6] It is no wonder that some researchers have reported patients with misdiagnosis for more than 2 years.[7]

PIOL is known to begin as monocular disease, with more than half of the patients progressing to binocular disease. This is likely to be due to the destruction of blood-eye barrier resulting in the affection of the fellow eye. It occurs mainly in the elderly, which may be due to weak immune system and mutation accumulation.[4]

An analysis of 87 studies involving 1484 patients found that about 19% of PIOL patients are already CNS-involved when

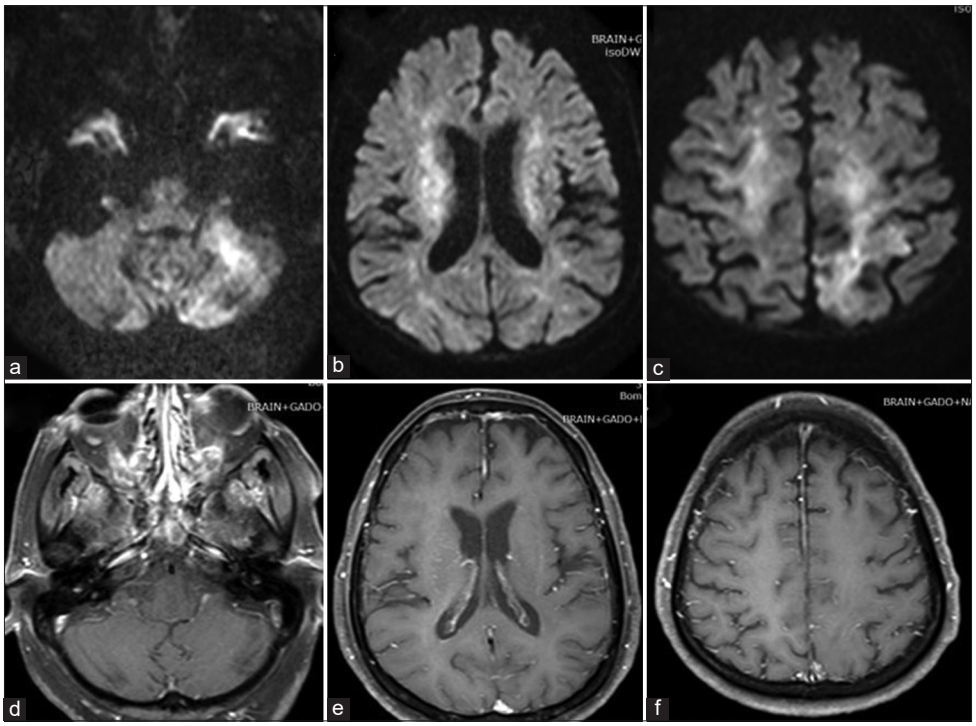

Figure 4: MRI brain of a 53-year-old gentleman with diffusion-weighted images showing restricted diffusion (bright signal) in the cerebellum (a) and cerebral white matter (b and c) with no appreciable post-contrast enhancement (d-f). The FLAIR axial images of the same patient showed ill-defined hyperintense areas. This picture though atypical for lymphoma was highly suspicious from past experience to be consistent with "lymphomatosis cerebri"

diagnosed, defined as "the ocular symptoms occurred before the diagnosis of CNS involvement." This percentage, further, increases to 58% during the course of the disease. The delayed diagnosis rate is found to be 85%, and the misdiagnosed rate 64%.

While giving a diagnosis of intraocular lymphoma, the ophthalmologist must specify whether CNS is involved, as such involvement worsens the prognosis. The prognosis of PIOL patients without CNS involvement is much better than those with CNS involvement, such as death rate during follow-up (5% vs. 56%), 2-year survival rate (98% vs. 77%), 5-year survival rate (97% vs. 54%), and recurrence rate (20% vs. 70%). This understanding justifies and may also mandate routine MRI brain and even CSF examination at baseline when lymphoma is suspected if atypicality is encountered in the presentation or progress of a uveitis patient.[8]

The leading three complaints of PIOL patients found are blurred vision, decreased vision acuity, and floaters, the most common signs are vitreous opacities, fine keratic precipitates, and retinal or subretinal infiltration. These are mainly caused by the aggressive destruction of the retinal photosensitive structure by invading lymphoma cells or by the production of space-occupying turbidity of the hypercellular vitreous. Besides this, it is important to know that PIOL can not only present with fine keratic precipitates, but also as stellate keratic precipitates.[8]

In ocular coherence tomogram (OCT) scans, more than half of the patients with vitreoretinal lymphoma have hyper-reflective foci in posterior vitreous, combined with retinal hyperreflectivity, subretinal lesions, and intra-RPE lesions, representing the functional abnormality and structural interruption caused by the infiltration of lymphoma cells in different layers of the retina, which would not appear in inflammatory eye diseases.[9] OCT can, thus, show more detailed features of lymphoma infiltration and have definite diagnostic significance for PIOL, as a non-invasive method to document the therapeutic effect and progress of PIOL once diagnosis is made and the patient is on treatment.[9]

In a fundus fluorescein angiogram (FFA), FFA/fundus autofluorescence (FAF) reverse, defined as high autofluorescence spot on FAF corresponding to a low autofluorescence spot without leakage in this region on FFA is the most frequent finding.[8]

When it comes to treatment of a lymphoma, oncologists usually depend on the cytologic evidence of malignant lymphocytes on vitreous specimen before initiating treatment. Thus, the diagnosis of PIOL can be best established by cytologic examination of the vitreous specimen obtained through vitreous biopsy.[2] However as seen in our series, vitreous biopsy may be negative due to the fact that the lymphoma cells are fragile and easily degenerate in the vitreous. While observing lymphoma cells in cytological examination directly are still the gold standard with the highest specificity, the sensitivity is only around 80%.[8] Hence, multiple biopsies from different sites may be needed. Aqueous humor tests emerge as an ideal technique due to minimal trauma and valid

positive rate compared to vitreous fluid. The most promising test on the aqueous specimen is IL10/IL6 ratio >1 with a positive rate near 98% in PIOL patients. The positive rate of IL10 >50 pg/ml is also as high as 94%.[10] IL10 is expressed by malignant tumor cells, inhibiting various immune-related cell populations to achieve immune escape, while the rise of IL6 occurred in inflammation-indicated stronger immune response. Thus, the levels of IL10 and IL6 have a great potential to distinguish PIOL from uveitis. This has led some authors to suggest that for patients with clinical manifestations and imaging characteristics supporting PIOL, the aqueous humor test should be the first choice for confirming the diagnosis and a diagnostic PPV should be reserved for later.[8]

We agree with authors who have recommended that for accurate diagnosis, when a patient experiences vision loss, has fine KPs, retinal or subretinal infiltration and vitreous inflammatory opacity, hyper-reflective foci in posterior vitreous, retinal hyperreflectivity on OCT, and FA/FAF reversal on FFA; ophthalmologists should consider the possibility of PIOL, especially in the elderly individuals. Aqueous humor test and MRI brain may be routinely conducted to prompt the need for further invasive procedures to make timely diagnosis and treatment.[8] The analysis of MYD88 L265P mutation in the vitreous has been found to be reliable and efficient in the diagnosis of PIOL.[11] Finally, clinicians should recognize that PIOL can occur and manifest as PCNSL even when CSF analysis shows negative cytology[8] and that at times cytologic analysis from three vitreous biopsies, done from different centes, may not be helpful in pinning this masquerading entity, as is obvious from case no. 4 above, which is described in much greater detail in our previous publication.[12]

CONCLUSION

The eye indeed is a window to the brain or the body for an ophthalmologist to suspect/diagnose intraocular lymphoma, a disorder masquerading as intraocular inflammation, before its CNS spread.

The lessons learned by an ophthalmologist could be summarized as:

1. Remember the typical morphology of the masquerades
2. Suspect masquerades while dealing with uveitis in extreme age groups – very young and very old age groups, which is the "typical" age group for masquerades
3. Discuss an "atypical uveitis" and the possibility of a masquerade clearly with the patient even if the age group is "typical for uveitis"
4. Discuss and if possible, request for an MRI Brain in all "atypical" uveitis even if the age group is "typical for uveitis"
5. Discuss and counsel the possibility of a masquerade even if it has been "ruled out" by neuroimaging, vitreous biopsy and lumbar puncture especially in the "typical" age group.

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