Journal of Clinical Ophthalmology and Eye Disorders

Short Communication
Published: 22 Mar, 2021

Beware the Masquerade!

*Elewys H[1] and Susan L[2]**

[1]Department of Clinical Ophthalmology, ST4 Severn Deanery, UK

[2]Department of Clinical Ophthalmology, University of the Highlands and Islands, UK

Abstract

Background: This case is a young woman presenting with apparent bilateral intermediate uveitis where the final diagnosis is of bilateral Primary Intraocular Lymphoma (PIOL). The diagnostic challenges are reviewed, and the clinical features are described.

Case Report: A 32-year-old lady presented with a 3-month history of bilateral floaters, with no past medical history, no medications, and a normal systems review. Examination revealed her Visual Acuity (VA) was 6/6 in both eyes, 1+ of anterior chamber cells and 3+ of vitreous cells in both eyes. OCT illustrated normal maculae and optic discs, and an initial diagnosis of bilateral intermediate uveitis was made. The treatment of high dose oral steroids made no change clinically and VA remained at 6/6 in both eyes. A vitreous biopsy gave the correct diagnosis of a bilateral diffuse large B-cell lymphoma. MRI head and orbits illustrated no concurrent primary Central Nervous System (CNS) involvement. Ocular irradiation with prophylactic CNS treatment was given in combination with systemic chemotherapy. Initially there was a good response to treatment, but both eyes then relapsed so intravitreal methotrexate was administered.

Conclusion: We report a rare case of bilateral PIOL with no concurrent Primary Central System Lymphoma (PCNSL), initially diagnosed as bilateral intermediate uveitis presenting to the uveitis clinic at Moorfield's Eye Hospital. PIOL is a great imitator so a high degree of clinical suspicion is essential in uveitis refractive to treatment to avoid prolonging the delay in diagnosis.

Introduction

Primary Intraocular Lymphoma (PIOL) is a rare subtype of primary central nervous system lymphoma [1] and differs from Secondary Intraocular Lymphoma (SIOL), where the infiltrating lymphoma cells come from outside the central nervous system and metastasize to the eye [2]. Ocular lymphoma features vitreous opacity with either the presence or absence of infiltrative lesions in the retina, subretinal pigment epithelium, and/or the optic nerve [3]. PIOL is typically a diffuse large B-cell non-Hodgkin lymphoma [4]. Intraocular lymphoma is rare at approximately 1.86% of all ocular malignant tumors [5]. Although the incidence is low there has been a surge of cases recently, most likely due to the increase in the number of immunosuppressed and immunodeficient patients [6] a rise in life expectancy [1] and better diagnostic entities [7]. There is no gender bias, and the typical age of onset is within the patients 50's and 60's [8] although there are ever-increasing numbers of cases being described in young adults, and even children [6]. Epstein-Barr virus has been associated in some patients but not all [9], so the etiology of IOL remains uncertain [1].

Results and Discussion

A 32-year-old lady presented to the emergency eye service with a 3-month history of floaters, with no past medical history, no medications, and a normal systems review. She was well in herself with no headaches, night sweats or recent travel. Examination revealed her Visual Acuity (VA) was 6/6 in both eyes, 1+ of anterior chamber cells in both eyes and 3+ of vitreous cells in both eyes (Figure 1). OCT illustrated normal maculae and optic discs. Nothing on examination or history suggested multiple sclerosis or infectious etiologies and malignancy were deemed less likely due to the fact that she was healthy and young. A full uveitis work up was undertaken (Table 1). High dose oral steroids were started at prednisolone 60 mg for 1 week, followed by 40 mg for 1 week then she was scheduled to be reviewed. At her next review at the uveitis clinic there was no improvement in her clinical signs, although vision remained 6/6 in both eyes. All investigations were negative. The patient was further reviewed in 4 weeks after 30 mg prednisolone for 2 weeks then 20 mg daily for 2 weeks. Again, there was no change clinically and VA remained 6/6 in both eyes. At this stage the diagnosis was reviewed. There was nothing to suggest an infective cause, an inflammatory cause

OPEN ACCESS

Correspondence:
Susan Lightman, Department of Clinical Ophthalmology, University of the Highlands and Islands, UK, E-mail: s.lightman@ucl.ac.uk

Received Date: *22 Feb 2021*
Accepted Date: *18 Mar 2021*
Published Date: *22 Mar 2021*

Citation:
Elewys H, Susan L. Beware the Masquerade!. J Clin Ophthalmol Eye Disord. 2021; 5(1): 1036.

Table 1: Basic uveitis work up.

Chest X-ray
Full blood count
Urea and electrolytes and creatinine
Liver function tests
Serum Angiotensin converting enzyme
Antinuclear antibody
Syphilis serology
Quantiferon gold

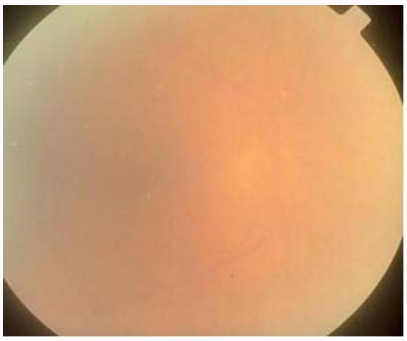

Figure 1: Diffuse vitritis.

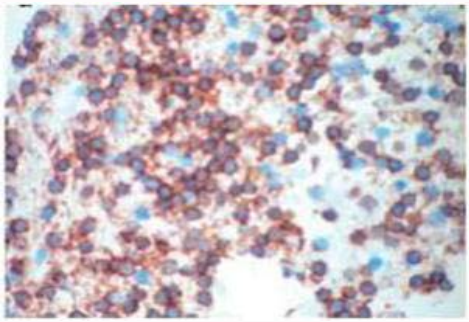

Figure 2: Histological analysis demonstrating CD19+ lymphocytes confirming a diffuse large B-cell lymphoma.

would have responded by this point, so the next step was to exclude malignancy. The prednisolone dose was reduced rapidly and stopped over the next 2 weeks. A vitreous biopsy was untaken 2 weeks after the steroids were stopped. This showed a high level of CD19+ lymphocytes (Figure 2), confirming a diffuse large B-cell lymphoma. MRI head and orbits illustrated no concurrent Primary Central System Lymphoma (PCNSL). The patient was referring to the oncologist for staging and no other evidence for CNS involvement was found. Fractionated ocular irradiation with prophylactic Central Nervous System (CNS) treatment was given in combination with systemic chemotherapy. Initially there was a good response to treatment and the vitritis was significantly reduced but both eyes later relapsed so intravitreal methotrexate was administered. The patient has not relapsed for 5 years at the point of publication so is considered a long-term disease-free survivor.

Intraocular lymphoma may masquerade as a chronic intermediate or posterior uveitis. It can be primary CNS or secondary but SIOL lesions are usually limited to the uvea, particularly the choroid [10], as this is their route of spread. Skin is the most common primary site for SIOL [11]. There should be a suspicion of PIOL in all cases

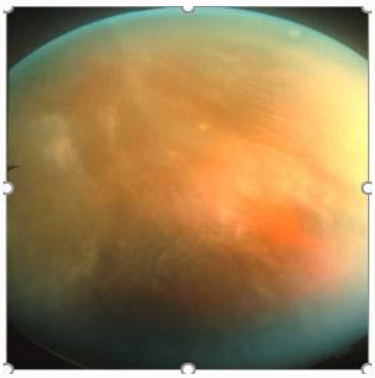

Figure 3: Vitreous veils.

of new-onset uveitis over the age of 60, but we are now getting increasing numbers of younger patients being diagnosed also. The key sign to look out for is much better vision that you would expect from the findings on examination, for example in this case the VA was 6/6 with a dense vitritis. Cystoid Macular Oedema (CMO) is usually absent also [12]. Other signs to look out for include clumping of cells or veils in the vitreous (Figure 3), serous retinal detachment, leopard spotting and occasionally posterior vitreous detachment and hemorrhage [13]. PIOL may respond to systemic corticosteroids by temporarily decreasing cells in the vitreous, so prior to vitreous sampling it is important to stop steroid treatment for at least two weeks. Histological conformation of the diagnosis is required before treatment can commence.

Vitreous sample cytokine analysis can help with a diagnosis of PIOL, looking for elevated Interleukin (IL)-10 levels with an IL-10:IL-6 ratio >1.0 [14]. Flow cytometry can distinguish monoclonal B-cell populations and molecular analysis pinpoints *IgH* gene rearrangements in B-cell lymphoma or within T-cell lymphoma T-cell gene rearrangements [15]. In the event of negative vitreous samples but a very high clinical suspicion continues then retinal or chorioretinal biopsies must be considered as the next step [16]. Once the histological diagnosis is confirmed, the patient must be referred to the oncologists for further work up which includes; a systemic review, lumber puncture and further imaging if needed [17].

Treatment approaches differ according to the specific case and department but include intravitreal Methotrexate (MTX) injections [18,19], intravitreal Rituximab (anti-CD 20 monoclonal antibody), and/or binocular external beam radiation [6]. Systemic chemotherapy with or without autologous stem cell transplantation is also used in some bilateral cases or those with CNS involvement [20]. Repeated intraocular injections of MTX or rituximab are often used for ocular relapses [21]. Survival time for PIOL patients is increasing and was recently published at 44 months [22]. Long-term disease-free survivors are becoming more common especially if there is no CNS involvement at presentation [23] as described in this case, however they are still in the minority.

Conclusion

PIOL is a great imitator so a high degree of clinical suspicion is essential in uveitis refractive to treatment to avoid prolonging the delay in diagnosis, whatever the age of the patient.

References

1. Tang LJ, Gu CL, Zhang P. Intraocular lymphoma. Int J Ophthalmol.

2017;10(8):1301-7.

2. Matsuo T, Tanaka T. Are there primary intraocular lymphomas that do not develop into central nervous system lymphomas? J Clin Exp Hematop. 2019;59(4):168-74.
3. Abu Samra K, Oray M, Ebrahimiadib N, Lee S, Anesi S, Foster CS. Intraocular lymphoma: Descriptive data of 26 patients including clinico-pathologic features, vitreous findings, and treatment outcomes. Ocul Immunol Inflamm. 2018;26(3):347-52.
4. Coupland SE, Heimann H, Bechrakis NE. Primary intraocular lymphoma: A review of the clinical, histopathological and molecular biological features. Graefes Arch Clin Exp Ophthalmol. 2004;242(11):901-13.
5. Reddy EK, Bhatia P, Evans RG. Primary orbital lymphomas. Int J Radiat Oncol Biol Phys. 1988;15(5):1239-41.
6. Sagoo MS, Mehta H, Swampillai AJ, Cohen VM, Amin SZ, Plowman PN, et al. Primary intraocular lymphoma. Surv Ophthalmol. 2014;59(5):503-16.
7. Mulay KNR, Honavar SG. Primary vitreoretinal lymphoma. Indian J Ophthalmol. 2015;63(3):180-6.
8. Fend F, Ferreri AJ, Coupland SE. How we diagnose and treat vitreoretinal lymphoma. Br J Haematol. 2016;173(5):680-92.
9. Gonzales J, Doan T, Shantha JG, Bloomer M, Wilson MR, DeRisi JL, et al. Metagenomic deep sequencing of aqueous fluid detects intraocular lymphomas. Br J Ophthalmol. 2018;102(1):6-8.
10. Chan CC, Buggage RR, Nussenblatt RB. Intraocular lymphoma. Curr Opin Ophthalmol. 2002;13(6):411-8.
11. Levy-Clarke GA, Sieving PC, Byrnes G, Greenman D, Nussenblatt R, Chan CC. Ophthalmic manifestations, cytology, immunohistochemistry, and molecular analysis of intraocular metastatic T-cell lymphoma: Report of a case and review of the literature. Surv Ophthalmol. 2008;53(3):285-95.
12. Fardeau C, Lee CP, Merle-Béral H, Cassoux N, Bodaghi B, Davi F, et al. Retinal fluorescein, indocyanine green angiography, and optic coherence tomography in non-Hodgkin primary intraocular lymphoma. Am J Ophthalmol. 2009;147(5):886-94,894.e1.
13. Gill MK, Jampol LM. Variations in the presentation of primary intraocular lymphoma: case reports and a review. Surv Ophthalmol. 2001;45(6):463-71.
14. Sugita S, Takase H, Sugamoto Y, Arai A, Miura O, Mochizuki M. Diagnosis of intraocular lymphoma by polymerase chain reaction analysis and cytokine profiling of the vitreous fluid. Jpn J Ophthalmol. 2009;53(3):209-14.
15. Wang Y, Shen D, Wang VM, Sen HN, Chan CC. Molecular biomarkers for the diagnosis of primary vitreoretinal lymphoma. Int J Mol Sci. 2011;12(9):5684-97.
16. Mastropasqua R, Thaung C, Pavesio C, Lightman S, Westcott M. Okhravi N, et al. The role of chorioretinal biopsy in the diagnosis of intraocular lymphoma. Am J Ophthalmol. 2015;160(6):1127-32.e1.
17. Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R, et al. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol. 2015;16(7):e322-32.
18. Frenkel S, Hendler K, Siegal T, Shalom E, Pe'er J. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. Br J Ophthalmol. 2008;92(3):383-8.
19. Akiyama H, Takase H, Kubo F, Miki T, Yamamoto M, Tomita M, et al. High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. Cancer Sci. 2016;107(10):1458-64.
20. Kvopka M, Lake SR, Smith JR. Intraocular chemotherapy for vitreoretinal lymphoma: A review. Clin Exp Ophthalmol. 2020;48(2):240-8.
21. Pulido JS, Johnston PB, Nowakowski GS, Castellino A, Raja H. The diagnosis and treatment of primary vitreoretinal lymphoma: A review. Int J Retina Vitreous. 2018;4:18.
22. Riemens A, Bromberg J, Touitou V, Sobolewska B, Missotten T, Baarsma S, et al. Treatment strategies in primary vitreoretinal lymphoma: A 17-center European collaborative study. JAMA Ophthalmol. 2015;133(2):191-7.
23. Kim MM, Dabaja BS, Medeiros J, Kim S, Allen P, Chevez-Barrios P, et al. Survival outcomes of primary intraocular lymphoma: A single-institution experience. Am J Clin Oncol. 2016;39(2):109-13.