Systemic lymphoma masquerading as Vogt-Koyanagi-Harada syndrome: Report of a case with multimodal imaging and histopathology

Kareem Moussa a,b,*, Tedi Begaj b,c, Kevin Ma b,d, Paula Cortes Barrantes e, Dean Eliott b, Lucia Sobrin b

a Department of Ophthalmology & Vision Science, University of California, Davis, 4860 Y Street, Suite 2400, Sacramento, CA, 95817, USA
b Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA, 02114, USA
c Department of Ophthalmology, Byers Eye Institute, Stanford University School of Medicine, 2452 Watson Ct, Palo Alto, CA, 94303, USA
d Department of Ophthalmology, Associated Retinal Consultants, William Beaumont Hospital, 9555 W, Thirteen Mile Road, Suite LL-20, Royal Oak, MI, 48073, USA
e Vision Science, University of California, Davis, 4860 Y Street, Suite 2400, Sacramento, CA, 95817-2307, USA.

A 51-year-old Caucasian man presented with headache, ear pain, and blurry vision in both eyes. He was found to have bilateral exudative retinal detachments. After a short period of initial improvement with high dose systemic corticosteroid, his condition significantly worsened. An extensive work-up, including a kidney biopsy, led to a diagnosis of systemic diffuse large B cell lymphoma. He had excellent recovery following treatment with appropriate chemotherapy.

Conclusions and Importance: Systemic malignancy may present with ocular manifestations and may masquerade as another diagnosis. An unexpected clinical course may suggest an alternative diagnosis. A broad systemic work-up including an evaluation for malignancy should be considered for patients presenting with unexplained exam or systemic findings.

1. Introduction

Ocular involvement in systemic lymphoma usually includes the choroid. Rarely, it can present with vitreoretinal involvement. We report a unique case of systemic lymphoma presenting with neurologic symptoms and bilateral exudative retinal detachments suggestive of Vogt-Koyanagi-Harada (VKH) syndrome, expanding the spectrum of ocular manifestations of systemic lymphoma.

2. Case report

A 51-year-old Caucasian man presented to the Massachusetts Eye and Ear Emergency Department (ED) with blurry vision in both eyes (OU). He reported flu-like symptoms commencing three weeks prior to presentation, followed by headache, ear pain, and blurry vision. In addition, he reported transient weakness in his extremities. Visual acuity (VA) was 20/80 in the right eye (OD) and 20/40 in the left eye (OS). Intraocular pressures were normal OU. No cells were noted in the anterior chamber or anterior vitreous OU. Dilated fundus exam was notable for multiple exudative retinal detachments OU. Multimodal imaging findings are presented in Fig. 1. Fluorescein angiography (FA) showed multiple pinpoint areas of hyperfluorescence with leakage and pooling OU. Optical coherence tomography (OCT) showed choroidal thickening and subretinal fluid OU. He declined an evaluation by the neurology service. He was diagnosed with Vogt-Koyanagi-Harada (VKH) syndrome and treated with oral prednisone 60 mg daily. He returned two days later with dizziness and confusion and was admitted to the neurology service. Magnetic resonance imaging (MRI) of the brain showed areas of hyperintensities in the subcortical white matter (Fig. 2A), which were thought to be consistent with VKH. He was treated with a 3-day course of intravenous methylprednisolone 1g daily. His neurologic symptoms improved, VA improved to 20/20 OU and the subretinal fluid improved OU. He was discharged with oral prednisone 60 mg daily.

One week later, he returned with altered mental status and worsening vision. Repeat retinal imaging showed further accumulation of
subretinal fluid suggesting progression of disease. Repeat MRI of the brain showed progression of the hyperintensities in the subcortical white matter and new foci of hemorrhage (Fig. 2B). Given the atypical course while being actively immunosuppressed, a brain biopsy was performed, which showed only an inflammatory infiltrate. Whole body and brain position emission tomography-computed tomography showed increased uptake in both adrenal glands and kidneys. Given the non-diagnostic brain biopsy, a renal biopsy was performed, which showed infiltration of the kidney with lymphoma cells and a diagnosis of diffuse large B cell lymphoma was made (Fig. 3).

He was treated with a chemotherapy regimen consisting of rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride,
vincristine, and prednisone. At last follow-up 20 months after initial presentation, VA was 20/20 OU with resolution of subretinal fluid (Fig. 4). His cancer remains in remission.

3. Discussion

The differential diagnosis for exudative retinal detachments is wide and includes inflammatory diseases such as VKH syndrome, sympathetic ophthalma, and posterior scleritis; neoplastic diseases such as choroidal metastasis, choroidal melanoma, leukemia, and paraproteinemias; and
other entities such as uveal effusion syndrome and multifocal central serous chorioretinopathy. Several features in this case overlap with features of VKH: auditory disturbances, exudative retinal detachments, choroidal thickening, and the multifocal areas of pinpoint leakage on fluorescein angiography with pooling of the fluorescein dye in the subretinal space. Several features, however, are atypical for VKH and raise the suspicion for an alternative etiology. These include Caucasian ethnicity, absence of vitritis, and absence of optic disc hyperemia.\(^3\)–\(^11\)

While these features are not incompatible with a diagnosis of VKH, they should prompt careful consideration of other diagnostic possibilities, including leukemia and lymphoma, which can present similarly.\(^3\)–\(^11\)

The initial response to high dose systemic corticosteroid in this case, followed by a refractory and worsening course despite continued high dose systemic corticosteroid and immunosuppression, should alert the clinician that this is likely a masquerade syndrome, and further work-up, including systemic imaging to consider malignancy, should be strongly considered. A unique aspect of this case is the absence of other inflammatory signs reported in other cases, such as vitritis, retinitis, intra-retinal or subretinal infiltration, or vitreous hemorrhage, suggesting that systemic lymphoma can present with exudative retinal detachments as the only ocular manifestation.\(^3\)–\(^9\)

A few mechanisms may explain the ocular manifestations observed in this case. First, it is possible that hematogenous spread of lymphoma cells led to infiltration of the choroid with subsequent dysfunction of the retinal pigment epithelium and accumulation of fluid in the subretinal space, leading to exudative retinal detachments. Thickening of the choroid on OCT may support this hypothesis. Second, CNS involvement as well as eye involvement may represent a paraneoplastic response that resolved following treatment of the primary malignancy. Support for this mechanism is the demonstration of inflammatory cells and absence of malignant cells in the brain specimen obtained by biopsy, though it is possible lymphoma cells were missed given the inherent sample limitation of brain biopsies. Third, CNS involvement may be due to primarily intravascular lymphomatous involvement, in which the lymphoma cells proliferate within the lumen of blood vessels. While we cannot state with certainty which of these mechanisms is ultimately responsible for the eye involvement, the neurology and oncology services believe intravascular lymphoma is most likely given the previous transient ischemic attack-like symptoms at presentation as well as the CNS hemorrhages. In this rare subset of patients, the VKH-like inflammatory response appears to mimic robust T-cell mediated inflammation. Future studies may provide insight into the mechanism of disease.

4. Conclusions

Systemic malignancy can affect various ocular structures, and it is an important consideration in the evaluation of patients with unexplained ocular findings. As demonstrated in this case, eye involvement may precede systemic involvement, and a multidisciplinary approach is necessary for prompt diagnosis. Masquerade syndromes should be considered when the constellation of findings is atypical for known inflammatory disorders, and systemic imaging should be considered early in the course of disease when malignancy is suspected.

Patient consent

As the images included in this manuscript are entirely anonymized and do not allow for identification of the patient whose clinical course is described, formal patient consent is not required per Elsevier policy.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None of the authors have financial disclosures.

Acknowledgements

None.

References

1. Mashayekhi A, Shukla SY, Shields JA, Shields CL. Choroidal lymphoma: clinical features and association with systemic lymphoma. Ophthalmology. 2014;121(1):342–351. https://doi.org/10.1016/j.ophtha.2013.06.046.
2. Mashayekhi A, Dalvin LA, Lim LAS, et al. Association of vitreoretinal lymphoma with systemic lymphoma. Retina. 2021;41(2):259–265. https://doi.org/10.1097/IAE.0000000000002855.
3. Fan KC, Tran KD, Harbour JW, Dubovy SA, Patel NA, Albini TA. Vitreoretinal lymphoma followed by systemic diffuse large B cell lymphoma. J Ophthalmic Inflamm Infect. 2019;9(1). https://doi.org/10.1186/s12348-019-0177-8.
4. Ryan ME, Shukla SY, Shields JA, Shields CL. Choroidal lymphoma: clinical features and association with systemic lymphoma. Retina. 2014;34(2):151–161. https://doi.org/10.1097/IAE.0000000000000285.
5. Echegaray JJ, Ilop S, Sepulveda M, Velez-Rosario R, Perez N, Oliver AL. Intravitreal rituximab for the treatment of a secondary intraocular relapse of a large B-cell lymphoma. Am J Ophthalmol Case Rep. 2019;8:77–79. https://doi.org/10.1016/j.ajoc.2018.01.002.
6. Say ET, Knappl CL, Gertsch KR, Chavala SH. Metastatic B-cell lymphoma masquerading as infectious retinitis and vasculitis. Oncol Lett. 2012;3(2):1245–1248. https://doi.org/10.3892/ol.2012.659.
7. Salomo BR, Pulido JS, Johnston PB, Canal-Fontcuberta I, Feldman AL. Vitreoretinal presentation of secondary large B-cell lymphoma in patients with systemic lymphoma. JAMA Ophthalmol. 2013;131(9):1151–1158. https://doi.org/10.1001/jamaophthalmol.2013.334.
8. Mathai A, Lall A, Jain P, Pathengay A. Systemic non-Hodgkin’s lymphoma masquerading as Vogt-Koyanagi-Harada disease in an HIV-positive patient. Clin Exp Ophthalmol. 2006;34(3):280–282. https://doi.org/10.1111/j.1442-8903.2006.01205.x.
9. Rivera ME, Kuppermann BD, Wiley CA, et al. Acquired immunodeficiency syndrome-related intraocular B-cell lymphoma. Arch Ophthalmol. 1999;117(5):616–622. https://doi.org/10.1001/archopht.117.5.616.
10. Kim IT, Park HY, Roh YJ. Bilateral adrenal gland lymphoma masquerading as vogt-koyanagi-harada syndrome. J Korum Ophthalmol Soc. 2008;1198–1202. Published online.
11. Angioi K, Bodaghi B, Kaminsky P, Mokhtari K, Lubetzki C, LeHoang P. Intravascular lymphoma mimicking a Vogt-Koyanagi-Harada Disease. Am J Ophthalmol. 2019;137(1):105–116. https://doi.org/10.1016/j.ajo.2018.11.012.
12. Pahk PJ, Todd DJ, Blaha GR, et al. Intravascular lymphoma masquerading as Vogt-Koyanagi-Harada Syndrome: case report based on multimodal imaging. Retina. 2017;37(10):e113–e115. https://doi.org/10.1097/IAE.0000000000001821.
13. Benet J, Forster DJ, Lean JS, Smith RE, Rao NA. Variations in clinical features of the Vogt-Koyanagi-Harada syndrome. Retina. 1991;11(3):275–280. https://doi.org/10.1097/00006982-199111030-00001.
14. Fackler TK, Bearellly S, Odom T, Fekrat S, Goonetilleke MJ. Acute lymphoblastic leukemia presenting as bilateral serous macular detachments. Retina. 2006;26(6):710–712. https://doi.org/10.1097/01.iae.0000236484.24808.bb.
15. Williams PJ, Robinson J. Multimodal imaging of presumed ocular manifestations in end-stage diffuse large B-cell lymphoma. Retina. 2017;37(10):e113–e115. https://doi.org/10.1097/IAE.0000000000001821.
16. Kurup SK, Levy-Clarke G, Calvo KR, Jaffe ES, Nussenblatt RB, Chan CC. Primary diffuse large B-cell lymphoma of the spleen with coincident serous retinal detachments responsive to corticosteroids. Clin Exp Ophthalmol. 2007;35(5):468–472. https://doi.org/10.1111/j.1442-9071.2007.01517.x.
17. Moussa K, Bradbury M, Wu DM. Middle-aged man with bilateral subretinal fluid. JAMA Ophthalmol. 2019;137(1):105–106. https://doi.org/10.1001/jamaophthalmol.2018.2759.
18. Lee KE, Kim YJ. Bilateral multiple retinal detachments associated with diffuse large B-cell lymphoma: masquerading as vogt-koyanagi-harada disease. Ocul Immunol Inflamm. 2021;1–4. https://doi.org/10.1080/09273948.2021.1952275. Published online September 14.
19. Fukutsu K, Namba K, Iwata D, et al. Pseudo-inflammatory manifestations of choroidal lymphoma resembling Vogt-Koyanagi-Harada disease: case report based on multimodal imaging. BMC Ophthalmol. 2020;21(1):94. https://doi.org/10.1186/s12886-020-01353-9.