American Journal of Ophthalmology Case Reports 24 (2021) 101218

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Case Series

Vitreoretinal lymphoma following primary testicular lymphoma: Report of two cases and review of the literature

Joseph B. Alsberge [a,*], Robert N. Johnson [b]

[a] Department of Ophthalmology, Northwest Permanente, Portland, OR, USA
[b] West Coast Retina Medical Group/California Pacific Medical Center, San Francisco, CA, USA

ARTICLE INFO

Keywords:
Diffuse large B-cell lymphoma
Testicular lymphoma
Vitreoretinal lymphoma
Vitreous biopsy

ABSTRACT

Purpose: To report two cases of vitreoretinal lymphoma that developed following primary testicular lymphoma and review the literature.

Observations: Two men, one age 66 and the other age 77, both with a history of diffuse large B-cell testicular lymphoma, diagnosed one and three years previously, respectively, presented with vitritis and yellow-white subretinal infiltrates. Diagnostic vitrectomy in both cases revealed diffuse large B-cell lymphoma. Systemic work up in both cases showed no evidence of disease relapse elsewhere. Each were treated with intravitreal methotrexate injections.

Conclusions: Vitreoretinal lymphoma can occur following primary testicular lymphoma, and may mimic primary vitreoretinal lymphoma. Monitoring of patients with a history of testicular lymphoma with regular dilated fundus examinations should be considered.

1. Introduction

Testicular lymphoma, while accounting for less than 5% of total testicular tumors, is the most common testicular malignancy in men over the age of 60 years.[1] It is an aggressive form of extranodal non-Hodgkin lymphoma with high rates of late relapse at other sites in the body, particularly the central nervous system (CNS).[1] There have been only occasional reports of vitreoretinal lymphoma following testicular lymphoma.[2–7] In order to raise increased awareness about this important association, we describe two cases of ocular relapse of testicular lymphoma that simulated the presentation of primary vitreoretinal lymphoma with vitritis and subretinal infiltrates. To our knowledge, this is the first report of ocular relapse of primary testicular lymphoma to include optical coherence tomography findings.

2. Findings

2.1. Case 1

A 66-year-old man presented with blurry vision in both eyes for two months. Past medical history was notable for activated B-cell diffuse large B-cell primary testicular lymphoma diagnosed one year previously and treated with orchiectomy of the affected testis, pelvic radiation (dosage details not available), and systemic rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. He also received concurrent intrathecal methotrexate for CNS prophylaxis. His course included adrenal gland involvement, for which he received radiation therapy. Visual acuity was 20/80 in both eyes. He had normal pupillary reflexes. Intraocular pressure was 12 mmHg in both eyes. Anterior examination revealed 3+ white cells in the anterior vitreous in both eyes. Posteriorly, there was vitreous debris and haze in both eyes, and elevated yellow-white subretinal infiltrates with overlying pigment speckling in the right eye (Fig. 1A and B). Fluorescein angiography showed blockage in the area of the subretinal infiltrates in the right eye and mottled retinal pigment epithelial (RPE) changes in both eyes (Fig. 1C and D). Optical coherence tomography scan through one of the retinal infiltrates in the right eye showed homogenous hyperreflective sub-RPE material (Fig. 2A), and small hyperreflective elevations at the level of the RPE in the macula (Fig. 2B).

Diagnostic vitrectomy of the right eye with fine-needle aspiration biopsy of one of the subretinal lesions was performed and sent for cytology, immunohistochemistry, and flow cytometry and confirmed diffuse large B-cell lymphoma with positive staining for CD45, CD20, and PAX-5. Whole body positron emission tomography/computed

* Corresponding author. Department of Ophthalmology, Northwest Permanente, 14406 NE 20th Ave., Vancouver, WA, 98686.
E-mail address: joseph.b.alsberge@kp.org (J.B. Alsberge).

https://doi.org/10.1016/j.ajoc.2021.101218
Received 5 March 2021; Received in revised form 14 July 2021; Accepted 4 October 2021
Available online 8 October 2021

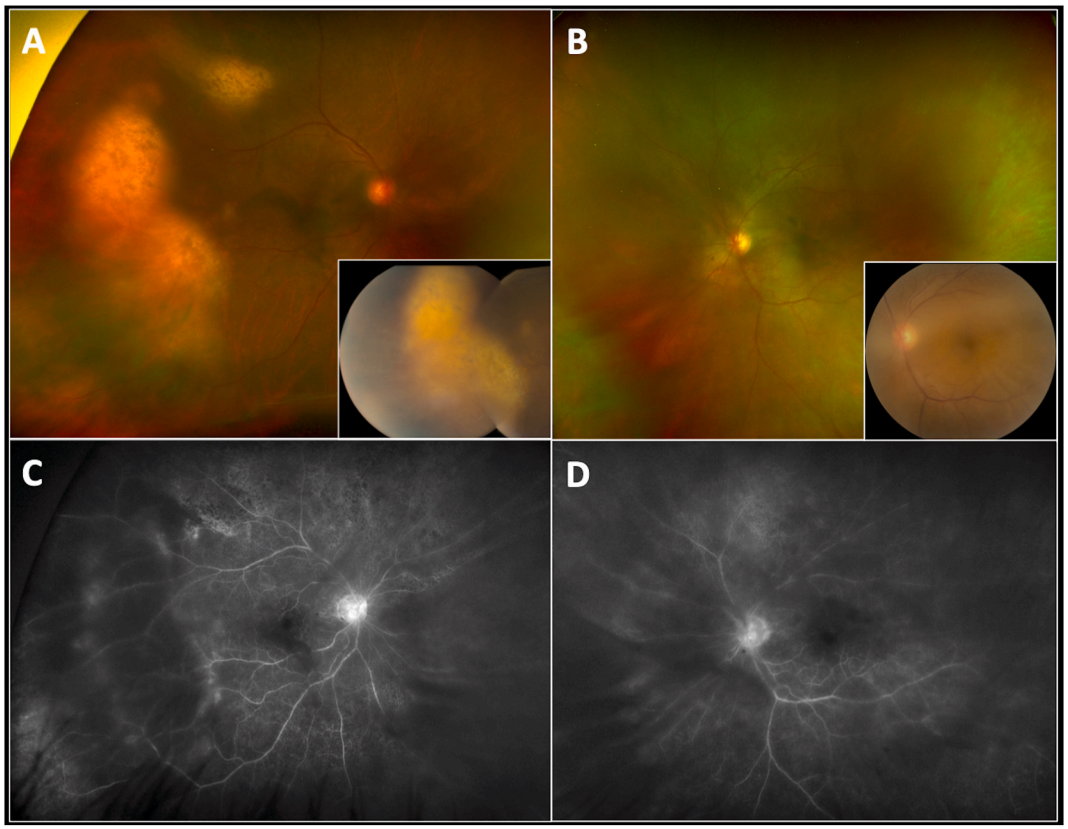

Fig. 1. Fundus photos and fluorescein angiography of the right (A and C, respectively) and left (B and D, respectively) eyes in case 1. Note the subretinal lesions in the right eye with overlying pigment speckling (A), and the appearance of the lesion at higher magnification (inset to A). There was vitritis but no subretinal lesions in the left eye (B and inset to B). Fluorescein angiography of the right eye (C) showed hypofluorescent blockage in the area of the temporal subretinal lesion. There were mottled retinal pigment epithelial changes in both eyes (C and D).

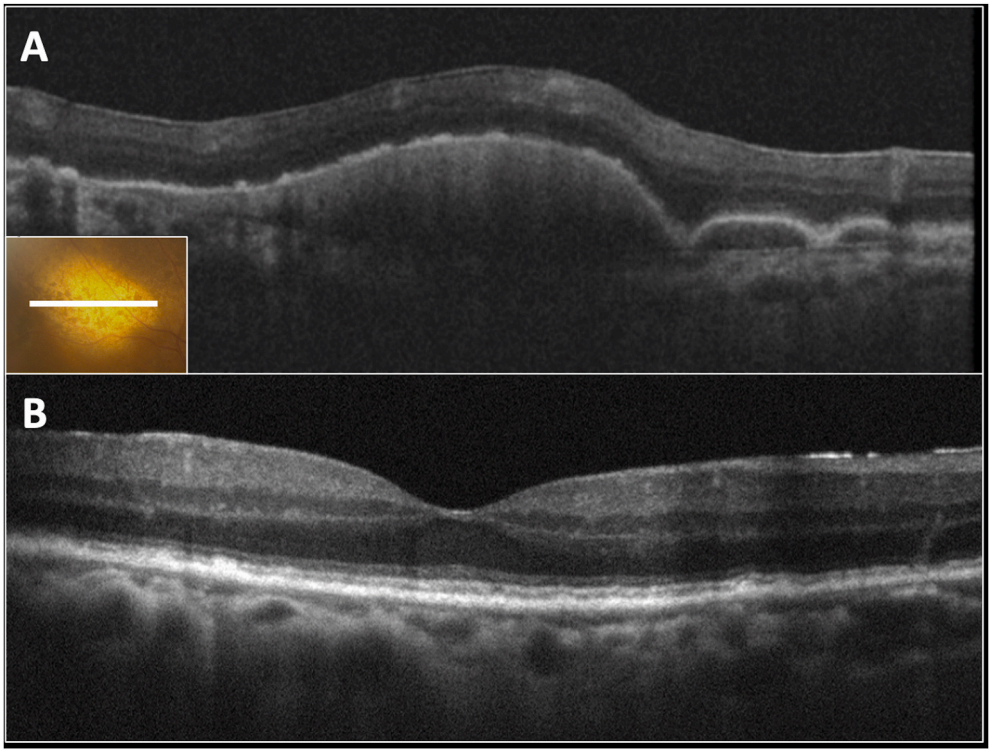

Fig. 2. Optical coherence tomography of the right eye in case 1. Cross-sectional scan (A) through one of the subretinal lesions (inset to A) showed homogenous hyperreflective material beneath the retinal pigment epithelium (RPE). Macular scan (B) showed small nodular hyperreflective elevations at the level of the RPE.

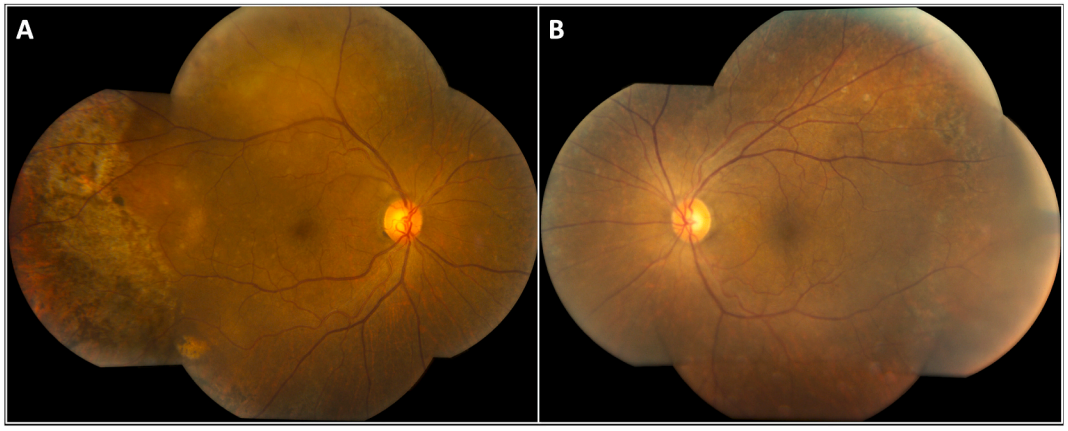

Fig. 3. Color fundus photographs of the right (A) and left (B) eyes in case 1 at 10 months follow up. The subretinal lesions have regressed and the vitritis has resolved. Note the pigmented retinal pigment epithelial changes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

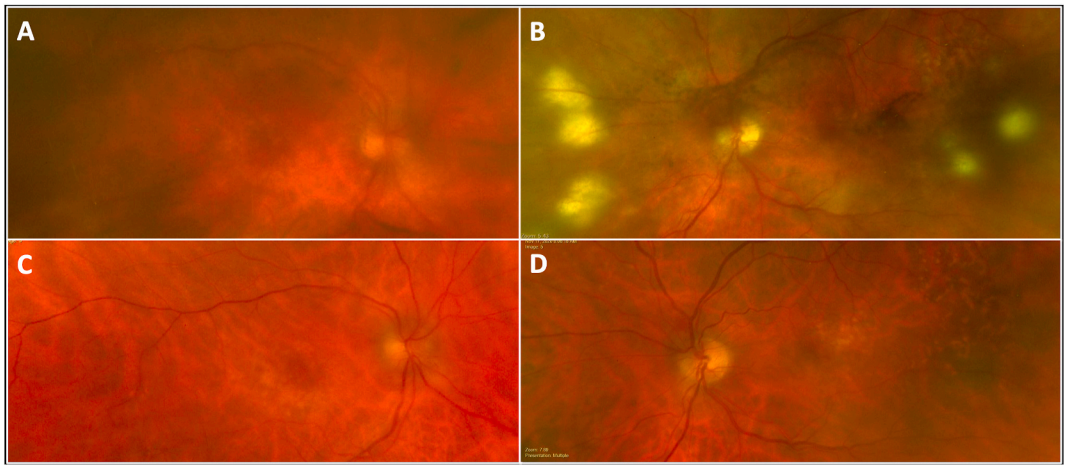

Fig. 4. Fundus photographs of both eyes in case 2 before (A and B) and two months after (C and D) initiating treatment with intravitreal methotrexate injections in both eyes. At presentation there were yellow-white subretinal lesions and vitritis in both eyes (A and B). Note: the subretinal lesions are not visible in the photograph of the right eye (A). The vitritis and subretinal lesions resolved following initiation of treatment (C and D). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tomography (PET/CT) scan, bone marrow aspiration, lumbar puncture, and brain magnetic resonance imaging (MRI) showed no evidence of lymphoma recurrence elsewhere. The patient was treated with bilateral intravitreal methotrexate injections at a dosage of 0.4 mg/0.1 mL. The treatment protocol was adjusted based on response and initially involved weekly injections, then every two weeks, then monthly, then every six weeks, and then every two months, after which the treatment was stopped. The vitritis and subretinal lesions were completely resolved bilaterally at 10 months follow up (Fig. 3). He received 25 total injections in the right eye; the left eye required more frequent injections early on in treatment and received 33 injections in total. No ocular steroids were used. The patient has remained stable without recurrence ten months following the last set of injections.

2.2. Case 2

A 77-year-old man presented with floaters in both eyes for three months. Past medical history was notable for anaplastic lymphoma kinase-positive diffuse large B-cell primary testicular lymphoma diagnosed three years previously. Initial treatment included orchiectomy of the affected testis and systemic chemotherapy with rituximab and methotrexate. Seven months following the testicular lymphoma diagnosis he developed CNS relapse of the lymphoma, treatment for which included intrathecal methotrexate chemotherapy. Other medical history included type 2 diabetes mellitus and renal cell carcinoma, the latter diagnosed and treated with nephrectomy 13 years prior. Visual acuity was 20/40 in the right eye and 20/50 in the left eye. He had normal pupillary reflexes. Intraocular pressure was 13 mmHg in the right eye and 10 mmHg in the left eye. He had 4+ anterior vitreous white cells on right and 2+ on the left. Posterior exam revealed vitreous haze and debris and multifocal elevated yellow-white subretinal infiltrates with overlying pigment speckling in both eyes (Fig. 4). Diagnostic vitrectomy of the right eye was performed and sent for cytology, immunohistochemistry, and flow cytometry and revealed diffuse large B-cell lymphoma.

Additional work up to evaluate for lymphoma recurrence elsewhere included whole body PET/CT scan, brain MRI, and ultrasound of the non-affected testis, all of which showed no evidence of lymphoma. The patient was initiated on bilateral intravitreal methotrexate injections at a dosage of 0.4 mg/0.1 mL. He received injections in each eye every one to two weeks for eight total injections per eye but was then lost to follow up. The subretinal lesions and vitritis resolved following three sets of injections (Fig. 4). No ocular steroids were used.

Table 1
Previously reported cases of vitreoretinal lymphoma following testicular lymphoma.

Reference	No. of cases	Findings	Time from testicular lymphoma to VRL (years)	Treatment of VRL
Davis et al.[2]	1	Details not provided	4.5	Orbital radiation
Wallace et al.[3]	2	Vitritis, subretinal infiltrates, RPE mottling	~4–8	Intravitreal MTX and dexamethasone
Aliferis et al.[4]	1	Vitritis, pinpoint creamy retinal lesions	10	Local radiotherapy
Pe'er et al.[5]	1	Elevated white-yellow subretinal lesion	3	Intravitreal MTX, simultaneous systemic MTX to prevent systemic recurrence
Grange et al.[6]	1	Creamy subretinal infiltrate, pinpoint infiltrates, pigmentary changes	11	Intravitreal MTX, systemic MTX and rituximab
Reimens et al.[7]	9	Details not provided	0–10	Various

MTX = methotrexate; RPE = retinal pigment epithelium; VRL = vitreoretinal lymphoma.

3. Discussion

Testicular lymphoma typically present as a painless, firm testicular mass.[1] 80–98% of cases are diffuse large B-cell tumors.[1] Treatment of testicular lymphoma usually involves excision of the affected testis (orchiectomy), radiation of the contralateral testis, and systemic chemotherapy.[1] Relapse is common and can occur at multiple extranodal sites including the contralateral testis, lung, adrenal glands, liver, and bone marrow, with the CNS being the most common site of relapse.[1] Relapses to extranodal sites can be late, and can occur greater than 15 years after initial treatment.[1] Because of the propensity for relapse in the CNS, prophylactic intrathecal chemotherapy is also sometimes performed at the time of initial treatment.[1,5] Primary testicular lymphoma may also relapse in the eye (Table 1).[2–7]

Whether testicular lymphoma develops primarily and then later metastasizes to the eye, or develops separately at both sites at different times—what might be called the multifocal origin hypothesis—is not definitively known.[3,7] While the lymphomatous B-cells from both sites may appear identical using conventional cytology and immunohistochemistry, they may differ genetically. Polymerase chain reaction (PCR) examination of immunoglobulin heavy (IgH) chain gene rearrangements has been used to evaluate for genetic differences between B cell populations in diffuse large B-cell lymphoma.[8] Wallace and colleagues compared IgH gene rearrangements in the testicular and ocular specimens of a patient who developed vitreoretinal lymphoma following testicular lymphoma and found differing rearrangement patterns, suggesting two distinct populations of B-cells, favoring the multifocal origin hypothesis in that specific case.[3] Further study is needed to clarify this issue. PCR examination for IgH gene rearrangements was not available in our cases.

Reports of both vitreoretinal and CNS lymphoma developing at different times following primary testicular lymphoma are rare.[5,7] In the second case we have reported here, the patient had previously developed secondary involvement of the brain, which was treated, and then later developed vitreoretinal lymphoma. The reason for the propensity of recurrence at these three specific sites is not clear, but may be related to the fact that the testis, CNS, and eye are all immune-privileged sites with tight blood-tissue barriers and altered local immune responses.[7,9,10] Lymphoma cells located in these immune privileged sites may thereby escape the usual host anti-tumor response and immune surveillance mechanisms, allowing the cells to proliferate.[4] Chemotherapy may also have reduced efficacy in these areas due to blood-tissue barriers, further giving neoplastic cells in these sites a proliferative advantage.[7]

As shown in the two cases reported here, the presentation of vitreoretinal lymphoma following testicular lymphoma can be identical to the presentation of primary vitreoretinal lymphoma, with vitritis and elevated white-yellow sub-RPE infiltrates with overlying pigment speckling.[11] Aliferis and colleagues also reported a case of vitreoretinal lymphoma following testicular lymphoma that presented with multiple pinpoint creamy retinal lesions that were hyperfluorescent on fluorescein angiography.[4] To our knowledge, this is the first report of testicular lymphoma recurrent to the eye to provide structural optical coherence tomography (OCT) imaging of the subretinal infiltrative lesions. The OCT features, which include nodular hyperreflective lesions at the level of the retinal pigment epithelium and dome shaped sub-retinal pigment epithelial hyperreflective deposits, appear to be identical to those that may be seen in primary vitreoretinal lymphoma.[12] It is important that clinicians be aware of the association between testicular lymphoma and vitreoretinal lymphoma, and that testicular lymphoma recurrent to the eye may present in an identical fashion to primary vitreoretinal lymphoma, as we have demonstrated here. We hope that this report will help to raise awareness about this infrequently reported association, and suggest that clinicians inquire about a history of testicular lymphoma in older male patients who present with signs of vitreoretinal lymphoma.

In the cases described here, vitreoretinal lymphoma occurred 1 year and 3 years following the diagnosis of testicular lymphoma. Ocular relapse up to 11 years following the testicular lymphoma diagnosis has been reported.[6] Both of the patients reported here previously received intrathecal methotrexate—case 1 for CNS prophylaxis, and case 2 for treatment of CNS recurrence—yet both later developed vitreoretinal lymphoma, suggesting that prior intrathecal therapy may not prevent ocular relapse. Long term monitoring of testicular lymphoma patients with regular dilated fundus examinations should be considered due to the possibility of late relapse. Clinicians should have a high index of suspicion for ocular relapse in patients with a history of testicular lymphoma who present with subretinal infiltrates and vitritis.

The use of intravitreal methotrexate in the treatment of vitreoretinal lymphoma is well-described.[11,13,14] Both cases reported here received treatment with intravitreal methotrexate monotherapy, which was well-tolerated and led to local tumor control. Given the absence of systemic involvement at the time of vitreoretinal recurrence, neither patient was treated with concurrent systemic chemotherapy. Intravitreal rituximab has also shown promise in the treatment of vitreoretinal lymphoma, and may be considered as an adjuvant or alternative intravitreal agent.[11,14] Orbital radiation has also been used, but may lead to radiation retinopathy.[11,14]

4. Conclusions

Primary testicular lymphoma may recur in the eye and may simulate primary vitreoretinal lymphoma. Clinicians should consider this diagnosis in older men who present with findings consistent with vitreoretinal lymphoma, and patients with a history of testicular lymphoma should be monitored for late relapse in the eye.

Patient consent

Consent to publish these cases was not obtained. This report does not contain any personal information that could lead to identification of the patients.

Funding

No funding or grant support.

Other disclosures

None.

Authorship

Both authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

Neither of the authors have a proprietary interest in the material presented in this study.

References

1. Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. *Blood*. 2014;123(4):486–493.
2. Davis JW, Moriarty RP, Schlossberg SM, et al. Bilateral testicular lymphoma treated with chemotherapy and radiation without orchiectomy: complete response relapsed at 52 months in the vitreous humor. *Urology*. 2001;57(3), 555xv-555xviii.
3. Wallace DJ, Altemare CR, Shen DF, et al. Primary testicular and intraocular lymphomas: two case reports and a review of the literature. *Surv Ophthalmol*. 2006;51(1):41–50.
4. Aliferis K, Donati G, Baglivo E, et al. Intraocular lymphoma following a primary testicular lymphoma in remission for 10 years. *Int Ophthalmol*. 2008;28(6):439–440.
5. Pe'er J, Rowe JM, Frenkel S, et al. Testicular lymphoma, intraocular (vitreoretinal) lymphoma, and brain lymphoma: involvement of three immunoprivileged sites in one patient. *Am J Hematol*. 2010;85(8):631–633.
6. Grange LK, Jacobs-El N, Wiley HE, et al. Intraocular (vitreoretinal) lymphoma following primary testicular lymphoma. *Can J Ophthalmol*. 2013;48(4):e95–97.
7. Riemens A, Missotten T, Baarsma S, et al. Diffuse large B-cell lymphoma in immunoprivileged sites: association of vitreoretinal, testicular, and central nervous system lymphoma. *Acta Ophthalmol*. 2014;92(2):e159–160.
8. Coupland SE, Hummel M, Stein H, et al. Demonstration of identical clonal derivation in a case of "oculocerebral" lymphoma. *Br J Ophthalmol*. 2005;89(2):238–239.
9. Taylor AW, Kaplan HJ. Ocular immune privilege in the year 2010: ocular immune privilege and uveitis. *Ocul Immunol Inflamm*. 2010;18(6):488–492.
10. Filippini A, Riccioli A, Padula F, et al. Control and impairment of immune privilege in the testis and in semen. *Hum Reprod Update*. 2001;7(5):444–449.
11. Sagoo MS, Mehta H, Swampillai AJ, et al. Primary intraocular lymphoma. *Surv Ophthalmol*. 2014;59(5):503–516.
12. Barry RJ, Tasiopoulou A, Murray PI, et al. Characteristic optical coherence tomography findings in patients with primary vitreoretinal lymphoma: a novel aid to early diagnosis. *Br J Ophthalmol*. 2018;102(10):1362–1366.
13. Frenkel S, Hendler K, Siegal T, et al. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. *Br J Ophthalmol*. 2008;92(3):383–388.
14. Pulido JS, Johnston PB, Nowakowski GS, et al. The diagnosis and treatment of primary vitreoretinal lymphoma: a review. *Int J Retina Vitreous*. 2018 May 7;4:18.