



Case report

Multimodal imaging of secondary vitreoretinal lymphoma with optic neuritis and retinal vasculitis

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ABSTRACT

Purpose: To report the findings determined by multimodal imaging in an eye with secondary vitreoretinal lymphoma (VRL) with optic neuritis and retinal vasculitis.

Observation: The case was a 71-year-old woman with a secondary VRL exhibiting optic neuritis and retinal vasculitis in her right eye. Color fundus photographs and fluorescein angiograms showed optic neuritis and vasculitis in the posterior pole of the right eye. Indocyanine green angiography showed dye staining of the retinal vein walls in the late phase. Fundus autofluorescence showed fuzzy hyper-autofluorescence surrounded by mottled hyper- and hypo-autofluorescence in the right eye. OCT showed a retina with uniform infiltration and a thickened retinal pigmented epithelium (RPE) layer, perforated RPE, small RPE detachments, and hyperreflective or isoreflective masses on the degenerated RPE layer in the marginal area. Her left eye showed a degenerated RPE and oval shaped iso-reflective lesions on the RPE.

Conclusion: The findings indicate that it is important to examine the marginal areas of eyes clinically diagnosed with VRL accompanied by optic neuritis and retinal vasculitis by multimodal imaging because these images can show the inflammatory signs of typical VRL including the sub-RPE lesions.

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1. Introduction

A vitreoretinal lymphoma (VRL) is a rare form of lymphomas that can affect the retina, vitreous, and occasionally the optic nerve head. It is mostly non-Hodgkin's diffuse large B-cell lymphoma (DLBCL). There are different types of VRL, e.g., primary VRL in which the presence of lymphoma is not detected in any other organ, and VRL with concurrent presence in the central nerve system (CNSL), and VRL secondary to a lymphoma of other systemic organs. The intraocular features in these different types of VRL are basically the same although the incidences may differ.^{1,2} The major ocular features of VRLs are an aurora-like vitreous opacity and a yellowish retinal or subretinal infiltration that is typically observed as a high intensity lesion between the retinal pigment epithelium (RPE) and Bruch's membrane in the optical coherence tomographic (OCT) images. There are also some minor clinical features such as optic disc swelling (1.8%) and retinal vasculitis (9.7%).³⁻⁶

The diagnosis of VRL is usually made by examining the vitreous fluid by histopathological examinations of the vitreal cells, polymerase chain reaction (PCR) targeting gene rearrangements of the immunoglobulin heavy chain, flow cytometric analysis of the vitreous cells, and cytokine measurements for the presence of interleukin (IL)-10 and IL-6 by enzyme-linked immunosorbent assay (ELISA).^{7,8}

However, prior to performing fluid examinations, the eyes with clinical features that suggest VRL should be carefully examined by fundus imaging techniques including OCT, fluorescein angiography (FA), indocyanine green angiography (ICGA), and fundus autofluorescence (FAF).

The quality of the retinal tomographic images has been greatly increased by the use of swept-source (SS) OCT. SS-OCT uses a light source with longer tuneable wavelengths than SD-OCT which reduces light scattering from the blood vessels and permits the acquisition of high-speed, high-resolution images.⁹

Optic neuritis and retinal vasculitis are rare disorders associated with VRLs, and only a few reports have described the findings of multimodal imaging in such cases.^{10,11} Because VRLs associated with optic neuritis and/or retinal vasculitis are difficult to differentiate from

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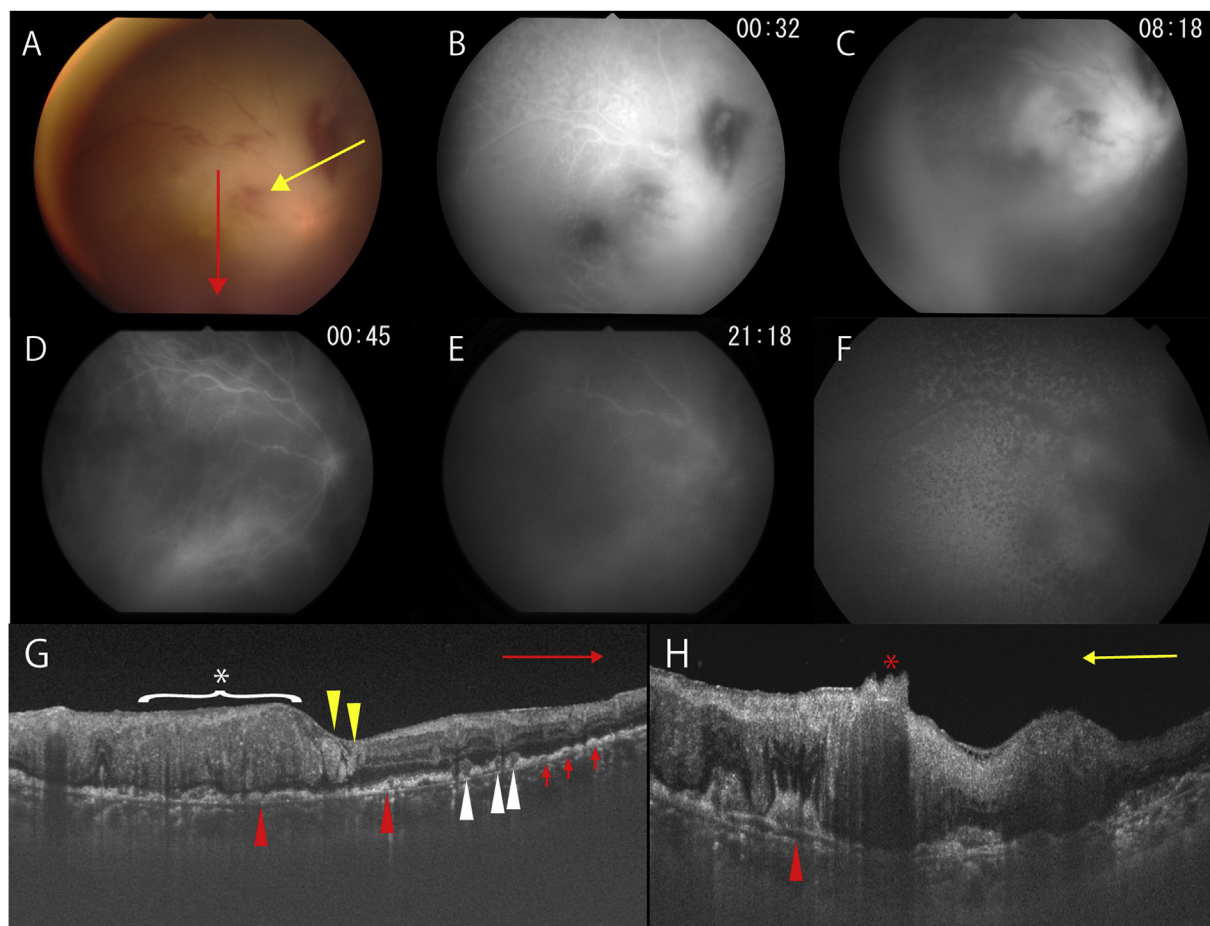


Fig. 1. Findings of the right eye of a case of vitreoretinal lymphoma (VRL) at the first examination. A: Color fundus photograph showing retinal edema, diffuse yellowish retinal changes, and inner retinal hemorrhages in the temporal to superior area around the swollen optic nerve head. B: Fluorescein angiography (FA) in the early phase reveals hyper-fluorescent lesion corresponding to the diffuse yellowish retinal lesion with a hyper-fluorescent optic nerve head. The segmental hyper-fluorescent sheaths of the retinal veins block the hemorrhages in the early phase of FA in the right eye. C: Fluorescein angiography in the late phase shows the diffuse mottled tissue staining with diffuse leakage. D: Indocyanine green angiography shows segmental hyper-fluorescent retinal veins in the diffuse yellowish lesion in the early phase. E: Indocyanine green angiography in the late phase also shows the retinal lesions as diffuse hyper-fluorescence and segmental hyper-fluorescent retinal veins. F: Fundus autofluorescence shows diffuse hyper-autofluorescence in the yellowish lesion with mottled pattern of hyper- and hypo-fluorescence around the lesion. G: OCT of macula shows the absence of retinal structures with hyper dots in the diffuse yellowish retina (*). OCT also shows a thickened RPE layer (red arrow heads), iso-reflective masses on the degenerated RPE layer (white arrowheads), small RPE detachments (red arrows), and hyperreflective oval-shaped masses (yellow heads). H: OCT around the optic nerve head shows a thick and upward hyperreflective uniform lesion with destroyed RPE, irregular fork-shaped lesion (red arrowhead), and irregular mass on the retina (red*). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

intraocular inflammatory diseases, it is important to collect data regarding the characteristic features of such types of VRL.

We report the unique findings obtained by multimodal imaging in an eye with secondary VRL associated with optic neuritis and vasculitis.

2. Case presentation

A 71-year-old woman complained of blurred vision in both eyes of three months duration. She had a history of ischemic heart disease, and was taking anticoagulant. Otherwise, her general condition was good and she had no systemic complaints.

At the first visit, her decimal best-corrected visual acuity (BCVA) was 0.2 in the right eye and 1.0 in the left eye. The intraocular pressure was within normal limits in both eyes. Slit-lamp microscopy showed 1+ cells in the anterior chamber of her right eye, the presence of intraocular lenses in both eyes, and cells in the anterior vitreous of both eyes: right eye, 2+; left eye, 1+.

Ophthalmoscopic examinations showed diffuse yellowish retinal changes and inner retinal hemorrhages in the temporal to superior area of the posterior pole. The right optic disc was swollen (Fig. 1A). The

fundus of her left eye showed many small round yellowish-white lesions in the posterior pole but the optic disc was normal (Fig. 2A).

Early phase FA of her right eye showed a hyperfluorescent lesion corresponding to the diffuse yellowish retinal lesion and a hyper-fluorescent optic nerve head, segmental hyperfluorescent sheath of the retinal veins, and hypofluorescence due to blocking by the retinal hemorrhages (Fig. 1B). In the late phase, FA showed diffuse mottled tissue staining accompanied by diffuse leakage in the right eye (Fig. 1C).

Her left eye showed many round hyperfluorescent staining corresponding to the yellowish-white lesions, and some of them showed dye leakage in the late phase (Fig. 2B and C).

ICGA showed segmental hyperfluorescent retinal veins in the diffuse yellowish lesions in the early phase and dye staining of the vessel walls in the late phase. The retinal lesions also had diffuse hyper-fluorescence in the late phase (Fig. 1D and E). Her left eye did not show significant findings in the ICGA images (Fig. 2D and E).

FAF showed fuzzy hyper-autofluorescence surrounded by mottled pattern of hyper- and hypo-autofluorescence in the region of the yellowish lesions in her right eye (Fig. 1F). In her left eye, FAF showed only mottled lesions with hyper- and hypo-autofluorescence

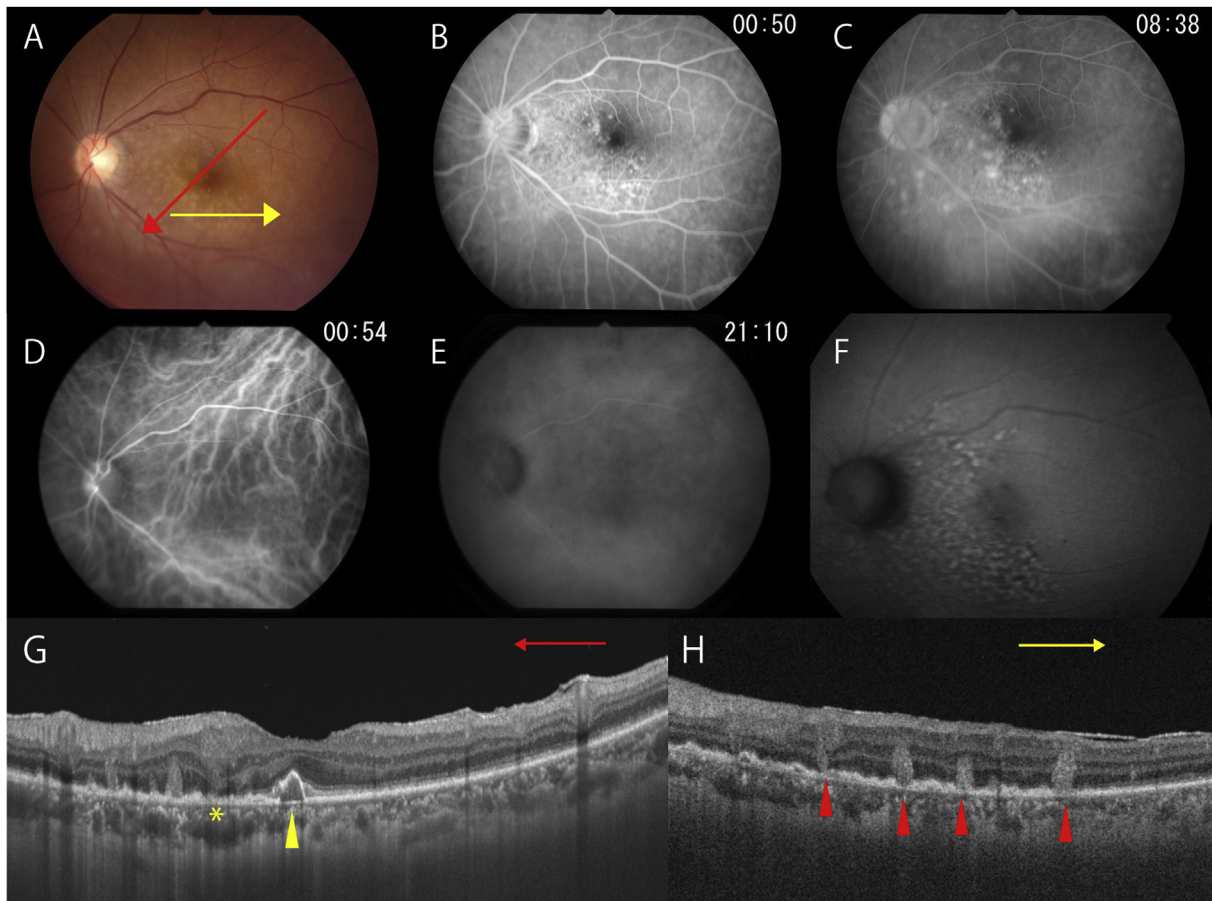


Fig. 2. Findings of the left eye of a patient with vitreoretinal lymphoma. at the first examination. A: Color fundus photograph showing many round small yellowish-white lesions in the posterior pole with normal optic nerve head. B: and C: Early phase fluorescein angiography shows many hyper-fluorescent staining of the round lesions corresponding to the yellowish-white lesions (B). Some of the lesions have signs of leakage in the late phase (C). D: and E: Indocyanine green angiogram does not show any abnormal findings. F: Fundus autofluorescence image shows mottled pattern of hyper- and hypo-fluorescence in the posterior pole. G: OCT of the macula shows degenerated RPE (*) and small pigmented epithelium detachment (yellow arrowhead). H: OCT of the mottled lesions show oval- or round-shaped hyperreflective lesions (red arrowheads) on a degenerated RPE. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

corresponding to the small yellowish-white lesions between the optic disc and the macula (Fig. 2F).

SS-OCT showed that the retinal layers were not identifiable in the area of diffuse yellowish retinal lesion in her right eye (Fig. 1G). The retinal lesion was thick, uniformly hyperreflective lesions. Hyperreflective dots and some hyperreflective irregular masses were observed intraretinally that appeared to perforate the intraretinal membrane (Fig. 1H). In the marginal areas of the uniformly infiltrated retina, a thickened retinal pigmented epithelial (RPE) layer, perforated RPE, hyperreflective or isorefractive masses on the degenerated RPE layer, and small RPE detachments were seen (Fig. 1G and H). The shapes of the masses were round, oval, or irregular fork-shaped lesion (Fig. 1G and H). SS-OCT examinations of her left eye showed degeneration of the RPE, small RPE detachments with atrophied RPE, and oval-shaped iso-reflective lesions on the RPE (Fig. 2G and H).

We performed systemic investigations including blood tests, chest X-rays were performed, and planned a brain magnetic resonance imaging (MRI). The blood tests including blood count, biochemical examinations were normal except for slightly elevated c reactive protein (1.1mg/dl). The screening blood tests for uveitis showed normal values of angiotensin converting enzyme and lysozyme, and negative results for syphilis, human T-cell leukemia virus type 1. We also examined for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus to prepare for systemic steroid treatment, immunosuppressive therapies, or surgery, but all were negative. Chest X-ray did not show

remarkable abnormality.

Although the fundus appearance and the FA findings of the right eye suggested the presence of severe optic neuritis and retinal vasculitis, FAF showed hyper-autofluorescence dots and SS-OCT showed retinal lesions in the marginal area of the yellowish retina. We therefore could not rule out the possibility of VRL, and we performed diagnostic vitrectomy on her right eye 10 days after her first visit.

The cytological examination of the vitreous cells showed that they were class IIIb. Cytokine analysis of the vitreous fluid detected IL-10 (237 pg/ml) and IL-6 (350 pg/ml) by enzyme-linked immunosorbent assay, and the IL-10/IL-6 ratio was 0.68. PCR detected monoclonal IgH gene rearrangement in multiple regions. Although the IgH rearrangement was detected by PCR and IL-10 was detected, the cytological findings were not strong, and the IL-10/IL-6 ratio was below 1. So, these results of the vitreous fluid supported the diagnosis of VRL, but they were not definitive.

However, brain MRI revealed the presence of a tumor in her right sinus cavity. Serum soluble IL-2 receptor was also measured, and was shown to be very high concentration (18300 U/ml). We then performed positron-emission tomography and computed tomography, and it revealed the presence of tumors in her right sinus cavity and pelvis, and many swollen lymph nodes in her axillary cavity, inguinal canal, and hilum of the lungs. The biopsy of the sinus cavity showed CD20-positive and CD79a-positive DLBCL.

Based on the ocular findings, vitreous fluid results, and systemic

investigations, we diagnosed this patient with VRL secondary to systemic DLBCL.

We performed combined chemotherapy using 400 µg of intravitreal methotrexate (MTX) injection weekly for 5 weeks in her both eyes according to the regimen we previously reported,² followed by systemic chemotherapy composed of R-THP-COP (pirarubicin, cyclophosphamide, vincristine, and prednisolone), and intravenous high-dose MTX therapy. The retinal lesions rapidly improved by the chemotherapies, but we lost track of the patient because she moved to another hospital for continuing the treatments.

3. Discussion

The major clinical findings of VRL are an aurora-like diffuse vitreous opacity and a yellowish retinal or subretinal infiltration. Such findings are commonly observed in different types of VRL including primary VRL, VRL with CNSL, and secondary VRL, and the incidence of retinal or subretinal infiltration is higher in primary VRL than in the other types of VRLs.¹ On the other hand, the incidence of the other minor findings, such as optic neuritis or retinal vasculitis, are reported to be low although the exact incidence among the different types of VRLs are not known. It is assumed that the difficulty to diagnose VRL from such findings may account for the low incidences. Therefore, it is important to carefully review such cases to identify clues to diagnose VRL with such minor findings.

VRLs showing such severe posterior intraocular inflammation may usually be misdiagnosed as posterior uveitis when examined only with indirect funduscopy or fluorescein angiographies although they are the essential diagnostic tools for intraocular inflammation. OCT may help to suspect masquerade syndrome, but its possibility may strongly be supported by FAF. We therefore recommend multimodal retinal imaging to differentially diagnose VRLs from posterior uveitis showing optic neuritis and retinal vasculitis. The OCT findings of areas of yellow-white vasculitis indicating destroyed retinal layers with hyperrefractive dots and perforated lesions. On the other hand, the OCT findings in the marginal area of the yellow-white lesion revealed a degenerated RPE, sub-RPE lesions, and the lesions on the proliferated from RPE layer. These observations confirm previous reports using SD-OCT in eyes with typical primary or secondary intraocular lymphoma.¹¹⁻¹⁴ The FAF findings of mottled pattern of hyper- and hypo-autofluorescence seen in the margins of the yellow-white retinal lesion were similar to the subretinal VRL lesions as we have reported.¹⁵ These OCT and FAF observations suggest that even if severe posterior segment intraocular inflammation masks the VRL, multimodal imaging can reveal them especially by searching the marginal areas of the inflammatory lesions. In this case, we first describe irregular fork-shaped lesion, which was due to an elongation of a lesion into the retina from the degenerated RPE. It is debatable whether lymphoma cells infiltrate from the retina to the sub-RPE,^{16,17} but the irregular fork-shaped lesion suggests that the invasion of lymphoma cells occur from the RPE layer into the retina.

FA showed severe vasculitis that resembled uveitis, and late phase ICGA showed dye staining of the vessel walls. Although the presence of retinal vasculitis is already reported,⁵ such severe vasculitis and its IA findings have not been reported in cases of VRLs. Such vascular staining seen in late-phase ICGA possibly reflect the presence of inflammation or lymphoma cells. There is no report about intravascular lymphoma in the retina, but the intravascular invasion of malignant lymphoma is reported as a rare type of lymphoma, which is one type of DLBCL.^{18,19} This type of lymphoma shows infiltration of the lymphoma cells to venous, artery and capillaries in the whole body. The cases of the intravascular lymphoma in the brain were also reported.^{20,21} The cause of the intraocular lymphoma with vasculitis is unknown but the possible hypothesis is that the intravascular invasion of DLBCL may also occur in the eyes and the vessel staining may be occurred by the infiltration of lymphoma cells. Additional evidence from other VRL cases

accompanied by severe retinal vasculitis are needed.

The diagnosis of VRL accompanied by severe optic neuritis and retinal vasculitis may be delayed because of the difficulty in differentiating VRL from uveitis. The early decision to perform diagnostic vitrectomy is important because of the poor life prognosis of patients with VRL.²

4. Conclusions

Severe optic neuritis and retinal vasculitis are rare findings in cases of VRL. The findings in our case indicate that observations of the marginal area of the inflammatory sites using multimodal imaging is important for the diagnosis of such forms of VRL. A meta-analysis of the multimodal imaging is needed to standardize the clinical features of the different types of VRL.

Patient's consent

Informed consent in writing was obtained from the patient for use their information and fundus photographs for research.

Authorship

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

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2020.100696>.

References

1. Cho BJ, Kim DY, Park UC, et al. Clinical features and treatment outcomes of vitreoretinal lymphoma according to its association with CNS lymphoma. *Ocul Immunol Inflamm.* 2018;26(3):365–371.
2. Akiyama H, Takase H, Kubo F, et al. High-dose methotrexate following intravitreal methotrexate administration in preventing central nervous system involvement of primary intraocular lymphoma. *Canc Sci.* 2016;107(10):1458–1464.
3. Kimura K, Usui Y, Goto H. Clinical features and diagnostic significance of the intraocular fluid of 217 patients with intraocular lymphoma. *Jpn J Ophthalmol.* 2012;56(4):383–389.
4. Say EA, Knupp CL, Gertsch KR, Chavala SH. Metastatic B-cell lymphoma masquerading as infectious retinitis and vasculitis. *Oncol Lett.* 2012;3(6):1245–1248.
5. Katoch D, Bansal R, Nijhawan R, Gupta A. Primary intraocular central nervous system lymphoma masquerading as diffuse retinal vasculitis. *BMJ Case Rep.* 2013. <https://doi.org/10.1136/bcr-2013-009354>.
6. Tsanaksidis G, McNeill O, Katelaris C. Primary central nervous system lymphoma masquerading as bilateral vitreous floaters. *Intern Med J.* 2012;42(4):e30–e33.
7. Sugita S, Takase H, Sugamoto Y, et al. Diagnosis of intraocular lymphoma by polymerase chain reaction analysis and cytokine profiling of the vitreous fluid. *Jpn J Ophthalmol.* 2009;53(3):209–214.
8. Kase S, Namba K, Iwata D, et al. Diagnostic efficacy of cell block method for vitreoretinal lymphoma. *Diagn Pathol.* 2016;11:29.
9. Li D, Taniguchi EV, Cai S, et al. Comparison of swept-source and enhanced depth imaging spectral-domain optical coherence tomography in quantitative characterization of the optic nerve head. *Br J Ophthalmol.* 2016;101(3):299–304.
10. Dolz-Marco R, Gallego-Pinazo R, Jung JJ, et al. Sequential multimodal imaging findings in a case of primary vitreoretinal lymphoma. *Retin Cases Brief Rep.* 2014;8(4):314–317.
11. Egawa M, Mitamura Y, Hayashi Y, Naito T. Spectral-domain optical coherence tomographic and fundus autofluorescence findings in eyes with primary intraocular

- lymphoma. *Clin Ophthalmol*. 2014;8:335–341.
12. Jang HS, Sepah YJ, Sophie R, et al. Longitudinal spectral domain optical coherence tomography changes in eyes with intraocular lymphoma. *J Ophthalmic Inflamm Infect*. 2013;3(1):59.
 13. Liang F, Barale PO, Hoang Xuan K, et al. Subretinal lymphomatous infiltration in primary intraocular lymphoma revealed by optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(9):1425–1427.
 14. 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.
 15. Ishida T, Ohno-Matsui K, Kaneko Y, et al. Fundus autofluorescence patterns in eyes with primary intraocular lymphoma. *Retina*. 2009;30(1):23–32.
 16. Salomao DR, Pulido JS, Johnston PB, et al. Vitreoretinal presentation of secondary large B-cell lymphoma in patients with systemic lymphoma. *JAMA Ophthalmol*. 2013;131(9):1151–1158.
 17. Keino H, Okada AA, Watanabe T, et al. Spectral-domain optical coherence tomography patterns in intraocular lymphoma. *Ocul Immunol Inflamm*. 2016;24(3):268–273.
 18. Matsue K, Abe Y, Narita K, et al. Diagnosis of intravascular large B-cell lymphoma: novel insights into clinicopathological features from 42 patients at a single institution over 20 years. *Br J Haematol*. 2019;187(3):328–336.
 19. Geer M, Roberts E, Shango M, et al. Multicentre retrospective study of intravascular large B-cell lymphoma treated at academic institutions within the United States. *Br J Haematol*. 2019;186(2):255–262.
 20. Prayson RA. Intravascular lymphoma mimicking vasculitis. *J Clin Neurosci*. 2016;34:224–225.
 21. Nizamutdinov D, Patel NP, Huang JH, Fonkem E. Intravascular lymphoma in the CNS: options for treatment. *Curr Treat Options Neurol*. 2017;19(10):35.