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Secondary vitreoretinal lymphoma with spontaneous regression

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ABSTRACT

Purpose: To report a patient with vitreoretinal lymphoma (VRL) secondary to systemic diffuse large B-cell lymphoma, who had two episodes of spontaneous regression.

Observations: An 80-year-old Nicaraguan male with a history of treated systemic diffuse large B-cell lymphoma presented with decreased vision in his right eye over one year. The patient was found to have subretinal lesions and moderate vitreous opacities in his right eye. Cytological analysis of vitreous confirmed B-cell lymphoma. Following his systemic work-up, spontaneous clinical improvement was noted. There were no vitreoretinal or systemic lymphoma recurrences during one year of follow-up until the patient had new onset decreased vision in the left eye. He was presumed to have a recurrence of VRL supported by optical coherence tomography findings. Repeat systemic workup was negative for reoccurrence and the ocular lesions resolved spontaneously over 4 weeks.

Conclusions: Spontaneous regression of intraocular lymphoma can rarely occur. Multimodal imaging has an essential role in diagnosing and monitoring recurrence of this disease.

1. Introduction

Primary vitreoretinal lymphoma (VRL) is a rare malignancy, with approximate incidence of 0.047 cases per 100,000 people per year[1] and is a subset of primary central nervous system lymphoma (PCNSL), and often associated with concomitant CNS lymphoma.[2] In contrast, secondary VRL develops outside the CNS from systemic lymphoma and accounts for 12–19% of cases of VRL.[3,4] Both primary and secondary VRL are most commonly diffuse large-B cell lymphoma (DLBCL) in origin.[1,3] Spontaneous remissions of DLBCL, regardless of location are rare.[5] We report a patient with VRL secondary to diffuse large B-cell lymphoma who had two episodes of spontaneous regression.

2. Case report

An 80-year-old Nicaraguan male presented with a history of painless decreased vision in his right eye. Three years earlier, he presented with a large retroperitoneal mass causing hydronephrosis, multiple gastric ulcers, and intra-abdominal lymphadenopathies. Following a gastric biopsy, he was diagnosed with diffuse-large B cell lymphoma (DLBCL) stage IIB. At the time of diagnosis, CNS or intraocular involvement was absent. Subsequently, he completed six cycles of the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy regimen and achieved remission. Prior to his ophthalmic evaluation, he had been monitored without any signs or symptoms suggestive of recurrence. Ocular history was significant for non-clearing vitreous hemorrhage of unclear etiology in the right eye for which pars plana vitrectomy was performed.

On initial ophthalmological examination, best-corrected visual acuity (BCVA) was hand movements (HM) in the right eye and 20/40 in the left eye. A right relative afferent pupillary defect was present. Slit-lamp examination revealed 1+ anterior chamber cell, 1+ vitreous cell, and trace vitreous haze in the right eye. His right fundus exam was notable for diffuse intraretinal and subretinal infiltration, affecting predominantly the optic disc and peripapillary area. (Fig. 1A and B). Examination of the left eye was unremarkable. Spectral-domain optical

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coherence tomography (SD-OCT) of the right eye revealed subretinal and sub-RPE deposits, pronounced intraretinal thickening, subretinal fluid and retinal pigment epithelium (RPE) irregularity (Fig. 1C). Fundus autofluorescence (FAF) showed an area of hypo-autofluorescence (due to the masking effect of the infiltrates) and areas of mottled hyper-and hypo-autofluorescence (Fig. 1D). Fluorescein angiography (FA) of the right eye showed leakage of the optic disc and peripapillary areas, as well as staining and leakage of lymphomatous lesions (Fig. 1E and F). The patient declined diagnostic pars plana vitrectomy. A vitreous tap in the right eye was performed and cytology of the vitreous sample revealed large atypical lymphoid cells with scanty basophilic cytoplasm and large segmented nuclei consistent with intraocular large B-cell lymphoma.

The patient was referred to oncology for evaluation and underwent extensive workup including blood work, positron emission tomography (PET) scan, brain magnetic resonance imaging (MRI), and lumbar puncture for cerebrospinal fluid (CSF) analysis, all of which were unremarkable for a reoccurrence of systemic disease. The patient was reluctant to pursue further treatment including local therapy. On subsequent follow-up two months after his presentation, visual acuity remained at HM and a significant reduction of intraretinal and subretinal infiltration was noted (Fig. 2A). FAF of the right eye also revealed a decrease in the hypo-autofluorescence area corresponding to an apparent improvement (Fig. 2B). Additionally, OCT macula of the right eye showed thinning and atrophy (Fig. 2C).

The patient was subsequently lost to follow up and presented 1-year later with new onset decreased vision in the left eye for 2 weeks. At this visit, the BCVA of his right eye was stable at HM while the left eye had declined to 20/63. Slit-lamp examination revealed a quiet anterior chamber bilaterally. Right fundus examination revealed no vitreous cells, an unchanged submacular scar and mottling of the RPE. In the left eye, new 2+ vitreous cell was noted without visible retinal lesions. OCT macula of the left eye showed disruption of ellipsoid zone and an intraretinal vertical hyperreflective lesion located inferotemporally to the fovea (Fig. 3B).

The patient was diagnosed with a presumed second isolated ocular

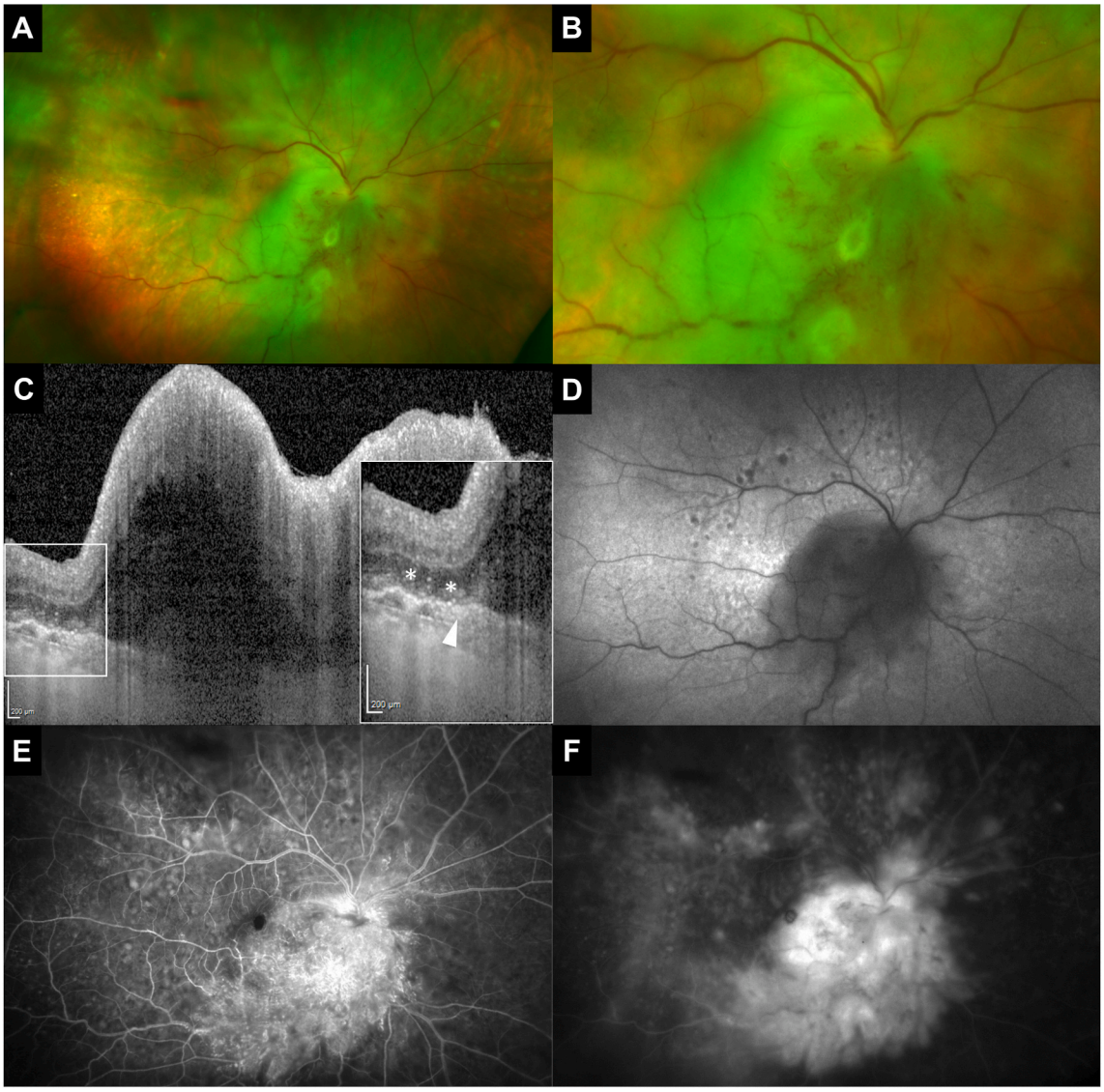

Fig. 1. Multimodal imaging of the right eye at initial presentation.
Color fundus photograph showed diffuse subretinal and retinal infiltrates, affecting predominantly the optic disc and the peripapillary area (A) with higher magnification (B) OCT macula showed diffuse retinal thickening with RPE irregularity as well as hyperreflective subretinal (asterisk) and sub-RPE deposits (arrow head) (C) Fundus autofluorescence showed area of hypo-autofluorescence corresponding to infiltrates surrounded by mottled pattern of hyper-and hypo-autofluorescence (D) Fluorescein angiography (FA) of the right eye showed leakage of the optic disc and peripapillary areas, as well as staining of lymphomatous lesions on early (E) and late frames (F). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

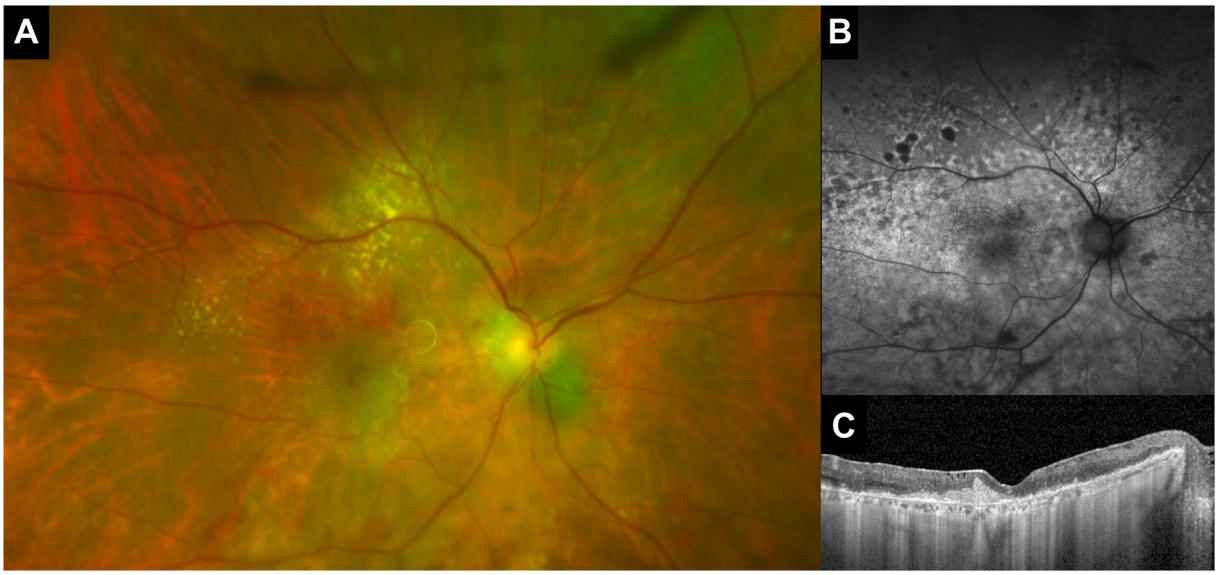

Fig. 2. Multimodal imaging of the right eye at 2 months after initial presentation.
Color fundus photograph showed spontaneous improvement of intraretinal and subretinal infiltrates (A) Fundus autofluorescence revealed decreased hypo-autofluorescence at the optic disc and the peripapillary area with a mottled pattern of hyper-and hypo-autofluorescence (B) OCT macula showed diffuse loss of outer retina layers, subretinal fibrosis, and an epiretinal membrane (C). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

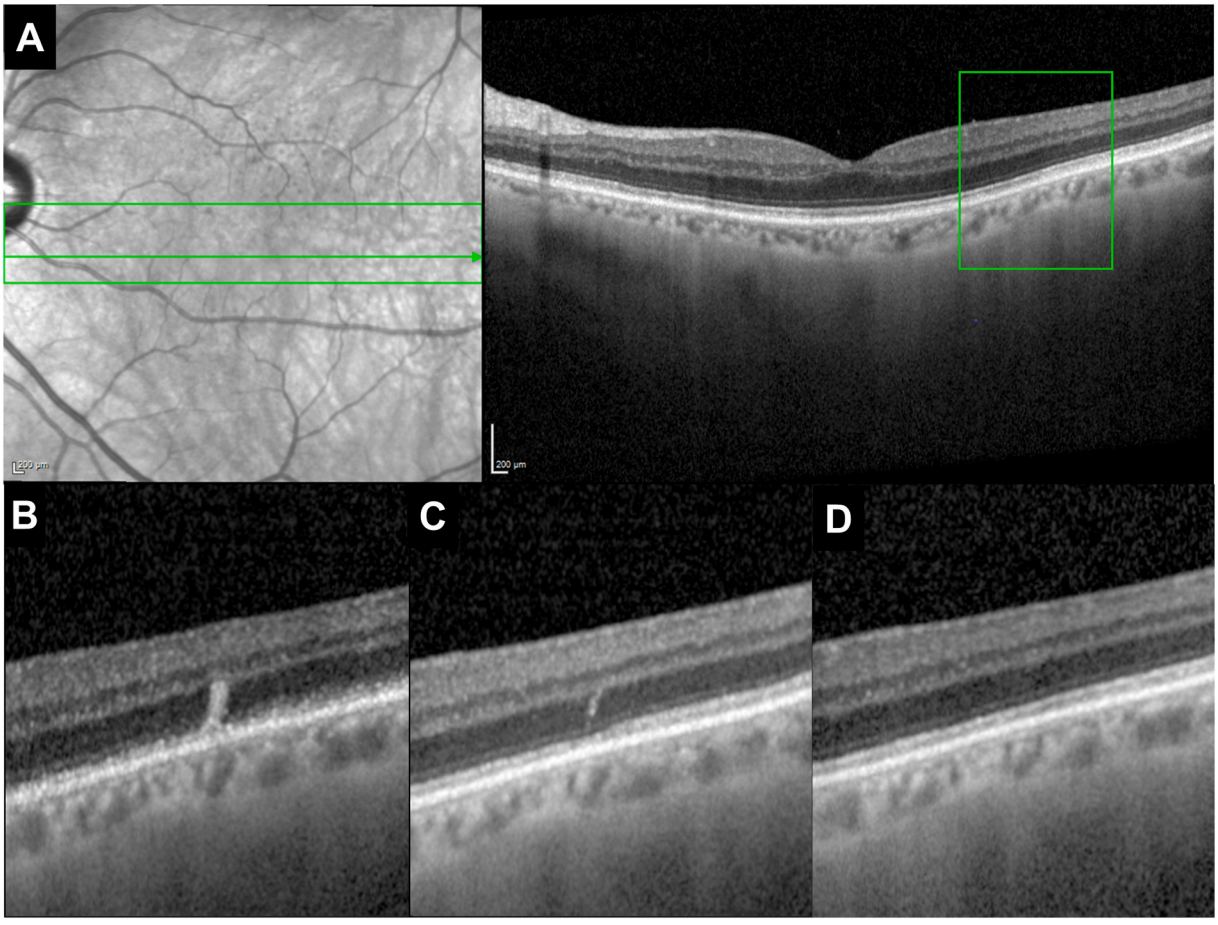

Fig. 3. Sequential OCT of the inferior macula. At initial presentation, OCT showed normal foveal contour without intraretinal lesion (A). At 1 year after initial presentation, disruption of ellipsoid zone (EZ) and a vertical hyperreflective lesion (VHRL) were noted (B). At 1 week after (B), spontaneous reconstitution of EZ was demonstrated and VHRL decreased in size and intensity (C). At 1 month follow up, EZ had fully reconstituted and VHRL completely resolved (D).

recurrence based on clinical appearance and OCT findings. MRI, PET scan, and lumbar puncture were repeated, and all were negative for a systemic reoccurrence. Following his systemic work up, on follow-up visits, he reported spontaneous improvement of vision associated with improved visual acuity to 20/40 in the left eye. Serial OCT demonstrated reconstitution of the ellipsoid zone. In addition, the vertical hyper-reflective lesion appeared to regress and resolved by 1 month (Fig. 3C and D). One month later, BCVA in the left eye improved to 20/32 and there were no signs of recurrence at subsequent appointments.

3. Discussion

This report describes spontaneous regression twice in a patient with secondary VRL. Notably, the first presentation in the right eye demonstrated significant intraretinal and subretinal lesion burden.

Secondary or metastatic vitreoretinal lymphoma is less common that primary VRL.[3,4] Most secondary lymphomas arise from non-Hodgkin lymphomas and primarily affect the uveal tissue because of the abundance of blood supply. However, other ocular presentations of secondary lymphoma have also been reported, including vitreoretinal involvement,[3,6,7] retinitis appearance,[8,9]vasculitis[10,11] and optic nerve infiltration.[12,13] In a series of 101 pathological specimens of VRL cases by Cao et al., only twelve cases of systemic lymphoma were identified with most having a B-cell origin.[3] Moreover, the nasopharynx, testis, and skin were common primary sites. More recently, a retrospective review found up to 19% of patients with VRL had an associated systemic lymphoma with the most primary sites included the skin, testis, liver, and breast.[4] Compared to those not associated with systemic lymphoma, both were comparable in terms of clinical features and ocular treatment response.[4] Both presentations in our patient had clinical features similar to PVRL. The vertical hyper-reflective lesion (VHRL) evident on OCT during the second recurrence has been described by Deák et al.[14] In their series, VHRLs were identified in 7 of 12 eyes with vitreoretinal lymphoma and postulated to be due to lymphomatous retinal infiltration arising from retinal vessels.

Spontaneous regression rarely occurs in lymphoma, in particular patients with diffuse large B cell lymphoma.[15] Notably, there have been a few reports to date of spontaneous regression of PVRL. Mantopoulos et al. described a 60-year-old female with PVRL who developed spontaneous regression of the subretinal and sub-RPE lesions, leaving areas of RPE atrophy within 3-months after her first diagnosis.[16] Additionally, Kase et al. reported an 80-year-old man with PVRL and with no light perception visual acuity, who underwent enucleation.[17] Spontaneous regression was determined based on the absence of lymphomatous cells in enucleated specimen. Interestingly, abundant $CD8^+$ T lymphocytes infiltrating the subretinal space were identified implicating host T lymphocytes and their cytotoxic anti-tumor activity. Although the exact mechanisms of regression are unclear, immunoregulatory mechanisms are thought to be involved including concurrent infection and host augmentation of the anti-host immune response by anti-tumor cellular and humoral immunity.[18–21] The spontaneous regression of tumors that has been observed in post-transplant patients following the cessation of immunomodulatory therapy is also suggestive of an anti-tumor host immune response. Additionally, surgery has also been implicated as a factor associated with spontaneous regression. Snijder et al. explored a cohort of 17 cases of DLBCL with spontaneous regression and identified that 95% of patients developed spontaneous regression after tissue biopsy and speculated that the pro-inflammatory stimulus of the biopsy may have "primed" the cytotoxic anti-tumor response.[22]

4. Conclusion

In summary, our case describes two episodes of spontaneous regression in a patient with vitreoretinal lymphoma secondary to systemic DLBCL with localized intraocular reoccurrences and highlights the utility of multimodality imaging in following these patients.

Patient consent

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

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Authorship

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

Declaration of competing interest

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References

1. Levasseur SD, Wittenberg LA, White VA. Vitreoretinal lymphoma: a 20-year review of incidence, clinical and cytologic features, treatment, and outcomes. *JAMA Ophthalmol*. 2013;131(1):50–55.
2. Fend F, Ferreri AJM, Coupland SE. How we diagnose and treat vitreoretinal lymphoma. *Br J Haematol*. 2016;173(5):680–692.
3. Cao X, Shen D, Callanan DG, Mochizuki M, Chan C-C. Diagnosis of systemic metastatic retinal lymphoma. *Acta Ophthalmol*. 2011;89(2):e149–e154.
4. Mashayekhi A, Dalvin LA, Lim L-AS, et al. Association of vitreoretinal lymphoma with systemic lymphoma. *Retina*. 2021;41(2):259–265.
5. Stanoszek LM, Smith LB, Grajewski K, Reneau JC, Wilcox R, Perry AM. Spontaneous regression of high-grade B-cell lymphoma with MYC and BCL2 rearrangements: case report and literature review. *Clin Lymphoma, Myeloma & Leukemia*. 2021;21(2):e120–e125.
6. Mashayekhi A, Shukla SY, Shields JA, Shields CL. Choroidal lymphoma: clinical features and association with systemic lymphoma. *Ophthalmology*. 2014;121(1):342–351.
7. Salomão DR, 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.
8. Reddy V, Winslow R, Cao JH, Robertson ZM, Chen B, Ufret-Vincenty RL. Vitreoretinal lymphoma, secondary to non-CNS systemic lymphoma, masquerading as an infectious retinitis. *Am J Ophthalmol Case Rep*. 2019;16:100545.
9. Ryan ME, Shantha JG, Grossniklaus HE, Yeh S. Secondary vitreoretinal lymphoma masquerading as acute retinal necrosis. *Ophthalmic Surg Laser Imag Retina*. 2015;46(10):1048–1050.
10. Ishida T, Takase H, Arai A, Ohno-Matsui K. Multimodal imaging of secondary vitreoretinal lymphoma with optic neuritis and retinal vasculitis. *Am J Ophthalmol Case Rep*. 2020;18:100696.
11. Say EAT, Knupp CL, Gertsch KR, Chavala SH. Metastatic B-cell lymphoma masquerading as infectious retinitis and vasculitis. *Oncol Lett*. 2012;3(6):1245–1248.
12. Mohd Fauzi Yap MFB, Mohd Zain A, Tumain NR, Palaniappan S, Nasaruddin RA, Md Din N. Optic nerve infiltration in systemic metastatic retinal lymphoma (SMRL): multimodal imaging and challenges in diagnosis. *Ocul Immunol Inflamm*. 2020:1–6. Published online September 24.
13. Wong D, Danesh-Meyer H, Pon J-A. Infiltrative lymphomatous optic neuropathy in non-Hodgkin lymphoma. *J Clin Neurosci*. 2015;22(9):1513–1515.
14. Deák GG, Goldstein DA, Zhou M, Fawzi AA, Jampol LM. Vertical hyperreflective lesions on optical coherence tomography in vitreoretinal lymphoma. *JAMA Ophthalmol*. 2019;137(2):194–198.
15. Abe R, Ogawa K, Maruyama Y, Nakamura N, Abe M. Spontaneous regression of diffuse large B-cell lymphoma harbouring Epstein-Barr virus: a case report and review of the literature. *J Clin Exp Hematop*. 2007;47(1):23–26.
16. Mantopoulos D, Cebulla CM. Multimodal imaging of spontaneously shifting primary vitreoretinal lymphoma. *Ocul Oncol Pathol*. 2015;1(4):237–240.
17. Kase S, Namba K, Jin X-H, Kubota KC, Ishida S. Spontaneous regression of intraocular lymphoma. *Ophthalmology*. 2012;119(5):1083–1084.
18. Gattiker HH, Wiltshaw E, Galton DA. Spontaneous regression in non-Hodgkin's lymphoma. *Cancer*. 1980;45(10):2627–2632.
19. Krikorian JG, Portlock CS, Cooney P, Rosenberg SA. Spontaneous regression of non-Hodgkin's lymphoma: a report of nine cases. *Cancer*. 1980;46(9):2093–2099.

20. Wiernik PH. Spontaneous regression of hematologic cancers. *Natl Cancer Inst Monogr*. 1976;44:35–38.
21. Grem JL, Hafez GR, Brandenburg JH, Carbone PP. Spontaneous remission in diffuse large cell lymphoma. *Cancer*. 1986;57(10):2042–2044.
22. Snijder J, Mihyawi N, Frolov A, Ewton A, Rivero G. Spontaneous remission in diffuse large cell lymphoma: a case report. *J Med Case Rep*. 2019;13(1):28.