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Diagnosis of Secondary Vitreoretinal Lymphoma With Neurosurgical Stereotactic Biopsy: A Multimodal Diagnostic and Imaging Approach

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Abstract

Purpose: To describe an atypical diagnostic approach with multimodal imaging analysis in a patient with primary testicular lymphoma who experienced secondary vitreoretinal recurrence. **Methods:** A single case was evaluated. **Results:** A complete ophthalmologic examination, including optical coherence tomography (OCT), fluorescein angiography (FA), fundus autofluorescence (FAF), neuroimaging, and stereotactic biopsy, was performed. A dilated fundus examination showed bilateral white subretinal lesions with pinpoint hyperfluorescence on FA and central hypoautofluorescence with peripheral hyperautofluorescence on FAF. OCT revealed bilateral subretinal hyperreflective material. Magnetic resonance imaging of the brain revealed a 7 mm contrast-enhancing lesion of the right thalamus. Following a negative diagnostic vitrectomy, subsequent stereotactic biopsy of the lesion confirmed recurrent lymphoma. **Conclusions:** This case emphasized the importance of using multidisciplinary methods to confirm a diagnosis of secondary vitreoretinal lymphoma and allowed an appropriate treatment plan to be made.

Keywords

ocular oncology, leukemia/lymphoma, imaging, OCT, widefield fundus imaging, ocular metastatic lesions, retina, surgical techniques and maneuvers, systemic conditions and the eye

Introduction

Vitreoretinal lymphoma is a rare intraocular malignancy that represents less than 1% of all cases of non-Hodgkin lymphoma.[1] Primary vitreoretinal lymphoma is classified as a variant of primary central nervous system (CNS) lymphoma and has a high association with concomitant CNS disease (16%–34% at time of presentation).[1,2] While up to 90% of patients with vitreoretinal lymphoma will ultimately develop CNS involvement, 15% to 25% of patients with primary CNS lymphoma have or will develop vitreoretinal lymphoma.[3–5] The recurrence of a systemic lymphoma in the vitreous, retina, or optic nerve is much less frequent and typically occurs through hematogenous spread.[6]

Primary testicular non-Hodgkin lymphoma is the most common testicular tumor in men older than 60 years.[7] The vast majority of testicular lymphomas, as well as primary CNS lymphomas and vitreoretinal lymphomas, are diffuse large B-cell lymphomas. The testes, CNS, and eye are considered immune-privileged by virtue of their respective blood–organ barriers, and each may be affected by relapse of testicular lymphoma. Although testicular lymphoma in general has a relapse rate of up to 50%, with as many as 72% of cases recurring in these immune-privileged extranodal sites, its association with vitreoretinal lymphoma is extremely rare.[8] B-cell lymphoma cells evade surveillance due to a structural loss of human leukocyte antigen class I and II expression in extranodal lymphoma cells.[9] These genetic alterations in the human leukocyte antigen region, including homozygous deletions of human leukocyte antigen class II genes in diffuse large B-cell lymphoma cells, allow lymphoma cells to evade recognition by CD4 and CD8 cytotoxic T-cells.[9] This mechanism may contribute to the high rate of relapse and reduced efficacy of chemotherapy for diffuse large B-cell lymphomas originating in extranodal sites.[10]

A known masquerader, vitreoretinal lymphoma (whether primary or secondary) often presents with an indolent clinical course mimicking chronic posterior uveitis and may respond to initial steroid therapy, lending to an often delayed definitive

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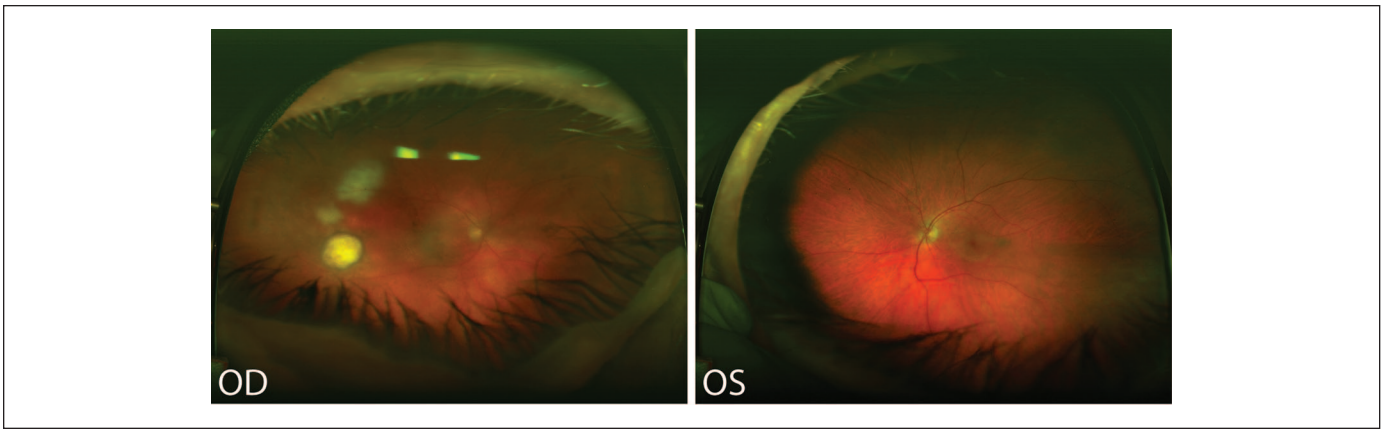

Figure 1. Widefield fundus images before symptom onset at initial examination show a peripheral, well-circumscribed area of retinal fibrosis in the right eye that appeared quiescent with no other evidence of inflammation when paired with dilated fundus examination. The examination of the left eye was unremarkable.

diagnosis. The gold standard of diagnosis involves cytology to identify lymphoma cells in the eye, which can be achieved after diagnostic vitrectomy, with or without chorioretinal biopsy. The diagnosis can be aided by molecular analysis (flow cytometry, cytokine ratios, and polymerase chain reaction [PCR] testing). Few studies[8,11–13] have reported secondary vitreoretinal lymphoma simultaneously or following primary testicular lymphoma, with many cases found through diagnostic vitrectomy with molecular analysis, tumor biopsy from the testes, and biopsy or cytologic analysis of cerebrospinal fluid (CSF).

In many cases, a negative vitrectomy or CSF sample with limited cells as a result of corticosteroid treatment, creates a challenge in diagnosis.[4] Absence of the anterior segment, and sometimes vitreous inflammation and spontaneous resolution of subretinal lesions, may limit the yield of an anterior chamber or vitreous tap or retinotomy with subretinal aspirate.[4] Although considered a standard for diagnosis of CNS lymphoma, brain/leptomeningeal biopsy represents a rare diagnostic approach for intraocular lymphoma given the availability of alternative diagnostic methods and the risks associated with stereotactic biopsy. Such risks include intracranial hemorrhage or postoperative neurologic deficit in up to 8% of cases.[14] To arrive at a definitive diagnosis, stereotactic brain biopsy can be performed in patients with suggestive lesions on magnetic resonance imaging (MRI) and negative vitrectomy and CSF samples.[15]

Our case highlights an uncommon diagnostic approach using a stereotactic brain biopsy for secondary vitreoretinal lymphoma and adds a depth of retinal imaging findings that may assist in the diagnosis and management of these cases.[2,11,16,17]

Case Report

A 77-year-old asymptomatic White man was referred for evaluation of a peripheral, solid, fibrotic chorioretinal lesion. He was diagnosed with diffuse large B-cell lymphoma of a single testicle 2 years before presentation and was in complete remission after radical orchiectomy and a chemotherapeutic regimen comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. Intrathecal methotrexate had previously been administered for CNS prophylaxis.

On initial evaluation, the patient's best-corrected visual acuity (BCVA) was 20/30 OD and 20/50 OS, without anterior chamber or vitreous inflammation. A dilated fundus examination showed a peripheral circumscribed area of retinal fibrosis temporally located in the right eye (Figure 1). The patient's age and the quiescent fibrotic appearance of the lesion, which remained stable in appearance for more than 6 months, suggested a diagnosis of peripheral exudative hemorrhagic chorioretinopathy.

Eight months after initial presentation, the patient experienced a dramatic decline in vision (20/200 OD and counting fingers OS) and developed photopsias in both eyes. Shortly before this abrupt change, the patient sought a second opinion, and a vitreous and chorioretinal biopsy of the retinal lesion in the right eye was performed. A 2 mL undiluted vitreous sample and a 10 mL diluted sample were obtained. The fluids were sent offsite for histopathologic evaluation, cytology, flow cytometry, culture, cell count, and cytokine expression. The biopsy was notable for extremely rare B cells, although no malignancy was identified; further analysis was not possible due to inadequacy and hypocellularity of the sample. A lumbar puncture was performed that was notable for elevated protein levels; however, cytology was inconclusive.

On examination, the anterior chamber and vitreous of both eyes remained quiet, but a dilated fundus examination of the left eye showed new, subretinal white lesions in the posterior pole (Figure 2A). In addition to the previously identified temporal lesion and biopsy site, numerous pinpoint lesions, characterized by hyperfluorescent signal with minimal leakage on fluorescein angiography (FA) (Figure 2B, top panel) and hypoautofluorescence on fundus autofluorescence imaging (FAF) (Figure 2C, top panel), were seen in the macula and superotemporal periphery of the right eye. Imaging of the left eye showed numerous lesions in the posterior pole, characterized by early hypofluorescent and late hyperfluorescent signal on FA (Figure 2B, bottom panel) and hypoautofluorescence with adjacent hyperautofluorescent stippling on FAF (Figure 2C, bottom panel).

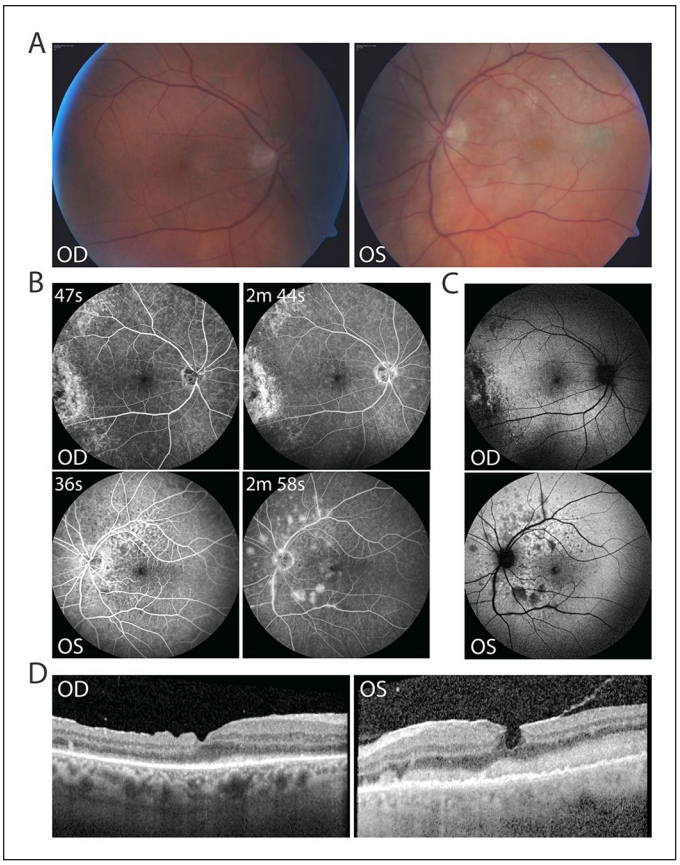

Figure 2. (A) Dilated fundus photographs at symptom onset show white parafoveal lesions that are more visible in the left eye compared with the right eye. (B) Fluorescein angiography (FA) of the right eye shows numerous lesions with minimal leakage as well as the previously identified temporal lesion, characterized by staining but no leakage. Imaging of the left eye shows numerous lesions with early hypofluorescence and late hyperfluorescent staining. (C) Fundus autofluorescence shows hypoautofluorescent lesions corresponding to lesions on FA. (D) Spectral-domain optical coherence tomography images in the horizontal raster across the fovea show a few columns of hyperreflective signal and dense, hyperreflective signal in the subretinal space that are more severe in the left eye than the right eye, suggesting an infiltrative process.

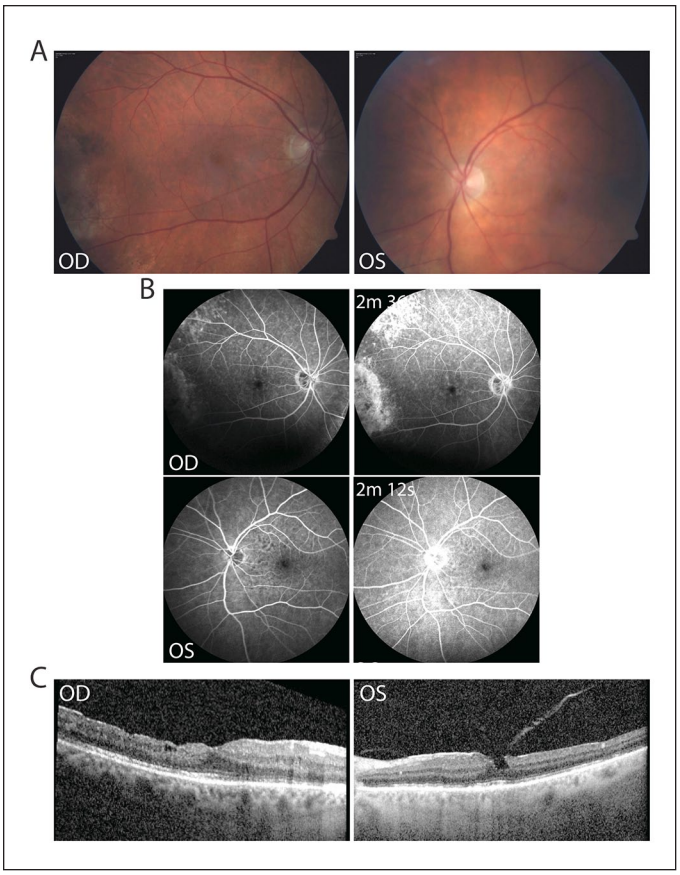

Figure 3. (A) Fundus photographs 4 months and 3 months after symptom onset and treatment initiation, respectively, show improvement in the white parafoveal lesions. (B) Fluorescein angiography shows persistence of late-staining lesions in the right eye; however, significant improvement in the previously visualized lesions is observed in the left eye. (C) Spectral-domain optical coherence tomography images in the horizontal raster across the fovea show disappearance of the intraretinal and subretinal hyperreflective signals, suggesting a robust intraocular therapeutic response to systemic therapy.

Spectral-domain optical coherence tomography (SD-OCT) showed hyperreflective material infiltrating the subretinal space of each macula (Figure 2D).

The patient had positive QuantiFERON gold testing as part of the infectious and inflammatory workup, but his treatment history was uncertain. Other etiologies (ie, sarcoidosis and syphilis) were excluded as part of his workup. An MRI of the brain and orbits revealed a 7 mm contrast-enhancing lesion involving the right thalamus.

Given the lack of cellular infiltrate in the vitreous and the patient's preference to avoid additional ocular surgery, neither a repeat diagnostic vitrectomy (eg, flow cytometry, cytokine analysis) nor a chorioretinal biopsy were performed. Because the patient's subsequent treatment course was dependent on a more certain diagnosis and after a multidisciplinary discussion with neurology and neurooncology, a stereotactic biopsy of the thalamic lesion was performed. Histopathology and flow cytometry confirmed diffuse large B-cell lymphoma. The diagnosis of vitreoretinal lymphoma secondary to relapsing testicular lymphoma was presumed based on tissue examination obtained from biopsy of the concomitant thalamic lesion, in lieu of tissue diagnosis from the vitreous and retina.

An evaluation by infectious disease and oncology resulted in initiation of 6 cycles of intravenous high-dose methotrexate, temozolomide, and rituximab and 2 cycles of intrathecal cytarabine. Subsequent QuantiFERON testing was negative, and the patient was carefully observed with the specified treatment.

Two months later, when treatment was nearly complete, there was significant radiographic improvement in the size of the brain lesion, and the patient's BCVA rapidly improved to 20/30 OD and 20/70 OS. Dilated fundus examination of the left eye showed a dramatic disappearance of the white infiltrative lesions. FA showed residual staining primarily in the left eye and in the temporal fibrotic lesion/superotemporal macula of the right eye (Figure 3, A–B), and SD-OCT (Figure 3C) showed

residual staining in both eyes. Given the patient's robust ocular response to therapy, no additional therapy was recommended.

Conclusions

Relapse of testicular lymphoma in extranodal sites such as the eye is uncommon. Several contributing mechanisms have been described, including homozygous deletions of human leukocyte antigen class II genes in diffuse large B-cell lymphomas arising in immune-privileged sites.[9] There have been several reported cases of relapse of testicular lymphoma in the eye, although all cases were diagnosed with vitreous, subretinal, or CSF samples, and none required stereotactic biopsy to aid in diagnosis.[8,11–13,18–20] One series found a successful diagnosis of diffuse large B-cell lymphoma from repeat diagnostic vitrectomy and flow cytometry after an initially negative sample.[12] Riemens et al[13] reported a series of 9 patients diagnosed with a combination of testicular and vitreoretinal diffuse large B-cell lymphoma, of whom 7 had concurrent CNS manifestations. However, CNS localization resulted from a combination of neuroimaging, biopsy, and cytologic analysis of CSF.

Like primary vitreoretinal lymphoma, ocular recurrence of testicular lymphoma presents a challenge in diagnosis and treatment.[11,19] This case is unique because it includes the appearance of secondary vitreoretinal lymphoma with a testicular lymphoma source on multimodal retinal imaging and showed improvement in ocular lesions with systemic treatment only. Recognizing the patterns by which vitreoretinal lymphoma manifests on SD-OCT can aid in early diagnosis.[2,11,16,17,21] Hyperreflective, diffuse subretinal infiltrates with derangement of the ellipsoid zone that ultimately improved after chemotherapy were found in this patient's case.

Vitreous biopsy with cytologic evaluation for lymphoma cells is the preferred method for diagnosis of intraocular lymphoma, although diagnostic sensitivity remains limited (45%-60%).[20] Poor sample yield in terms of volume and structural integrity of lymphoma cells contributes to a relatively low sensitivity, and thus multiple procedures, or a retinal biopsy, may be required for an accurate diagnosis.[1,20,22,23] Other methodologies that may provide additional diagnostic evidence include analysis of genetic mutations, such as *MYD88* and *CD79B*, and profiling of cytokine expression in which a diagnosis of lymphoma is supported by an increased interleukin-10:interleukin-6 ratio.[23] In our patient's case, the vitreous and retinal biopsies and lumbar puncture performed at the outside facility were inconclusive. Given these known pitfalls, the absence of vitritis, and a previously negative vitreous and CSF analysis, a stereotactic biopsy of the involved thalamus was pursued, leading to the presumed diagnosis.

Currently, there is no strong consensus on the appropriate treatment regimen for primary and secondary vitreoretinal lymphoma. External beam radiotherapy, particularly when bilateral, and intravitreal (IVT) injection of methotrexate, rituximab, or melphalan have been described. However, these local interventions have no effect on systemic disease, and CNS disease is accompanied by significant morbidity and mortality.[20,23] Of note, for unilateral involvement, Pulido et al[23] used a protocol in which IVT methotrexate and rituximab are injected weekly for the first month. As interleukin-10 levels in the anterior chamber decrease, the injection frequency is downtitrated. Patients with bilateral involvement of the eye and the brain are treated with intraocular rituximab or methotrexate with systemic methotrexate infusions, in addition to appropriate patients potentially receiving high-dose chemotherapy and autologous stem cell transplantation.[23]

Our patient had an impressive resolution of his ocular lesions with systemic treatment alone, and thus, after a detailed discussion about the risks and benefits of IVT therapy, the option of close observation was favored.

In conclusion, we present a rarely reported recurrence of testicular lymphoma in the eye and CNS. Stereotactic brain biopsy, via a multidisciplinary approach, can help confirm the diagnosis of vitreoretinal lymphoma in patients with suspicious lesions on MRI and negative vitrectomy and CSF samples.

Authors' Note

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Ethical Approval

Institutional review board approval was waived by the University of Illinois at Chicago. This retrospective review of patient data did not require ethical approval in accordance with local and national guidelines.

Statement of Informed Consent

Informed consent was not required because no identifying patient information is included.

Declaration of Conflicting Interests

Dr. Massengill receives patent royalties from Opus Genetics unrelated to this work. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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