PVRL: WHEN "UVEITIS" IS NOT UVEITIS

A steroid-responsive, uveitis-presenting phenotype was ultimately diagnosed as primary vitreoretinal lymphoma.

BY ANDREAS THEOCHARIS, MD; ROMY BEJJANI, MD; AND ERIN E. FLYNN, MD

A 58-year-old man presented with severe bilateral vision loss and flashes. His VA was counting fingers at 3 ft OU. There was no relative afferent pupillary defect, and his IOPs were 18 mm Hg OD and 16 mm Hg OS. His medical history was notable for human immunodeficiency virus, and he was on antiretroviral therapy with a reported undetectable viral load. He also had abdominal diffuse large B-cell lymphoma treated with a regimen of etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin, which had been in remission since 2017, as well as prior cryptococcal meningitis and prostate cancer, also in remission. His ocular history included glaucoma suspect, dry eye disease, and mild cataract in each eye.

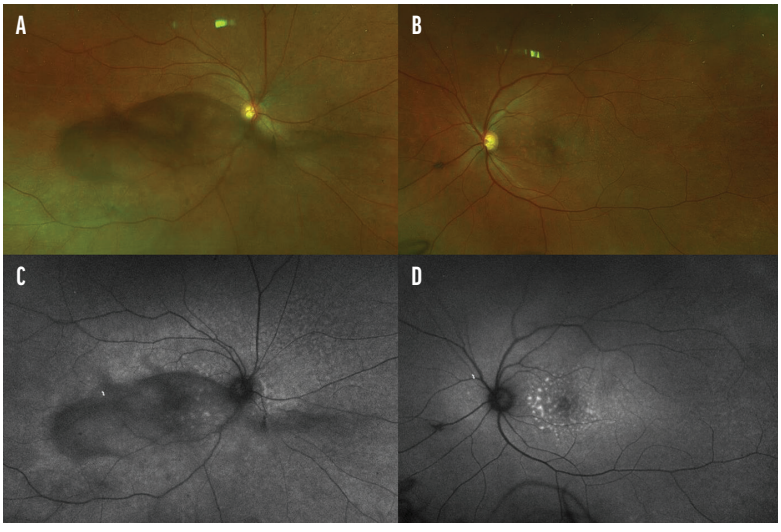

Figure 1. Widefield pseudocolor images of the right (A) and left (B) eye showed speckled yellow-white posterior pole lesions. Corresponding fundus autofluorescence images of the right (C) and left (D) eye demonstrated hyperautofluorescent abnormalities in the same regions.

IMAGING AND WORKUP

The anterior segment examination showed 2+ anterior chamber cells in each eye. There were also 3+ anterior vitreous cells with haze bilaterally, creating a panuveitis-like picture. Widefield fundus imaging demonstrated speckled, distinct, yellow-white posterior pole lesions (Figure 1A and B) with corresponding hyperautofluorescent abnormalities on fundus autofluorescence (Figure 1C and D). OCT revealed structural disruption, with subretinal and retinal pigment epithelium (RPE)-level hyperreflective material in each eye (Figure 2). Fluorescein angiography showed no evidence of vasculitis or other angiographic signs of active uveitic inflammation. The macular and subretinal lesions showed blockage, while patchy, granular staining in the midperiphery of each eye suggested RPE injury, possibly secondary to inflammation (Figure 3).

The differential diagnosis for bilateral vitritis with posterior pole lesions in an immunocompromised patient is broad, including infectious uveitis, inflammatory disease, and neoplastic masquerade syndromes, such as vitreoretinal lymphoma, choroidal metastasis, and bilateral diffuse uveal melanocytic proliferation.[1] Initial laboratory workup and chest radiography were unrevealing.

In the days following his initial examination, the patient presented to the emergency department with word-finding difficulty and blurry vision. A brain MRI demonstrated a 2.5-cm left frontal lobe lesion with surrounding edema, and a CT scan of his chest, abdomen, and pelvis showed no evidence of systemic metastatic disease. A stereotactic

brain biopsy was concerning for central nervous system (CNS) lymphoma, and a lumbar puncture was performed, which revealed large, atypical B cells positive for CD20, PAX5, and Ki-67. Immunostains were negative for CD30, CD34, CD117, and p53.

These findings were consistent with a diagnosis of diffuse large B-cell lymphoma. Hematology and oncology teams initiated treatment with intravenous methotrexate, rituximab, and dexamethasone. Given the absence of active systemic disease outside the eye and CNS, this presentation was most consistent with primary vitreoretinal lymphoma (PVRL) with concurrent CNS involvement rather than secondary ocular spread from systemic lymphoma.[2,3]

Because of persistent concern for PVRL, pars plana vitrectomy with vitreous biopsy was performed in his right eye. Cytology was nondiagnostic, showing predominantly macrophages and scattered lymphocytes without definitive evidence of lymphoma. Infectious evaluation was negative. The specimen also contained cohesive groups of bland-appearing cells of uncertain origin. There were too few B cells and insufficient remaining specimen for flow cytometry, interleukin (IL)-6 and -10 analysis, and immunohistochemistry. *MYD88* polymerase chain reaction testing was not available at the laboratory. However, given the biopsy-confirmed CNS diffuse large B-cell lymphoma, the ocular findings were presumed to represent PVRL.

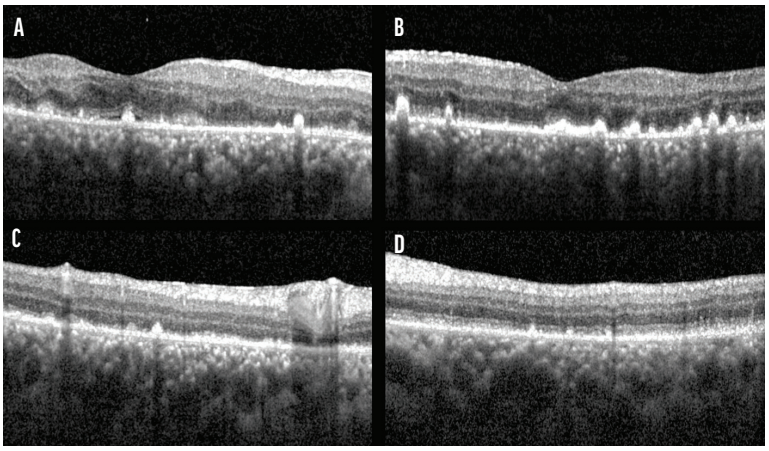

Figure 2. OCT images of the right (A, C) and left eye (B, D) showed subretinal and RPE-level hyperreflective material with associated outer retinal structural disruption. Panels A and B were centered on the fovea, whereas panels C and D highlighted additional macular involvement.

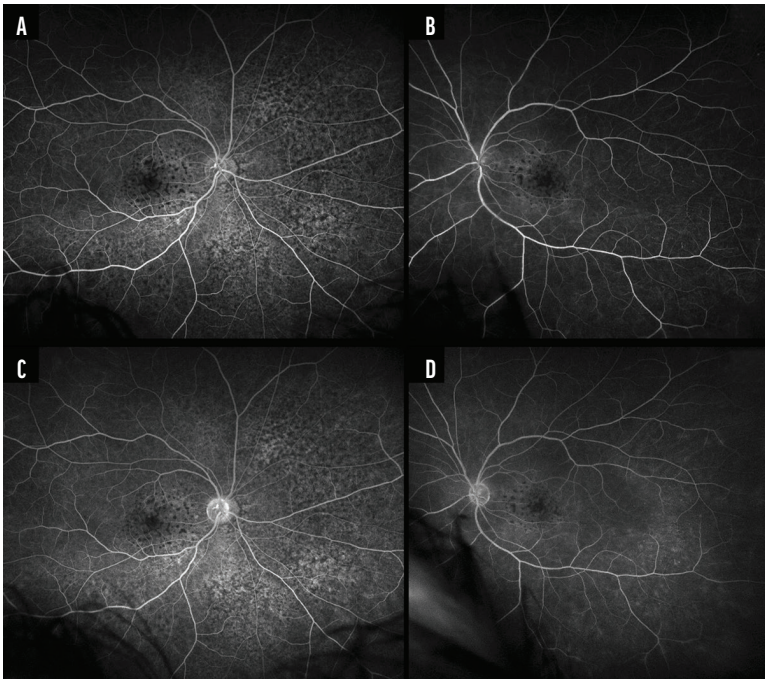

Figure 3. Fluorescein angiography of the right (A) and left (B) eye at 1 min and the right (C) and left (D) eye at 5 min demonstrated bilateral posterior pole abnormalities with blockage corresponding to the macular and subretinal lesions, without evidence of vasculitis or other angiographic signs of active uveitic inflammation.

REFRESHER ON PVRL

PVRL is a rare intraocular lymphoma within the spectrum of primary CNS lymphoma and is known for masquerading as chronic uveitis.[2,4,5] It often presents with vitritis and subretinal or sub-RPE infiltrates, and more than half of patients ultimately develop CNS involvement.[3,4] Ocular findings may be temporarily steroid responsive.[4]

A nondiagnostic vitreous biopsy does not exclude PVRL.[2] Diagnostic yield is limited by the fragility of lymphoma cells, low cellularity, prior corticosteroid exposure, and technical challenges of specimen processing.[2] Reported positive rates for vitreous cytology are variable, and current reviews recommend integrating cytology with adjunctive methods rather than relying on a single test.[3,5]

Adjunctive testing can substantially strengthen the diagnosis. Elevated IL-10 and increased IL-10/IL-6 ratio in aqueous or vitreous fluid support the diagnosis of PVRL over inflammatory uveitis, and *MYD88* mutation testing has emerged as a useful molecular adjunct, including in some aqueous humor samples.[5-8]

The case presented here highlights several practical points. First, the combination of bilateral vitritis, subretinal infiltrative-appearing lesions, and a CNS lesion should immediately raise suspicion for PVRL, even in a patient whose presentation may initially seem inflammatory.[4] Second, a negative or equivocal vitreous biopsy should not prematurely end the workup when the pretest probability for PVRL is high.[2] Finally, the diagnosis, staging, and treatment planning for PVRL require multidisciplinary coordination among ophthalmology, pathology/cytology, and oncology.[2,9]

Treatment strategies for PVRL vary, depending on whether disease is limited to the eye or accompanied

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KEY TAKEAWAYS

- The authors present a case of an immunocompromised patient with primary vitreoretinal lymphoma (PVRL) masquerading as chronic uveitis.
- The combination of bilateral vitritis, subretinal infiltrative-appearing lesions, and a central nervous system lesion should immediately raise suspicion for PVRL, even in a patient whose presentation may initially seem inflammatory.
- Intravitreal methotrexate and rituximab are effective local treatments for PVRL, whereas systemic methotrexate is commonly used when there is concurrent central nervous system disease.

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by CNS involvement.[2,3,10] Intravitreal methotrexate and rituximab are effective local treatments, whereas systemic methotrexate is commonly used when there is concurrent CNS disease.[2,3,10] In this case, the patient had difficulty with transport and expressed a preference to forgo intravitreal injections. Systemic rituximab and methotrexate were continued under the direction of hematology and oncology, along with topical prednisolone acetate for his anterior segment inflammation. His intraocular inflammation responded well to intravenous rituximab and methotrexate, and his vision improved to near baseline approximately a month after initiation of systemic therapy.

LOOK A LITTLE CLOSER

For retina specialists, the message is straightforward: Not all bilateral "uveitis" is inflammatory. In the right clinical setting, especially with subretinal infiltrates, atypical imaging, or concurrent neurologic findings, PVRL must remain high on the list.[3,4] Early suspicion and coordinated workup may reduce diagnostic delay in a disease where ocular and CNS involvement are often linked.[4,9] ■

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