Primary Vitreoretinal Lymphoma

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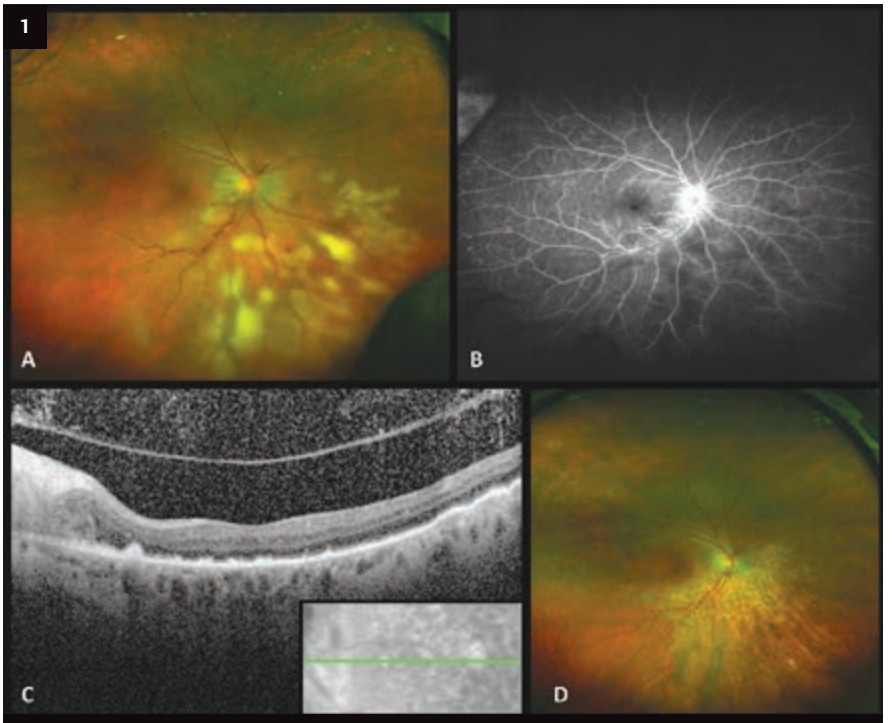
Primary vitreoretinal lymphoma (PVRL) has many names, including primary intraocular lymphoma or intraocular reticulum cell sarcoma, and it is a manifestation of primary central nervous system lymphoma (PCNSL). PVRL is a masquerade syndrome mimicking, for example, chronic uveitis; and its rarity, as well as the need for invasive diagnostic techniques, may delay diagnosis for up to 21 months after presentation.[1] The poor systemic prognosis for this condition makes it essential to keep PVRL in the differential for chronic inflammatory conditions.



CASE STUDY. This 63-year-old woman has PVRL with central nervous system involvement. (A) Discrete and coalescent elevated yellow subretinal lesions are visible inferior and nasal to the optic disc. (B) Fluorescein angiogram shows hypofluorescent spots corresponding to areas of retinal deposits. (C) Optical coherence tomography demonstrates several nodular subretinal lesions temporal to the optic disc. (D) Fundus image 2 months after beginning methotrexate therapy shows improvement and granularity of previously active nasal lesions.

Epidemiology

PVRL is a rare non-Hodgkin lymphoma. The true incidence of intraocular lymphoma is unknown, but based on its co-occurrence in approximately 20% of patients with PCNSL, the estimated incidence is between 0.02 and 0.1/100,000 in the United States.[2] While it has no race predilection, PVRL typically affects women in their fifth to sixth decade.

Association With CNS Lymphoma

PVRL often occurs concurrently with central nervous system lymphoma (CNSL); in fact, up to 90% of patients presenting with PVRL will develop CNSL within 29 months.[3] Conversely, as many as 28% of patients with PCNSL have concurrent intraocular involvement.[4] The most common form of PVRL is a diffuse large B-cell type that expresses specific ligands, leading to preferential homing to the retinal pigment epithelium (RPE) from choroidal vasculature.

Clinical Presentation

The disease's insidious onset coupled with vague complaints from patients with PVRL are among the factors that make early diagnosis difficult. The differential diagnosis is broad and includes other ocular lymphomas, non-lymphomatous neoplastic conditions, and non-neoplastic conditions of the retina (Table 1).

Symptoms. Nonetheless, a variety of clinical observations aid in diagnosis of PVRL. Typically, the disease mimics

a steroid-resistant chronic uveitis with associated vitritis. The most common ocular complaints reported by patients include blurred vision, painless loss of vision, floaters, red eye, and photophobia. If PVRL presents concurrently with CNSL, there may be behavioral changes and neurological findings such as hemiparesis and ataxia.

Signs. On exam, clinical signs may overlap with those of chronic posterior uveitis. Anterior chamber signs may include mild cells and flare, but more typically, these signs are absent.

Vitritis is common in PVRL and may manifest as an "aurora borealis" effect as cells gather along vitreal fibers, especially in the superior peripheral vitreous.[2] In addition, the vitreous cells in PVRL tend to be larger and less abundant than those found in typical vitritis. Although it is not common, the classic "leopard spot" collection of subretinal pigmented lesions that coalesce over time may appear on funduscopic examination (Fig. 1A).[2] Retinal whitening, as seen in viral retinitis, is not a hallmark of this disease. Rarely, PVRL may be associated with exudative retinal detachment, a fundus mass, or concurrent optic nerve swelling.

Diagnosis

A patient who is 50 years or older with steroid-resistant uveitis or persistent vitritis, minimal fundus changes, and generally preserved visual acuity should raise suspicion for PVRL.

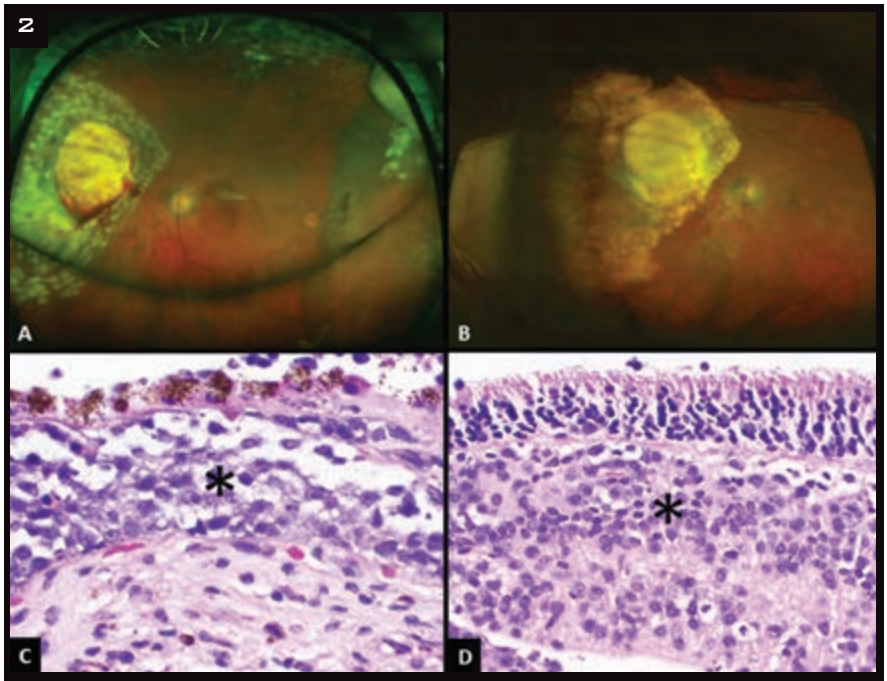
Imaging. Ophthalmic imaging studies, though not specific or diagnostic, may help validate clinical suspicion of the disease. Fluorescein and indocyanine green angiography may exhibit localized hypofluorescent spots from subretinal infiltrate (Fig. 1B) or hyperfluorescent window defects. Features present in other posterior uveitic conditions are not commonly seen, including perivascular staining, vessel leakage, cystoid macular edema, or optic nerve swelling.

Fundus autofluorescence patterns are typically normal but may highlight clinically observed areas of brown "leopard spots" as bright hyperautofluorescence. Chronic changes to the RPE may instead produce focal areas of dark hypoautofluoresence.

New findings that have been identified on optical coherence tomography include cellular infiltrates in the vitreous, focal pockets of subretinal hyperreflective material between the RPE and Bruch's membrane (Fig. 1C), and small pockets of RPE detachments.

Ophthalmic ultrasound is helpful to demonstrate choroidal thickening and rule out intraocular or orbital mass lesions as seen in choroidal lymphoma.

Laboratory testing. Once PVRL is considered in the differential diagnosis, more common causes of ocular inflammation should be eliminated, and directed systemic laboratory testing is



CHORIORETINAL BIOPSY. (A) Immediate postoperative appearance after full-thickness chorioretinal biopsy with fresh endolaser and silicone oil tamponade. (B) Healed retinal infiltration after systemic chemotherapy. (C) Infiltrate of malignant lymphoid cells (*) is seen between the RPE and choroid (H&E ×60). (D) Neurosensory retina with an infiltrate of malignant lymphoid cells (*). The outer nuclear layer is at the top of the image (H&E ×40).

Table 1 Differential Diagnosis of PVRL

Neoplastic Conditions	Non-Neoplastic Conditions	
	Infectious	Noninfectious
Amelanotic melanoma	Chronic endophthalmitis (*Propionibacterium acnes* lens–associated endophthalmitis; endogenous endophthalmitis)	Acute posterior multifocal placoid pigment epitheliopathy
Choroidal lymphoma	CMV retinitis	Atypical Fuchs heterochromic iridocyclitis
Metastatic malignancy	HSV retinitis	Behçet disease
Primary uveal lymphoma	Herpes zoster ophthalmicus	Birdshot chorioretinopathy
Secondary intraocular lymphoma	Retinochoroidal toxoplasmosis (extensive)	Branch retinal artery occlusion with multifocal chorioretinal scars
	Syphilis	Frosted branch angiitis
	Tuberculosis	Langerhans cell histiocytosis
	Whipple disease	Sarcoidosis

A, B: DUKE EYE CENTER; C, D: THOMAS J. CUMMINGS, MD

usually needed. Definitive diagnosis requires identification of malignant lymphoid cells in the eye.

When vitritis is the predominant clinical sign, diagnostic pars plana vitrectomy to obtain both undiluted and partially diluted vitreous specimens is preferable to aqueous fluid collection or bedside vitreous tap. If multifocal white subretinal deposits are seen with minimal vitreous cells, a diagnostic vitrectomy may be combined with full-thickness chorioretinal biopsy or needle aspiration of subretinal material (Fig. 2). Repeat biopsies may be required.

In all cases, specimens must be processed immediately and preferably hand-delivered by the operating surgeon to the laboratory for prompt analysis. After careful discussion with the pathologist, the surgeon should be certain that testing facilities are available for cytopathology.

Although cytopathology is most sensitive for detecting abnormal lymphoid cells, biomolecular analyses are available to bolster the diagnosis of B-cell PVRL, including detectable CD20, CD79, and PAX5. In rare cases, T-cell-dominated lymphoma may reveal CD3 and CD8 markers. Flow cytometric analysis may identify clonal B-cell populations on the basis of cell surface markers. Further tests include immunohistochemistry and elevated IL-10 to IL-6 ratio greater than 1, but clinicians should be aware of the low sensitivity of this method of testing.

If the diagnosis is confirmed, a team approach with a medical oncologist trained in treatment of CNS lymphoma is recommended to help coordinate systemic testing, including neuroimaging and lumbar puncture.

Treatment and Prognosis

Management of PVRL remains controversial, but it generally employs a multimodal approach including systemic therapy, radiotherapy, and intravitreal chemotherapy monitored by an oncologist. Systemic high-dose methotrexate (MTX)-based chemotherapy is used to treat both ocular and CNS disease. Many clinicians favor systemic therapy even for apparently isolated ocular disease, out of concern that subclinical CNS disease may be present concurrently.

Local ocular therapy may be used as monotherapy or as part of a combination that includes external beam radiotherapy to *both* globes and intravitreal MTX and rituximab.[5] The involvement of both eyes does not preclude the use of local therapy, but systemic therapy should be considered.

Prognosis. Relapse rates for PVRL are variable depending on treatment and follow-up. Despite advances in treatment and diagnosis, prognosis for those with PVRL/PCNSL remains dismal, with progression-free survival around 1 year and overall survival under 3 years. Although ocular therapy alone can achieve local control, it has little effect on overall survival.

Key Points

PVRL remains an elusive diagnosis, with vague signs and symptoms and difficult diagnostic confirmation. Appropriate suspicion of chronic, treatment-resistant uveitis can aid in earlier detection. Definitive diagnosis still requires the identification of lymphoma cells within the vitreous or retina. Although the prognosis is poor, newer treatment modalities have increased survival while helping limit visual and neurologic side effects. ■

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4 Hong JT et al. *J Neurooncol.* 2011;102(1): 139-145.
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