

NEOPLASTIC MASQUERADERS OF UVEITIS



Remember these various ocular malignancies as you prepare your differential diagnosis.

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Uveitis masquerade syndromes encompass a range of conditions that mimic the clinical presentation of uveitis but are caused by underlying pathologies such as malignancies, infections, or degenerative diseases.^{1,2} Neoplastic masqueraders, such as intraocular lymphoma, uveal melanoma, leukemia, and metastatic tumors, are among the most serious and challenging to diagnose due to the potential for systemic involvement and life-threatening progression. Such conditions account for about 2.5% of presumed uveitis patients in tertiary care settings.³ The incidence varies in terms of geographic location, access to health care, and presence of systemic malignancies. Early detection hinges on identifying atypical features, using advanced imaging modalities, and performing targeted diagnostic procedures such as vitreous biopsy.

INTRAOCULAR LYMPHOMA

Primary vitreoretinal lymphoma (PVRL) is most common in older adults, with a peak incidence between 50 and 70 years of age. It is a subset of primary central nervous system (CNS) lymphoma, which itself accounts for 1% to 2% of all non-Hodgkin lymphomas.^{4,5} Secondary intraocular lymphoma is more frequent in patients with systemic lymphoma and has no clear age predilection.

A high frequency of *MYD88* and *CD79B* mutations with VRL has been observed.⁴ In addition, it is important to remember the following pearls:⁵

- At the time of presentation with VRL, CNS involvement is present in 16% to 34% of patients.
- Of patients with primary CNS lymphoma, 25% have VRL at presentation.
- Of patients with VRL, 50% to 90% develop a CNS and/or spinal cord disease within 16 to 24 months.

Recent recommendations suggest the following elements should be used to obtain a PVRL diagnosis:⁶

- **Clinical History:** Most patients with PVRL are older than 50 years of age and present with floaters and painless vision loss without redness or photophobia. The disease may manifest unilaterally, but PVRL is predominantly bilateral.
- **Anterior Segment Findings:** Keratic precipitates of various types may or may not be present in VRL. Scleritis, pseudohypopyon, and hyphema are uncommon, while anterior synechiae and iris depigmentation are almost never seen.
- **Vitreous and Posterior Segment Findings:** Massive cellular infiltration (vitreous sheets or clumps) with the absence of macular edema, snowbanking, or vitreous hemorrhage may be present. There are usually multifocal creamy/white lesions in the outer retina (Figure 1) with or without a leopard-spot appearance, and retinal pigment epithelial (RPE) atrophy or fibrosis.
- **Ocular Imaging:** Multimodal imaging, including fundus autofluorescence (Figure 2), OCT (Figure 3),

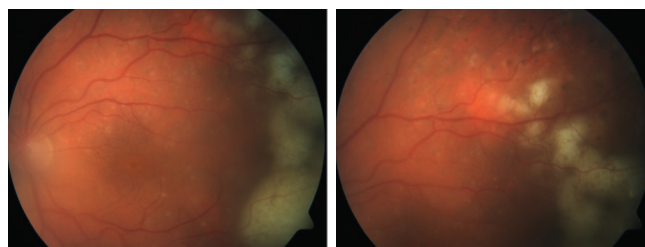


Figure 1. Fundus images of the right eye of a 55-year-old man on presentation showed multifocal creamy/white lesions in the outer retina with leopard-spot and RPE atrophy typical of intraocular lymphoma. This patient underwent vitrectomy, which confirmed the diagnosis, and he developed brain lymphoma 14 months later.

fluorescein angiography, and contrast-enhanced MRI of the brain, is also important to investigate.

- **Behavior With Systemic Steroids:** Systemic steroids should not be used as a sole treatment for VRL due to their limited effectiveness and should be stopped at least 2 weeks prior to a scheduled vitrectomy for ocular fluid study.
- **Ocular Fluid Diagnosis:** In cases of suspected VRL, diagnostic vitrectomy may be performed after oral steroids have been discontinued for at least 2 weeks. Early undiluted vitreous samples should be obtained with a low cut rate, and diluted and undiluted vitreous should be evaluated as soon as possible. Cell morphology and cytokine and gene analysis of the ocular fluid can aid in the diagnosis; the IL-10:IL-6 ratio and MYD88 gene mutation are strongly recommended. Immunophenotype (ie, flow cytometry, immunocytology, and histochemistry) and polymerous chain reaction testing should also be performed, if possible.

The Interleukin Score for Intraocular Lymphoma Diagnosis is a useful probability score for the diagnosis of PVRL that is based on a mathematical formula integrating both IL-10 and IL-6 levels in vitreous or aqueous samples with high

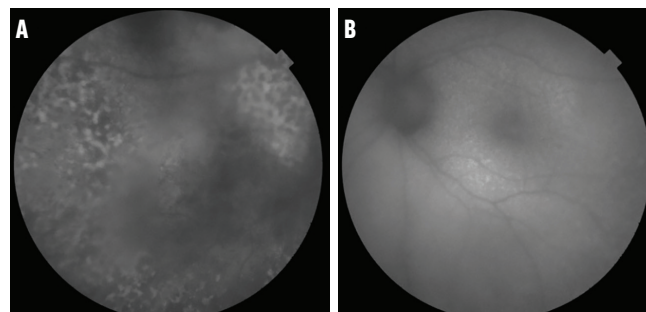


Figure 2. Fundus autofluorescence of the right (A) and left (B) eye of a 66-year-old woman showed a granular hyper- and hypoautofluorescence pattern indicative of VRL. This patient had a vitrectomy specimen labeled as “highly suspicious” for lymphoma and, indeed, developed brain lymphoma 2 months after presenting with ocular symptoms.

sensitivity and specificity (93% and 95%, respectively).⁷

Finally, VRL should be suspected when there is nonspecific posterior uveitis with better visual acuity than expected, minimal anterior chamber flare, dense vitritis, and absence of posterior synechiae or cystoid macular edema.

UVEAL MELANOMA

Uveal melanoma is the most common primary intraocular malignancy, with an annual incidence of five to

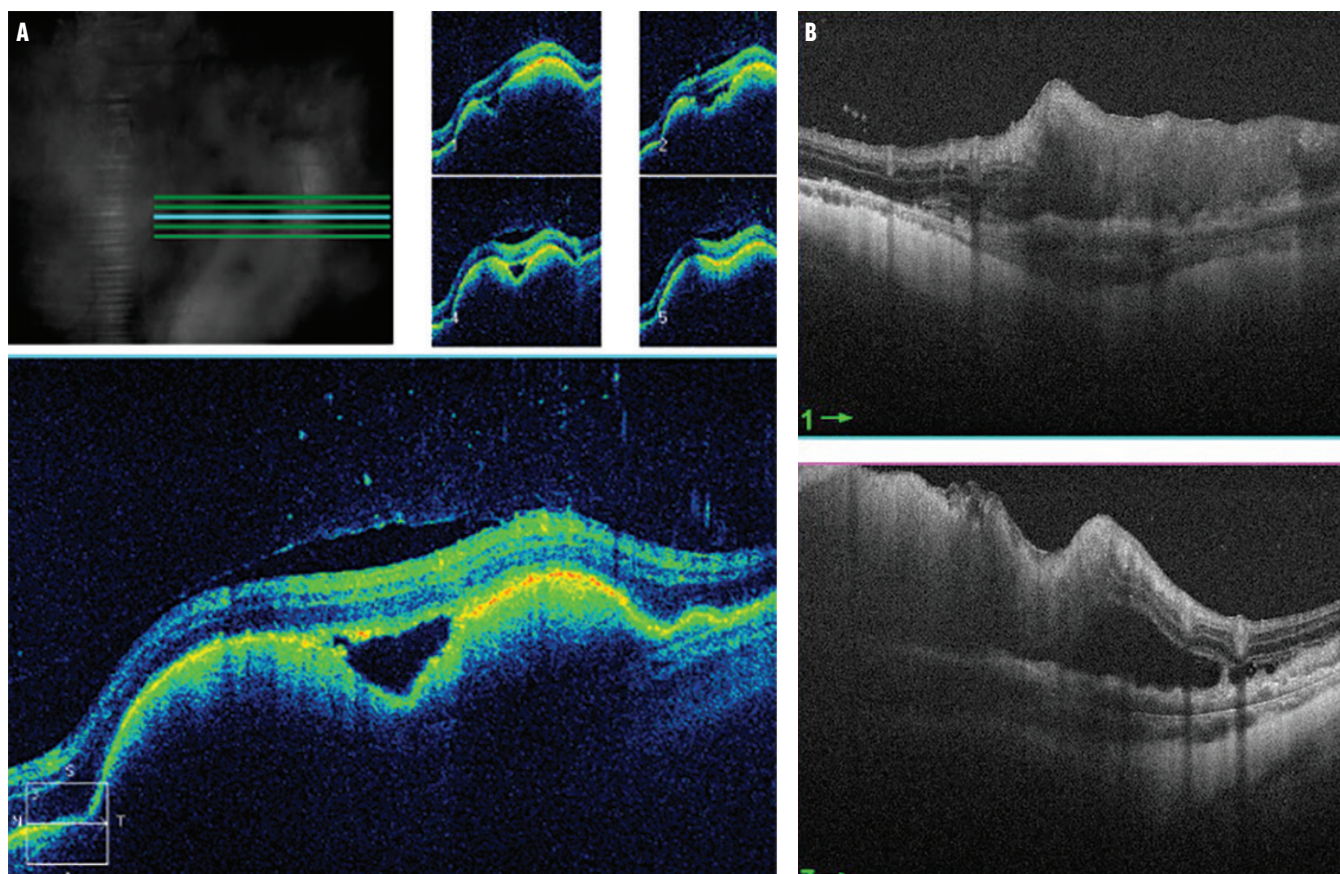


Figure 3. OCT of the patient in Figure 1 showed focal round lesions causing pigment epithelial detachment with RPE irregularities and subretinal fluid (A). In another case of PVRL in a 39-year-old man, whose ocular symptoms had been misdiagnosed as uveitis, RPE thickening, subretinal fluid, and diffuse highly reflective subretinal infiltration were observed (B).

seven cases per one million individuals in the United States. It predominantly affects White individuals and has a slightly higher prevalence in men. Risk factors include light iris color, ultraviolet light exposure, and a genetic predisposition, such as mutations in the *GNAQ*, *GNA11*, or *BAP1* genes.⁸

Melanomas appear as hypovascular, dome-shaped masses on B-scan ultrasonography and are characterized by a centrally located vessel with a “central pattern” of blood flow. Uveal melanoma may present as a masquerade syndrome, mimicking conditions such as endogenous endophthalmitis, subretinal fluid in the macula with pigment epithelial detachments, and a thickened choroid resembling central serous chorioretinopathy, choroidal vortex vein varix, or chronic unilateral uveitis.⁸⁻¹¹

LEUKEMIA

About 90% of patients with leukemia, especially those with the chronic form, experience ocular involvement.¹² In cases of acute leukemia, ocular signs often correlate with disease relapse or progression. Malignant cells have been documented to infiltrate the uvea, optic nerve, cranial nerves, and periorbital tissues.^{12,13} Ocular manifestations are more commonly associated with anterior uveitis presenting with hypopyon, while secondary extramedullary location of acute myeloid leukemia can present as anterior uveitis with dust-like pigmented keratic precipitates, iris bombe, ischemic bilateral retinal vasculitis, and anterior synechiae with retinal detachment and a lesion in the subretinal space.² Posterior segment involvement may result from direct ocular infiltration or indirect effects of systemic disease.^{2,12} Retinal hemorrhage, vitreous hemorrhage, vascular occlusion, and secondary infections may present as indirect sequelae of systemic malignant disease.^{2,12,13}

METASTATIC TUMOR

Metastatic tumors are the most common intraocular malignancy with the majority originating from breast (40%) and lung (30%) cancers. Choroidal metastases predominate due to the rich vascular supply of the posterior uvea. Many cases of lung cancer with masquerading ocular metastases have been documented, presenting as anterior uveitis with pseudokeratic precipitates, secondary glaucoma with goniosynechiae and iris nodules, bullous retinal detachment, and diffuse retinal vasculitis with vitritis and optic disc edema.^{14,15} Furthermore, ocular metastasis of mammary carcinoma may mimic bilateral anterior uveitis with hypopyon, partial third nerve palsy, and eyelid margin thickening.^{16,17}

Fewer cases of ocular metastasis from kidney carcinoma have been reported, masquerading as endogenous endophthalmitis, while eyelid and ocular metastases from gastrointestinal carcinoma may present as chalazion.^{18,19} Ocular metastases are most commonly found in the choroid (88%), iris (9%), and ciliary body (2%). Metastases typically appear

yellow in color and can be solitary, multiple, unilateral, or bilateral. They can cause blurred vision (70%), flashes and floaters (12%), or may be asymptomatic.^{18,19}

TIME IS OF THE ESSENCE

The primary diagnostic method for masquerade syndromes remains the cytological and histological analysis of a vitreous biopsy via pars plana vitrectomy.^{5,15,20} Further research into molecular diagnostics and targeted treatments is essential to enhance prognosis and quality of life for affected patients. ■

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