Multimodal diagnostic imaging in primary vitreoretinal lymphoma

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Abstract

Background: Primary vitreoretinal lymphoma (PVRL) is an aggressive lymphoma that may present with protean features and represents a diagnostic challenge. Given that patients with PVRL are at high risk of CNS involvement with a high mortality and morbidity rate, prompt diagnosis is crucial to initiate treatment early in the disease course. A multimodality imaging approach including fundus photography, fundus autofluorescence (FAF), optical coherence tomography (OCT), fluorescein and indocyanine angiography, and electroretinography (ERG) can provide information to establish a diagnosis and provide objective measures for management. We review key findings seen via these imaging modalities in patients with PVRL.

Observations: Fundus photography can highlight commonly seen patterns of PVRL including vitritis, subretinal disease, retinal pigment epithelial (RPE) abnormalities, optic nerve edema, retinal detachment, and less typical retinitis-like lesions. FAF can identify characteristic patterns of hyper- and hypoautofluorescent signal abnormalities in the macula. Spectral-domain OCT will demonstrate vitreous cells, RPE nodularity, and hyperreflectivity of the outer retina. The presence of a hyper-reflective band in the subretinal space and infiltrates between the RPE and Bruch’s membrane can assist in distinguishing PVRL from choroidal lymphoma. Vertical hyperreflective columns (VHRLs) are another pertinent finding that may represent microinfiltrates of the tumor. OCT has proven to be a particularly useful modality in assessing the progress of treatment in PVRL. Fluorescein angiography can show RPE changes, which include granularity, late staining at the RPE level, and blockage. Indocyanine green angiography (ICGA) primarily shows hypocyanescence, which corresponds to PVRL lesions on fundus photography and may occur secondary to loss of RPE and choriocapillaris.

Conclusion: While PVRL remains a challenging disease to diagnose and follow, the use of a multimodality imaging approach may assist in establishing a diagnosis. Because of the anatomic spaces PVRL may affect, fundus photography, OCT, FAF, angiography, and ERG can identify key characteristics of the disease, differentiate PVRL from other diseases, and provide baseline information for targeted systemic and local therapies. Further assessment of anatomic and functional targets will aid our clinical application of multimodal imaging in the management of PVRL.

Keywords: Primary vitreoretinal lymphoma, Multimodal imaging, Fundus photography, Fundus autofluorescence, Optical coherence tomography, Fluorescein angiography, Indocyanine green angiography, Electroretinography

Background

Primary vitreoretinal lymphoma (PVRL), also known as primary intraocular lymphoma, is the most common intraocular lymphoma with approximately 380 incident cases in the United States annually [1]. It is an aggressive high-grade lymphoma, usually of the diffuse large B-cell subtype [2]. PVRL is a rare subset of primary central
nervous system (CNS) lymphoma. While approximately
15% of patients with primary CNS lymphoma develop
PVRL, 65–90% of patients with PVRL develop primary
CNS lymphoma [1]. Primary CNS lymphoma is a rare
primary CNS tumor comprising only 2% of primary
CNS tumors that most frequently presents in the elderly
or immunocompromised populations [3]. However, it
is associated with high mortality and morbidity. Spe-
cifically, the median survival for patients is 10 months,
and for those older than 70, the median survival is
6–7 months [4, 5].

PVRL is a well-known masquerade syndrome that
may be challenging to diagnose [6]. The mean time from
ocular symptoms to diagnosis is 40 months, but the tim-
ing from symptom onset to diagnosis has been reported
to be up to 12 years in some instances [7]. The delay in
PVRL diagnosis can subsequently impede primary CNS
lymphoma diagnosis and treatment, impacting survival
outcomes for the patient. Thus, an accurate and timely
diagnosis of PVRL is imperative. The gold standard of
diagnosis is histologic and immunochemical confirma-
tion via a sample obtained by a diagnostic vitrectomy,
retinal or subretinal biopsy [1]. However, recent advances
in ophthalmic imaging have identified features that sup-
port the diagnosis of PVRL. These features can be used
to reduce the need for invasive tissue diagnosis in some
cases, decrease time to achieve a definitive diagnosis,
and provide objective measures to monitor treatment
response (see Table 1). In this review, we summarize the
multimodal findings on ophthalmic ancillary testing pre-
\[9\]. In 47% of eyes, ultra-widefield fundus
photography detected more abnormalities than standard
30 degree images [9]. Fundus photography may also assist
in monitoring PVRL changes over time. Mantopoulous
and Cebulla report a biopsy-proven case of PVRL with
spontaneous regression of a sub-RPE lesion documented
on color fundus photographs and OCT [10].

In addition to the typical findings of vitritis, subretinal
lesions, and RPE change, fundus photography can also
document atypical lesions. For example, PVRL and sec-
ondary vitreoretinal lymphoma (VRL) may rarely present
with a retinitis-like picture [11–13]. Suspicion for PVRL
should be raised if individuals with retinitis-like lesions
fail to respond to antiviral therapy, particularly if molecu-
lar diagnostics for a viral etiology are negative.

**Fundus autofluorescence**

A variety of fundus autofluorescence (FAF) patterns has
been reported. During active PVRL, hyperautofluores-
cence of the sub-RPE lesions and alternating hyper- and
hypoautofluorescence of the macula are the most com-
monly seen patterns [9, 14, 15]. The hyperautofluores-
cent spots have also been found to correlate with nodular
hyperreflective spots on OCT [14]. The granular hyper-
autofluorescence and hypoautofluorescence pattern on
FAF was reversed on fluorescein angiogram [16]
(Figs. 1B, C). Egawa et al. hypothesized that lymphoma-
tous RPE infiltration in the form of sub-RPE lesions
could alter RPE metabolism and manifest as hyperauto-
fluorescence [16] (Fig. 2B). In areas where there appears
to be lymphomatous infiltration above the RPE, the FAF
pattern is hypoautofluorescent, possibly due to tumor
blockage of normal RPE fluorescence [16, 17] (Fig. 3B).
Hypoautofluorescence can also be seen in cases of RPE
atrophy after regression of the lesion [14, 15, 17]. Inter-
estingly, these lesions often appear hook-shaped [17].
Hyperautofluorescent dots were also seen in an inactive
eye that was previously active [9]. Thus, while FAF pat-
terns can be extremely helpful to identify diffuse and
focal areas of RPE disturbance, the variegated pattern
makes it challenging to draw conclusions about disease
activity based solely on FAF patterns.

Importantly, a normal fundus autofluorescence does
not rule out PVRL. In a report by Casady et al., seven of
18 eyes (39%) did not have any remarkable findings on
FAF [14]. Of these, two eyes (one patient) were in remis-
sion, and five eyes (four patients) were active [14].

**Optical coherence tomography**

OCT often demonstrates vitreous cells (100% of eyes),
RPE nodularity (63%), and outer retina hyperreflect-
tivities (43%) [9, 18, 19] (Figs. 2C and 3C). Less common
findings included pigment epithelial detachments (PEDs)
(30%-50%) (Figs. 1D and 3C), epiretinal membranes

**Fundus Photography (Fig. 1A)**

Clinical features of PVRL seen on fundus photography
include vitreous haze or clumps, optic nerve edema,
perivascular sheathing, sub-retinal pigment epithe-
lum (RPE) lesions, cream-colored lesions, or serous
retinal detachments [8]. In an evaluation of 43 eyes of
23 patients with PVRL, four patterns were detected
on fundus photography: vitritis (46% of eyes), subreti-

nal lesions (46%), optic nerve edema (10%), and retinal
detachment (12%) [9]. Specifically, eyes with only vitritis
showed visual acuities of 20/27 at 6 months and 20/34 at
12 months post-presentation. Conversely, eyes with optic
disc edema or retinal detachment had an averaged visual
acuity of hand motion at 6 months and light perception
at 12 months [9]. In 47% of eyes, ultra-widefield fundus
photography detected more abnormalities than standard
**Table 1** Findings on imaging of primary vitreoretinal lymphoma

| Imaging modality                  | Features found on imaging of PVRL                                                                 | Utility in diagnosis or workup of PVRL                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Fundus photography               | Visualization of vitreous haze and cellular debris, optic nerve edema, perivascular sheathing, sub-retinal pigment epithelium cream-colored lesions, serous retinal detachments, atypical features mimicking viral retinitis | Direct visualization of findings and monitoring disease progression over time                           |
| Fundus autofluorescence (FAF)    | Hyperautofluorescence of sub-RPE lesions and alternating or stippled hyper/hypoautofluorescence of the macula | Identification of diffuse and focal areas of RPE disturbance                                           |
| Optical coherence tomography (OCT)| Vitreous cells, RPE nodularity, outer retinal hyperreflectivities                                 | Monitor response to treatment by assessing for presence of hyperreflective subretinal lesions (representative of lymphomatous infiltrate) |
| Fluorescein angiography (FA)     | Granularity, late staining at RPE level, blockage; reversed granular pattern of hyperfluorescence and hypofluorescence compared to FAF | May assist in monitoring for progression of disease or recurrence                                      |
| Indocyanine green angiography (ICGA)| Hypocyanescence                                                                                    | Can help rule out other syndromes with characteristic ICGA findings (i.e. sarcoidosis or white dot syndromes) that can be similar to PVRL |
| Electrotretinography (ERG)       | Reduced cone and rod responses; negative wave-form ERG on bright flash response with diminished b-wave response smaller than corresponding a-wave | More research on utility of ERG needed for PVRL                                                      |

**Fig. 1** Clinical imaging features of a patient with a diagnosis of PVRL and macular degeneration. A Color fundus photograph of the right eye showing vitreous opacity and multiple chorioretinal lesions with variable pigmentation. B Fluorescein angiography showing staining of chorioretinal lesions and retinal pigment epithelial (RPE) changes. C Fundus autofluorescence of the right eye showing corresponding areas of hypoautofluorescence. D OCT showing RPE elevation and overlying cystoid edema.
and retinal fluid or disorganization (13–17%) [9, 19–21].

Barry et al. describe specific findings that are highly suggestive of PVRL, including a confluent hyperreflective band in the subretinal space and infiltrates localized between the RPE and Bruch’s membrane. These characteristics can help distinguish PVRL from choroidal lymphoma, which presents with infiltrates deep to Bruch’s [22].

OCT is an excellent tool to monitor response to treatment in PVRL. There are multiple reports of hyperreflective subretinal lesions on OCT that likely represent lymphomatous infiltrate as they resolve or develop into subretinal fibrosis with treatment [19, 20, 23–27]. In one report, after completion of treatment, all abnormalities on initial OCT vanished, including subretinal fluid, outer retinal fuzzy borders, PED, and intraretinal infiltration [19]. However, stigmata of retinal destruction appeared, including subretinal fibrosis, disruption of the outer retina, and retinal thinning [19].

An OCT imaging finding termed “vertical hyperreflective columns” (VHRLs) was found in 58.3% of eyes with vitreoretinal lymphoma [28]. Of note, 2 of the 7 patients had secondary vitreoretinal lymphoma [28]. Hyperreflective intraretinal bands had previously been described in studies; however, these VHRLs extended from the inner retina to the RPE and varied in width [22, 28, 29]. They were commonly located along major vessel arcades or temporally to the fovea but were not detectable on color or infrared photography [28]. VHRLs are thought to represent microinfiltrates of tumor [28].

Anterior segment OCT has been used to diagnose recurrence of PVRL in a previously vitrectomized patient [30]. The patient was symptomatic with decreased vision and was clinically found to have anterior vitreous opacification and cells [30]. The anterior segment OCT demonstrated vitreous debris in the retro-lobular space [30].

**Fluorescein angiography**

RPE changes from PVRL are highlighted on FA and are the most common finding. These changes include granularity, late staining at the RPE level, and blockage [31] (Fig. 1B). The granular pattern of hyperfluorescence and hypofluorescence seen on FA is reversed in FAF [16].
patterns in PVRL patients often have a “mottled” appearance despite the absence of clinical RPE disturbances. It is hypothesized that diffuse lymphomatous infiltrates under the RPE are impermeable to fluorescein since tumor cell membranes act as a barrier, and the infiltrates would also block choroidal hyperfluorescence [31]. However, some infiltrates behave like drusen and manifest as late staining on FA [31].

PEDs in PVRL patients present with varying patterns on FA. Some demonstrate filling patterns typical for a serous PED: a discrete well-circumscribed area of fluorescence through the transit phase with pooling in the late phase. These findings are thought to result from injured or dead tumor cells with a resultant zone of hyperfluorescence or a serous PED with a sparse collection of tumor cells [31]. PEDs may also be hypofluorescent on FA, likely from a dense collection of viable tumor cells [9, 31].

One prior report described capillary dropout by FA in a patient with biopsy-proven PVRL [32]. The FA demonstrated well-defined areas of capillary dropout across the retina in one eye without disc leakage, cystoid macular edema (CME), or vascular leakage [32]. There was also no evidence of vascular occlusion or findings indicating diabetic retinopathy [32]. The authors hypothesized that the capillary dropout might be due to lymphomatous cells in the inner retinal layer and subsequent retinal vascular occlusion.

Notably, more common evidence of active uveitis, including optic nerve staining/leakage, perivascular staining/leakage, and petaloid leakage of CME, are less prevalent in PVRL patients. Optic nerve leakage/staining was present in 4–45% of patients [7, 31]. Vascular leakage was present in 6–36% of patients [31, 33]. In one study, leakage improved after treatment in all patients and reappeared upon disease recurrence [9]. CME was seen in six eyes (19%) in one study but only in one eye that did not have a prior history of intraocular surgery [31]. Thus, while CME, optic disc leakage, and retinal vascular leakage may be less prevalent than in other cases of endogenous uveitis, the presence of these findings should not exclude lymphoma in the differential diagnosis.

Indocyanine green angiography
The most commonly observed finding on indocyanine green angiography (ICGA) in PVRL is hypocyanescence. Hypocyanescent lesions were found in 77% of eyes in one study [33]. Another study found that 26% of eyes with PVRL had small round hypocyanescent lesions.
that erased at the late phase and that 12% of eyes demonstrated large hypocyanescent lesions [23]. Lavine et al. noted the hypocyanesence found in 10 of 12 eyes (83%) in their series correlated with scleral staining [9]. These areas of scleral staining corresponded to white lesions on fundus photos as well as hypautofluorescence and late hyperfluorescence on FA. This constellation of findings on multi-modal imaging indicates a loss of both RPE and choriocapillaris, making “scleral staining” a more apt term than “window defects” [9]. ICGA was unremarkable in areas of active sub-RPE lesions and active FA leakage [9]. The utility of ICGA in the diagnosis of PVRL is limited due to its inability to demonstrate findings missed by FA or FAF [9]. However, ICGA can help rule out other syndromes with more characteristic ICGA findings, such as sarcoidosis, birdshot retinochoroidopathy, or other white dot syndromes, that often can be difficult to differentiate from PVRL.

Electroretinography
One case report of a patient with suspected PVRL demonstrated reduced cone and rod responses on full-field electroretinography (ERG) [34]. The patient also had a negative waveform ERG on the bright flash response with a diminished b-wave response that was reduced when compared to its corresponding a-wave [34]. 8 weeks after systemic chemotherapy, rod and cone responses improved but did not fully normalize [34]. However, the negative waveform reverted to normal [34]. By 3 years of follow-up, the amplitudes continued to improve but still remained abnormal [34].

Conclusion
PVRL can often mimic other ocular diseases, making diagnosis difficult and delayed. Identification of key findings on multimodality ophthalmic imaging modalities can help to identify pathologic lesions that raise the level of suspicion for PVRL, potentially triggering a definitive diagnostic procedure. Characteristic findings include vitritis and subretinal or sub-RPE lesions that may represent tumor infiltrates. Sub-RPE lesions can be hypo- or hyper-autofluorescent and do not always correlate with disease activity. Granular fundus autofluorescent changes commonly present with a reversed pattern on FA.

OCT can be used to assess disease activity. OCT can demonstrate a confluent hyper-reflective band in the subretinal space and infiltrates localized between the RPE and Bruch’s membrane. Active lesions can often present with outer retinal fuzzy borders, PED, and subretinal fluid, which resolve with treatment and may leave behind subretinal fibrosis, disruption of the outer retina, and retinal thinning. FA and ICGA also provide additional structural information about disease processes associated with PVRL. While FA findings including optic disc leakage, retinal vascular leakage or petaloid edema may be observed in other endogenous uveitis syndromes, their presence should not exclude the possibility of PVRL. Moreover, ICGA can help to distinguish PVRL from other uveitides with more characteristic ICGA findings.

Given the advances in ultra-wide field imaging to document and follow lesions, complemented by OCT, fundus autofluorescence, and traditional angiography, multimodal imaging is a mainstay for the diagnosis and management of PVRL. There is a continued need for quantitative research using these methods, as well as functional assessments including ERG [35]. Applying a multimodal approach enhances the physician’s ability to accurately and promptly diagnose PVRL. Specifically, fundus photography allows for direct visualization of retinal and subretinal lesions as well as detection of subtle changes, particularly in the context of prior diffuse RPE changes. In addition, fundus autofluorescence and OCT provide meaningful structural information including outer retina, RPE, and sub-RPE lesions that may guide a clinician towards a definitive vitreous or retinal biopsy. Early diagnosis of PVRL not only hastens potentially vision-improving treatment but may also spur urgent investigation and management for primary CNS lymphoma, significantly improving patient health and quality of life.

Abbreviations
PVRL: Primary vitreoretinal lymphoma; FAF: Fundus autofluorescence; OCT: Optical coherence tomography; CNS: Central nervous system; RPE: Retinal pigment epithelium; VHRL: Vertical hyperreflective column; ICGA: Indocyanine green angiography; FA: Fluorescein angiography; ERG: Electroretinography; PED: Pigment epithelial detachment; CME: Cystoid macular edema.

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Author contributions
LX played a key role in conception, conducted the literature review, and wrote the manuscript. YH assisted with literature review and contributed in writing and revising the manuscript. CA and AL gathered data, revised and approved the final manuscript. SY played a key role in conception, revised the manuscript, and provided the figures shown. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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