Published in final edited form as:

Am J Ophthalmol. 2009 May ; 147(5): 764–765. doi:10.1016/j.ajo.2008.12.029.

Ocular imaging in primary retinal lymphoma

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In this issue of THE JOURNAL, Fardeau and collaborators study primary ocular non-Hodgkin's lymphoma, commonly referred to as "primary intraocular lymphoma (PIOL)".¹ This lymphoma is a neoplasm, most frequently of B-lymphoid cell origin and rarely of T-lymphoid cell origin, arising from or initially presenting in the retina and spreading into the vitreous.² Since this lymphoma mostly infiltrates the neuronal tissues of the retina, optic nerve and brain, but rarely the choroid, the term "primary retinal lymphoma" is recommended and more appropriate.³ The B-cell type of primary retinal lymphoma is a non-Hodgkin's diffuse large B-cell lymphoma, and a subtype of primary central nervous system lymphoma (PCNSL). Primary retinal lymphoma usually presents as a masquerade syndrome with clinical manifestations as intraocular inflammation. It differs from metastatic systemic lymphoma to the eye, which occurs much less frequently and typically affects the uvea and ocular adnexa via hematogenous route.

Since primary retinal lymphoma is a potentially fatal, high-grade malignancy, knowledge of both non-specific and quasi-specific presentations can help to suspect and diagnose the disease; consequently, appropriate therapy can be initiated.^{2, 4} Typically, patients are of 50-70 years of age and experience blurred vision and/or floaters. Ophthalmic examination often reveals numerous cells in the vitreous, and various sized yellowish lesions in the subretinal space and/or retina. Primary retinal lymphoma frequently mimics uveitis and is the most common entity of masquerade syndrome.^{5, 6} Moreover, these patients may have been treated with, but failed to respond to anti-inflammatory therapy, most frequently, corticosteroids. Although primary retinal lymphoma is a relatively rare malignancy, its prognosis is poor and can be fatal. Early accurate diagnosis is critical. Imaging of the eye and brain is the first step in evaluating diagnostic suspicion of primary retinal lymphoma.⁷ For these reasons, the article by Fardeau and colleagues is welcome.

Fardeau and colleagues report the results of fluorescein angiography (FA), indocyanine green (ICG) angiography, and optical coherence tomography (OCT) images in 53 patients with primary retinal lymphoma.¹ The findings were evaluated in a masked fashion and were compared to those of 42 patients with infectious uveitis, 34 patients with immune-mediated uveitis, and 6 patients with systemic metastatic tumors. The authors found that 24/53 (45.3%) of FA and 9/34 (26.4%) of ICG showed clusters of small round hypofluorescent lesions (50-250 μ m in diameter) in the posterior pole; 5/12 (41.7%) of OCT showed RPE nodular hyperreflective lesions in the macular map of the lymphoma cases. In contrast, these lesions

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The authors indicate no financial disclosure.

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were significantly less observed in non-lymphoma cases: 3/133 (2.2%) in FA, 8/93 (8.6%) in ICG, and 9/61 (14.7%) in OCT. The combination of the three images yielded a positive predictive value of 88.9% and negative predictive value of 85%. For the FA and ICG, the relative odds ratio risk for retinal lymphoma was 45.2. It would be useful for the authors to provide more detailed information and discuss those non-lymphoma cases, which presented with similar imaging results (retina and brain) as the lymphoma cases.

The data of this study are encouraging and offer clinical applicability. FA has been widely used in retinal vascular diseases including diabetic retinopathy, choroidal neovascularization, and retinal vasculitis. The FA findings in primary retinal lymphoma have been characterized, particularly in RPE disturbances.^{8, 9} This study emphasizes the unique pattern of the small, round hypofluorescent clusters, which likely indicate primary retinal lymphoma cellular infiltrates in RPE.¹ ICG provides ample information on visualizing the choroidal vasculature and subretinal choroidal diseases such as various uveitides involving the choroid.¹⁰ Since the malignant cells tend to locate in the retina, not choroid, the yield of positive ICG should be low in primary retinal lymphoma. The rare small, round hypofluorescent lesions becoming erased at late phase in ICG may indicate a reactive lymphocytic response in the choroid, which has been published in eyes with primary retinal lymphoma.¹¹ The macular map of OCT enables analysis of the cross-sectional area of the lesions at the RPE level and sub-RPE space,¹² hence it can discover tumors localized only to the macular area.⁷

Fardeau and colleagues suggest a prompt work up for primary retinal lymphoma in the presence of clusters of small, round hypofluorescent lesions in both early and late phase of FA, but not or rarely in ICG.¹ They recommend diagnostic procedures including spinal and vitreous taps for cytology, IL-10 measurement, and molecular detection of immunoglobulin heavy-chain gene rearrangement. Although their recommendations are not novel, the authors should be commended for this retrospective study consisting of a large number of cases with primary retinal lymphoma and uveitides (infectious and immune-mediated) in a single institute. Their results reinforce the appropriate diagnostic steps for us to approach this devastating, life-threatening malignancy and to achieve an early correct diagnosis.

Imaging (FA, ICG, OCT) is an adjunctive and helpful tool for diagnosing primary retinal lymphoma; however, for a definitive diagnosis, pathological specimens are still essential and indispensable. Once the diagnosis of primary retinal lymphoma is made, oncology consultation with a neuro-oncologist and/or hemato-oncologist is highly recommended for selection of a targeted therapy with a high likelihood of durable response and low likelihood of adverse effects.^{2, 13, 14}

Acknowledgments

The NEI Intramural Research program supports the study.

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