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Case of the Month – September 2019

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A 64-year-old female presented for follow-up with a chief complaint of intermittent, but worsening floaters in both eyes. She had a known history of familial exudative vitreoretinopathy (FEVR), with stage 2b disease in the right eye and stage 1a disease in the left eye and had undergone previous treatment with panretinal photocoagulation in the right eye. Vision was 20/20 in both eyes (OU). Intraocular pressure and the anterior segment exam was unremarkable OU. Dilated fundus exam revealed mild straightening of vessels in the periphery OU, and a mild epiretinal membrane and peripheral laser scars in the right eye. There were no hemorrhages, exudates, nor active neovascularization OU.

Widefield fluorescein angiography (WFA; Figure 1) of the right eye conveyed vascular changes called late-phase angiographic posterior and peripheral vascular leakage (LAPPEL), that were new compared to the quiescent WFA six months prior. There was a mild epiretinal membrane without edema on optical coherence tomography imaging (Figure 2). After a thorough discussion of the findings, as well as all treatment options, the decision was made for fill-in panretinal photocoagulation (PRP) in the right eye.

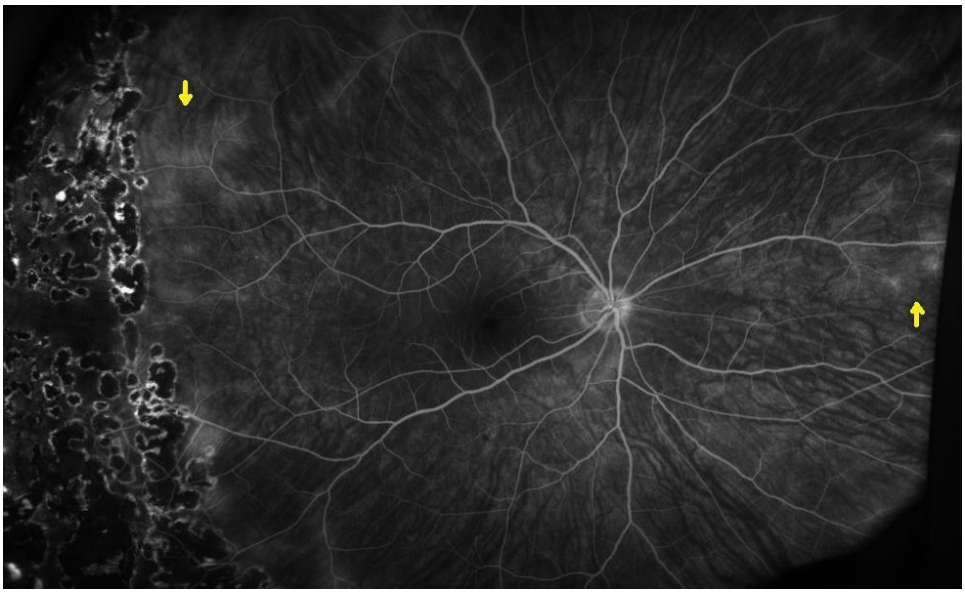

Figure 1: Widefield Fluorescein Angiogram (WFA) of the right eye showing new, worsening hyperfluorescence – a marker of capillary inflammation termed late-phase angiographic posterior and peripheral vascular leakage (LAPPEL; yellow arrows), despite previous laser treatment. Also noted are areas of capillary dropout and some straightening of blood vessels. Worsening LAPPEL is often an indication for treatment with photocoagulation.

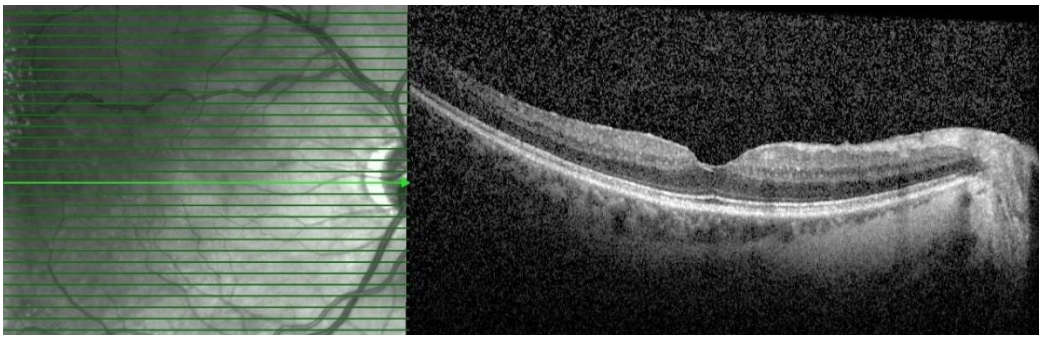

Figure 2: Optical coherence tomography of the macula of the right eye. There is a mild epiretinal membrane with a normal foveal contour. There is no macular edema and no exudates. The external limiting membrane and ellipsoid zone band are intact, without irregularities.

Clinical Course:

The patient returned for follow-up one month after fill-in PRP without complaints. Exam revealed adequate treatment to the retina underlying the previous areas of LAPPEL. At three months follow-up, repeat WFA revealed resolution of LAPPEL and quiescence. At follow-up six months later, clinical examination and WFA conveyed maintained quiescence of the disease.

Discussion:

Familial exudative vitreoretinopathy (FEVR) is an inherited disease characterized by aberrant retinal angiogenesis. Clinical manifestations include an abnormal vitreous and vitreoretinal interface, avascular peripheral retina, abnormal retinal vasculature, subretinal exudates, neovascularization, temporal dragging, and retinal detachments. Widefield fluorescein angiography (WFA) is critical for the monitoring of patients with FEVR because there can be changes on WFA, such as late-phase angiographic posterior and peripheral vascular leakage (LAPPEL), that are not discernable on clinical examination.

FEVR can be inherited in an autosomal dominant (most common), autosomal recessive, or X-linked recessive pattern. To date, mutations in six genes have been identified: *FZD4*, *NDP*, *LRP5*, *TSPAN12*, *KIF11*, and *ZN408*. These genes play a critical role in retinal angiogenesis via the Frizzled4/Norrin signaling pathway. Müller glial cells secrete Norrin, which binds to Frizzled-4 on retinal endothelial cells and drives Wnt signaling. Knockout models of Frizzled-4/Norrin in mice, show retinal vascular abnormalities that we also see in humans.

Findings on WFA include: peripheral capillary nonperfusion, capillary inflammation or leakage (LAPPEL), and venous-venous and arteriovenous shunting. Patients may also convey a characteristic straightening or "wind-blown" appearance to their blood vessels. Recently, we identified noninvasive vascular biomarkers on OCTA that correlate with findings on WFA. Decreasing macular vessel density on OCTA correlated with increasing peripheral capillary nonperfusion on WFA. Decreased macular fractal dimension (vessel branching) on OCTA correlated with increasing LAPPEL severity on WFA. Mild LAPPEL may be treated with topical non-steroidal and corticosteroid drops, while worsening LAPPEL may require ablative laser therapy.

FEVR is classified according to the severity of disease (Table 1). The diagnosis should be made by clinical examination and WFA, with consideration of the patient's history, birth history, and family history. Early or mild stages of FEVR often go undiagnosed, as patients can be asymptomatic. Sometimes, making the diagnosis in a symptomatic child will lead to diagnosing other affected family members. We recommend screening direct family members of an affected patient. FEVR is a life-long disease that can reactivate or intensify at any point during a person's lifetime. Thus, even patients with mild FEVR should be monitored.

Table 1. Familial Exudative Vitreoretinopathy Clinical Staging System

1 Avascular periphery or anomalous intraretinal vascularization 1A Without exudate or leakage 1B With exudate or leakage
2 Avascular retinal periphery with extraretinal vascularization 2A Without exudate or leakage 2B With exudate or leakage
3 Extramacular retinal detachment 3A Without exudate or leakage 3B With exudate or leakage
4 Macula-involving retinal detachment 4A Without exudate or leakage 4B With exudate or leakage
5 Total retinal detachment 5A Open funnel 5B Closed funnel

In advanced stages of FEVR, patients present with retinal detachments, most commonly of various tractional configurations. Patients may also present with exudative detachments, and less commonly combined tractional and rhegmatogenous detachments. Temporal dragging of vessels and radial retinal folds are also common. Wet radial folds may be addressed surgically, but dry, knife-like folds are not. In Stage 5 cases, it is critical for the surgeon to understand where to enter the eye (to avoid iatrogenic breaks) and how to manage the intraocular pressure during dissections to distinguish membranes from disorganized retina.

It is important for the vitreoretinal surgeon to understand the tractional vectors responsible for the patient's pathology, as well as how they change over time as the patient ages and the eye grows. Vitrectomy with membrane peeling is a reasonable first choice for most of these tractional retinal detachments, though in some cases scleral buckles with radial elements may be a better option. Surgical decision making should be personalized to each patient.

A thorough preoperative discussion is important so that the patient and the family have realistic expectations of anatomic and visual outcomes. For children with FEVR, their families need to understand the critical importance of treatment of amblyopia after surgery and maximizing the treatment of anisometropia and/or strabismus with their pediatric ophthalmologist. The partnership between the vitreoretinal surgeon and the pediatric ophthalmologist is critical for obtaining the best possible outcomes.

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Take Home Points

- Familial Exudative Vitreoretinopathy (FEVR) is an inherited, lifelong disease. Patients need routine monitoring with dilated fundus examination and widefield fluorescein angiography (WFA).
- Direct family members of patients with FEVR should be screened for the disease with a dilated fundus examination and WFA.
- Patients with advanced stages of FEVR present with complex retinal detachments. The surgical plan should be personalized to each patient. The care of children with FEVR should be closely coordinated with the Pediatric Ophthalmologist.


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