

# Familial Exudative Vitreoretinopathy (FEVR) Presenting with Vitreous Hemorrhage in 60-year-old and 22-year-old Thai Women

ผู้ป่วย Familial exudative vitreoretinopathy (FEVR) ที่มาด้วยอาการเลือดออกในวุ้นตาในหญิงไทยอายุ 60 และ 22 ปี

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## Abstract

**Purpose:** To report vitreous hemorrhage as the initial manifestation of adult-onset familial exudative vitreoretinopathy (FEVR)

**Methods:** Case reports

**Results:** A 60-year-old and 22-year-old women presented with vitreous hemorrhage in one eye. Fundus examination and wide field fluorescein angiography of both patients showed typical characteristics of FEVR including an increased number of peripheral vessel, straightening of vessels and peripheral avascular retina with neovascularization. Fundus fluorescein angiography-guided laser photocoagulation were performed with good visual outcome in both patients.

**Conclusion:** Although FEVR is an uncommon cause of vitreous hemorrhage in adult, ophthalmologists should be aware of this condition. Misdiagnosis can lead to serious complications such as retinal detachment and vitreous hemorrhage. Meticulous peripheral retinal examination is needed. Moreover, wide-field fluorescein angiography is essential in diagnosis and management of FEVR.

**Keywords:** Familial exudative vitreoretinopathy, vitreous hemorrhage, adult

## บทคัดย่อ

ผู้ป่วย Familial exudative vitreoretinopathy (FEVR) ที่มาด้วยอาการเลือดออกในวุ้นตาในหญิงไทยอายุ 60 และ 22 ปี

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**วัตถุประสงค์:** เพื่อรายงานผู้ป่วยโรค Familial exudative vitreoretinopathy (FEVR) ที่มาด้วยอาการเลือดออกในวุ้นตา

**วิธีการวิจัย:** กรณีศึกษาในผู้ป่วยที่ได้รับการรักษาที่โรงพยาบาลระยอง

**ผลการวิจัย:** ผู้ป่วยหญิงไทยอายุ 60 และ 22 ปี มาโรงพยาบาลด้วยอาการตามัว ตรวจร่างกายพบว่ามีเลือดออกในวุ้นตา ภาพถ่ายจอประสาทตามุมกว้างและการตรวจจอตาโดยการฉีดสี (wide field fundus fluorescein angiography) แสดงให้เห็นลักษณะของโรค FEVR ซึ่งประกอบด้วย การเพิ่มจำนวนของหลอดเลือด และหลอดเลือดจอตามีความเหี่ยยตรงในบริเวณด้านนอกของจอตา ร่วมกับมีบริเวณของจอตาด้านนอกที่ไม่มีหลอดเลือดมาเลี้ยงรวมถึงมีหลอดเลือดงอกใหม่ผิดปกติ ผู้ป่วยทั้งสองรายได้รับการรักษาโดยการยิงเลเซอร์บริเวณจอตาด้านนอกที่ไม่มีหลอดเลือดมาเลี้ยง หลังได้รับการรักษาการมองเห็นของผู้ป่วยทั้งสองรายดีขึ้น

**สรุป:** แม้ว่าภาวะเลือดออกในวุ้นตาที่พบในผู้ใหญ่มีเพียงส่วนน้อยที่เกิดจาก FEVR จักษุแพทย์ควรระลึกว่าภาวะเลือดออกในวุ้นตาที่พบในผู้ใหญ่สามารถเกิดจากโรค FEVR ได้ เนื่องจากการวินิจฉัยที่ผิดพลาดสามารถนำไปสู่ภาวะแทรกซ้อนที่ร้ายแรงเช่น จอตาหลุดลอกได้ การตรวจจอตาอย่างละเอียดร่วมกับการใช้ภาพถ่ายจอประสาทตามุมกว้างและการตรวจจอตาโดยการฉีดสี (wide field fundus fluorescein angiography) มีความจำเป็นในการวินิจฉัยภาวะดังกล่าว

## Introduction

Familial exudative vitreoretinopathy (FEVR) is a hereditary retinal vascular disorder first described by Criswick and Schepens in 1969.<sup>1</sup> They reported six patients from two families who demonstrated unique clinical presentations characterized by various ocular findings including macular dragging, temporal radial retinal fold, retinal neovascularization, preretinal vitreous organization, vitreous hemorrhage, tractional retinal detachment, and subretinal exudation. Those findings were remarkably similar to the findings of retinopathy of prematurity (ROP). However, none of their patients had history of premature birth. Subsequent studies reported that FEVR patients could present with high degree of asymmetry between eyes in which finding could range from peripheral

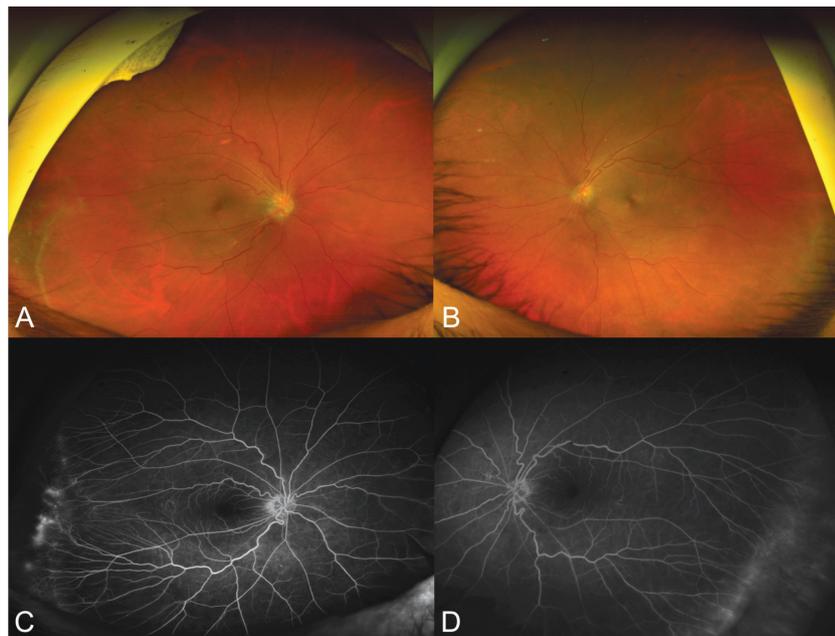
avascular retina to total tractional retinal detachment.<sup>2</sup> Angiographic findings of FEVR were first described by Canny and Oliver, ranging from peripheral avascularity to leakage around fibrotic tissue.<sup>3</sup> For genetics aspect, inheritance, penetrance, and expressivity of FEVR are highly variable.<sup>4</sup> Average age at presentation of FEVR reported by Ranchod et al and Kashani et al was 6 years (ranging from less than 1 month to 49 years) and 7 years (ranging from less than 1 month to 47 years), respectively.<sup>5,6</sup> While in an Indian study conducted by Shukla et al, they reported relatively older population with an average age at presentation of 23.6 years (ranging from 2 to 55 years).<sup>7</sup> Herein, we report two cases of FEVR presented with vitreous hemorrhage late in life at the age of 60 and 22 years.

## Case Presentation

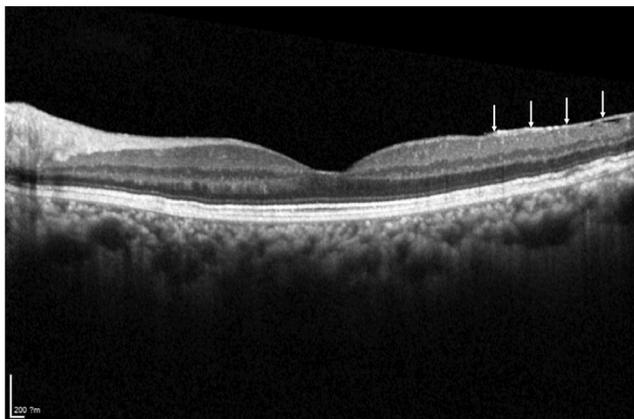
### Case 1

A 60-year-old Thai woman presented with blurring of vision and floater on the left eye for 1 week. She denied any history of ocular trauma. She was a full-term baby without any history of previous hospital admissions and was otherwise healthy. She was the second child out of 10 siblings with no family history of blindness. On examination by first ophthalmologist, her best-corrected visual acuity was 20/30 on the right and 20/70 on the left eye. Anterior segment examination was normal except for nuclear sclerosis on both eyes. Dilated fundus examination showed vitreous hemorrhage grade 1 on left eye and bilateral optic disc elevation. Cranial and orbital magnetic resonance imaging did not reveal any abnormalities

of anterior visual pathway. She was then referred to our vitreoretinal service. On examination at our service, her best-corrected visual acuity of left eye was spontaneously improved to 20/40. A systemic physical examination revealed no profound abnormality except for her eyes. Mild bilateral nuclear sclerosis was noted on anterior segment examination. Dilated fundus examination showed small amount of vitreous hemorrhage on left eye. Bilateral peripheral retinal abnormalities were observed including an increased number of peripheral vessel, straightening of vessels and peripheral avascular retina with neovascularization (Figure 1A and 1B). Wide-field fundus fluorescein angiography showed peripheral avascular area with leakage from neovascular vessel at avascular junction in both eyes (Figure 1C and 1D) which consistency with FEVR stage 2A.6 Spectral-domain optical coherence



**Figure 1** Case 1. (A) and (B) Wide-field fundus photography showed optic disc elevation and very small cup-to-disc ratio on right and left eye, respectively. Buried optic nerve head drusen of the right eye was confirmed by B-scan ultrasound. Tortuosity of retinal veins were noted in both eyes. Retinal neovascularization and fibrosis at the junction between vascular and avascular retina at temporal area of both eyes were noted (more prominent on right eye). (C) and (D) Wide-field fundus fluorescein angiography demonstrated peripheral avascularity at temporal retina of both eyes with V-shape pattern on right eye. Retinal neovascular leakage at the posterior border of the vascular-avascular junction was noted in both eyes (more prominent on right eye).



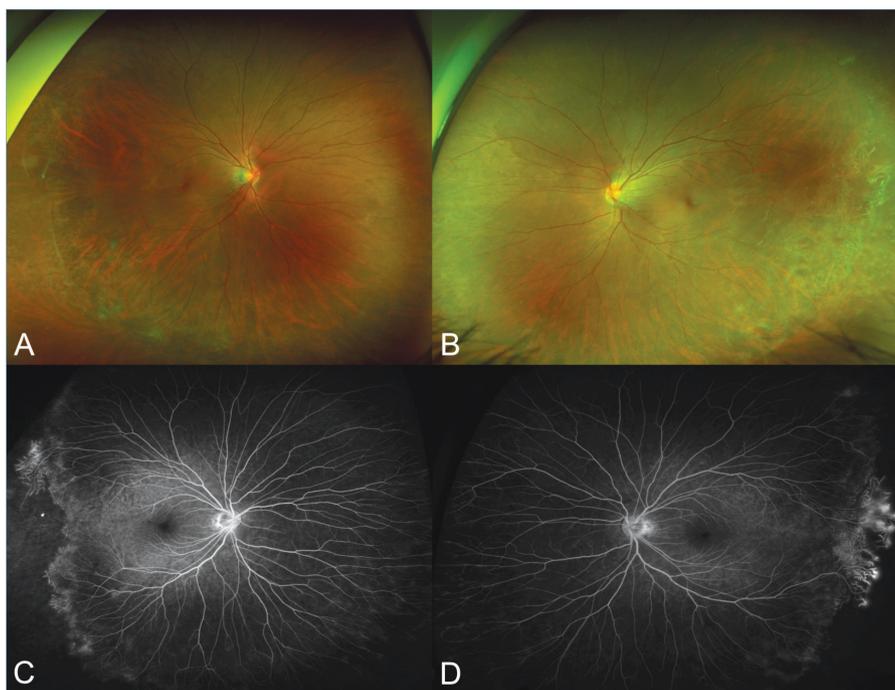
**Figure 2** SD-OCT of macula in case 1 demonstrated thin hyperreflective layer of epiretinal membrane (arrows) at temporal macula without retinal distortion.

tomography (SD-OCT) of macula demonstrated thin epiretinal membrane at temporal macula without retinal distortion (Figure 2). Her right optic disc had elevated swollen appearance, while left optic disc had very small cup-to-disc ratio. Fundus autofluorescence and B-scan ultrasound showed hyperautofluorescence

and hyperechogenicity with posterior acoustic shadow at the right optic disc, respectively. These findings confirmed the presence of buried optic nerve head drusen. Fundus fluorescein angiography-guided laser photocoagulation was performed at avascular retina of both eyes. One month after laser treatment, her vision improved to 20/30 on both eyes and remained stable throughout a follow-up period of one year. We informed the patient regarding the hereditary nature of FEVR. Ophthalmic examination with wide-field fundus fluorescein angiography of her first-degree relatives was advised. However, none of her siblings were able to visit our center.

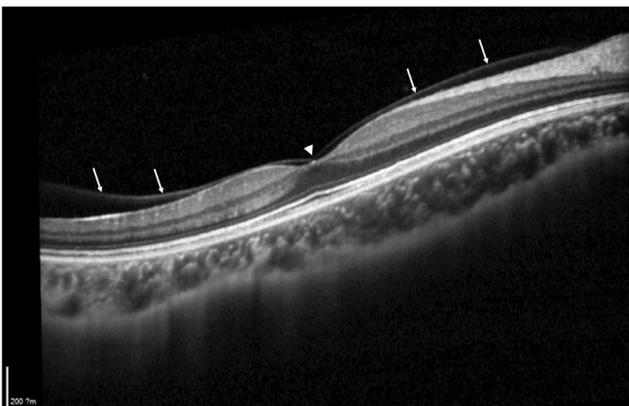
### Case 2

A 22-year-old female Thai woman presented with blurring of vision and floater on the right eye for 5 months. She was born full term in an uncomplicated pregnancy and delivery. No oxygen therapy was used



**Figure 3** Case 2. (A) and (B) Wide-field fundus photography showed an increased number of peripheral vessel, straightening of vessels and peripheral avascular retina with neovascularization and fibrosis. (C) and (D) Wide-field fundus fluorescein angiography demonstrated peripheral avascularity at temporal retina and neovascular leakage of both eyes.

after birth. She was otherwise a healthy child. She is a single child without any history of blindness in her family. On examination, her systemic physical examination was normal except for her eyes, her best-corrected visual acuity was 20/70 and 20/30 with myopia -9.0 diopters and -6.0 diopters on right and left eye, respectively. Anterior segment examination was normal. Dilated fundus examination showed small amount of vitreous hemorrhage on the right eye. Bilateral peripheral retinal abnormalities were observed including an increased number of peripheral vessels, straightening of vessels and peripheral avascular retina with neovascularization (Figure 3A and 3B). Wide-field fundus fluorescein angiography showed peripheral avascular area with leakage from neovascular vessels at avascular junction on both eyes (Figure 3C and 3D) which consistence with FEVR stage 2A.<sup>6</sup> Thick posterior hyaloid with focal vitreomacular adhesion<sup>9</sup> was observed in SD-OCT of macula. (Figure 4.) Fundus fluorescein angiography-guided laser photocoagulation was performed at avascular retina of both eyes. Two months after laser treatment, her best-corrected visual acuity of the right eye improved to 20/50 and remained stable after 6-month follow up.



**Figure 4** SD-OCT of case 2 revealed a thick hyperreflective layer of posterior hyaloid (arrows) with focal vitreomacular adhesion (arrow head).

## Discussion

The incidence of spontaneous vitreous hemorrhage is approximately 7 cases per 100,000 population. Proliferative diabetic retinopathy (32%) is the most common cause of adult-onset vitreous hemorrhage follow by retinal tear (30%), proliferative retinopathy after retinal vein occlusion (11%,) and posterior vitreous detachment without retinal tear (8%).<sup>8</sup>

We reported two cases of vitreous hemorrhage in 60-year-old and 22-year-old women caused by FEVR, which is an uncommon cause of vitreous hemorrhage especially in adult. Diagnosis of FEVR is mainly based on retinal findings including peripheral avascularity, an increased number and caliber of new vessels in the periphery (more common in temporal area), dragging of retinal blood vessels and displacement of the macula secondary to traction.<sup>1,5</sup> FEVR are usually presented bilaterally but have wide variability in symmetry on initial presentation.<sup>5</sup> In asymmetric presentations, the less involved eye may be grossly normal on clinical examination but demonstrate subtle peripheral vascular abnormalities on fluorescein angiography. Thus, clinical examination alone is not sufficient to identify these subtle vascular changes of early-stage FEVR, requiring the aid of wide-field fluorescein angiography.<sup>6</sup> In our cases, wide-field fluorescein angiography can highlight the presence of neovascular vessel and demonstrates an avascular area. While SD-OCT serves as an importance tool to identify microstructural anomalies in FEVR patients. As much as 75% of patients with FEVR have abnormal SD-OCT finding including abnormal posterior hyaloidal organization, vitreomacular traction, vitreopapillary traction, vitreo-fold traction, vitreo-laser scar adhesion, diminished foveal contour, persistent fetal foveal architecture,

cystoid macular edema (CME), intraretinal exudates and subretinal lipid aggregation, dry or edematous radial folds, and disruption of the ellipsoid zone.<sup>10</sup> Both patients in this study had subtle abnormalities revealed by SD-OCT, in which no surgical management was indicated. Although a positive family history on presentation may support the diagnosis of FEVR, a negative family history does not rule out the diagnosis. Moreover, asymptomatic family members of FEVR patients frequently have early manifestations of FEVR (stage 1 or 2) which can progress to more advanced stages and result in severe visual loss.<sup>6</sup> Thus, clinical examination and angiographic screening should be performed in immediate relatives of FEVR patients. Differential diagnosis of presented cases as adult presenting with vitreous hemorrhage, peripheral neovascularization and peripheral avascular retina includes ROP, incontinentia pigmenti (IP), Norrie disease and Coats disease. FEVR and ROP can be distinguished by birth history, oxygenation supplement at birth, and familial pattern. However, in some circumstance such as in case 1, a remote history of prematurity in the 60-year-old female could be uncertain. With ROP, the nature of disease is acute after birth and usually does not progress or recur in adulthood. Moreover, fundus fluorescein angiography finding in ROP also differ from fundus fluorescein angiography finding in FEVR. In ROP, vascular ridge representing arteriovenous shunting is regularly observed whereas in FEVR, neither vascular ridge nor arteriovenous shunting is observed. With IP, patient also has peripheral avascular retina, neovascularization and vitreous hemorrhage but most patients with IP have manifestation at birth or early childhood with cardinal skin lesion. With Norrie disease, the disease affects

almost only in male because the disease inherits by X-linked recessive. Moreover, patients with Norrie disease may suffer from other systemic involvement including childhood-onset hearing loss, abnormal sleep wake cycle, peripheral vascular disease and learning or behavioral problems. With Coats disease, males are affected more than females and most of disease affects unilaterally. In addition to clinical finding and multimodal imagings, genetic analysis including Norrin Disease Protein (NDP)<sup>11</sup>, Frizzled-4 (FZD4)<sup>12</sup>, low-density lipoprotein receptor-related protein 5 (LRP5)<sup>13</sup>, and tetraspanin-12 (TSPAN12)<sup>14</sup> could be helpful in making accurate diagnosis of FEVR.

Treatment options of patients in this study which both had stage 2A included laser photocoagulation, intravitreal anti-vascular endothelial growth factor (Anti-VEGF) and combined laser photocoagulation and Anti-VEGF. Few reports regarding effectiveness of Anti-VEGF for treatment of FEVR have been published.<sup>15,16</sup> Anti-VEGF combined with laser photocoagulation may have benefit in more advanced stage of FEVR by reduce retinal hemorrhage and exudate which facilitate the photocoagulation effect with minimal intensity. In this study, both patients had minimal vitreous hemorrhage without exudate. Thus, Anti-VEGF before laser photocoagulation was not considered. While Anti-VEGF alone was not considered because there is not enough evidence for long term effectiveness and safety. Therefore, laser photocoagulation alone was performed in both patient. Accurate diagnosis of FEVR is important because the unpredictable timeline of progression is a nature of the disease. Thus, lifelong monitoring is necessary. In this study, I followed up both patients monthly until vitreous hemorrhage was resolved then six-monthly and yearly

follow up period were made respectively. In first case, optic nerve head drusen was found incidentally. There was no previous report regarding association between optic nerve head drusen and FEVR.

In summary, we reported two cases of FEVR stage 2A presented with adult-onset vitreous hemorrhage. Meticulous peripheral retinal examination and wide-field fluorescein angiography can lead to accurate diagnosis and proper management. Good visual outcomes were achieved in both patients after laser treatment performed.

### Conflicts of Interest

The authors declare that there are no conflicts of interest pertaining to the publication of this article.

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