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Case Report

Outer Retina Rupture from Subretinal Blood with Spontaneous Sealing and Visual Recovery in Frosted Branch Angiitis from Familial Mediterranean Fever: A Case Report

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Abstract

Familial Mediterranean fever (FMF) is a rare autoinflammatory disorder. Ocular involvement is rare. The full spectrum and response to treatment is poorly understood. An 18-year-old girl previously diagnosed with FMF presented with sudden loss of vision in the left eye (LE). Best-corrected visual acuity (BCVA) in the LE was finger counting at 1.5 meters. Angiitis with mild "frosting," hemi-central retinal vein occlusion (HCRVO), and acute outer retina rupture (ORR) were observed in the LE. Systemic steroids were initiated immediately. The ORR was sealed 2 weeks later while vision improved to 6/15 (near vision: J2) 5 months later. No recurrences were observed over 5 years of follow-up. We report a rare manifestation of frosted branch angiitis with concomitant HCRVO and ORR in a young patient with FMF. Closure of ORR was attained and vision recovered after treatment with high-dose steroids.

Keywords: Frosted branch angiitis, outer retina rupture, hemicentral retinal vein occlusion, Familial Mediterranean Fever, posterior uveitis, retinal vascular sheathing, sudden loss of vision

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Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by mutations in the Mediterranean Fever (MEFV) gene on chromosome 16 and predominantly affects populations of Jewish, Arab, Armenian, and Turkish descent who originated from around the Mediterranean Sea.[1,2,3] Inheritance is autosomal recessive and it manifests with episodes of fever, arthritis, abdominal pain, and erythema that occur sporadically and are self-limiting.[1] Ocular involvement with uveitis is a rare manifestation of the disease. There are a few case reports of anterior, posterior, and intermediate uveitis, frosted branch angiitis (FBA), acute posterior multifocal placoid epitheliopathy, episcleritis, scleritis, and panuveitis.[4,5,6,7,8,9,10,11,12,13,14,15] Due to the plethora of clinical manifestations, some of these cases can be misdiagnosed and pose therapeutic challenges.[16] In this case report, we present the long-term follow-up of a young patient with FMF who presented with acute rupture of the outer retinal layers secondary to FBA-associated hemicentral retinal vein occlusion (HCRVO).

Case Report

An 18-year-old Jewish girl with known FMF confirmed by genetic testing (carrier of M694V and M694I mutations of the *MEFV* gene) and previously treated with colchicine (discontinued 5 years prior to presentation) presented with a sudden loss of vision in the left eye (LE) on awakening from sleep, without any other constitutional symptoms. Best-corrected visual acuity in the LE was finger counting at 1.5 meters and 6/6 in the right eye. Fundoscopy of the LE revealed angiitis with mild frosting in the nasal retina and HCRVO with retinal hemorrhages in the superior retina (Figure 1). Examination of the right eye was normal. Fluorescein angiography of the LE revealed areas of blocked fluorescence, vascular leakage in the superior retina, optic disc leakage and macular hypofluorescence (Figure 2A,B). Spectral-domain optical coherence tomography of the LE demonstrated rupture of the outer retinal layers in the macular area as a result of exudative retinal detachment, with sparing of the inner retina with its internal limiting membrane (ILM) and nerve fiber layer. The outer retinal rupture (ORR) measured more than 400 µm, and the edges had the typical "anvil-shaped" deformity. Vitreous cells and hyperreflective dots were observed along the outer plexiform layer (Figure 2C).

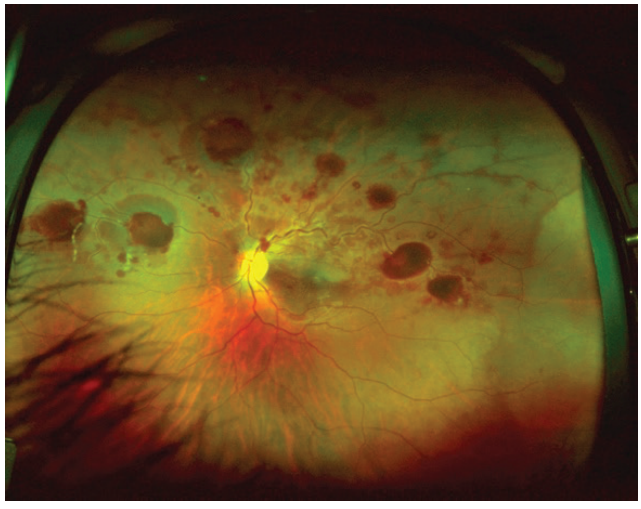

Figure 1. Wide-field pseudo-color fundus image of the left eye shows vasculitis with "mild frosting" in the nasal retina and hemi-central retinal vein occlusion with retinal hemorrhages in the superior retina.

Systemic evaluation ruled out the presence of orogenital ulcers, skin rash, joint pain, and respiratory or gastrointestinal symptoms. Systemic work-up revealed normal liver and kidney function tests. There was mild leukocytosis ($12.6x10^9$/L; normal range: $4.05\text{-}11.84x10^9$/L), ESR was 32 mm/hour (normal range: 0-20 mm/hour), and CRP was 8 mg/L (normal range: 0-5 mg/L). Rheumatic markers were negative (antinuclear antibodies, rheumatoid factor, complement C3, complement C4, anti-cyclic citrullinated peptide antibodies, anti-tissue transglutaminase immunoglobulin (Ig) A [anti-tTG-IgA], cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies). Serological tests for infectious etiologies (Epstein-Barr virus, Venereal Disease Research Laboratory test, *Treponema pallidum* hemagglutination test, *Brucella, Toxoplasma* IgG and IgM, cytomegalovirus IgM) were negative. Mantoux test was negative and chest X-ray was normal. Hematological work-up revealed a slightly elevated lupus anti-coagulant IgM of 72 IgM phospholipid (MPL) units (U)/mL (normal range: 20-39 MPL U/mL), antithrombin activity was 122% (normal range: 80-120%), and anti-cardiolipin IgG was 16.55 U/mL (upper limit 10 U/mL). Factor V Leiden, anti-cardiolipin IgM, anti-B2-glycoprotein (IgG and IgM), coronary artery calcium, dilute Russell viper venom time, and levels of protein C, S, and homocysteine were within normal range or negative.

Intravenous methylprednisolone (250 mg daily for 3 days) was initiated promptly and prednisone was introduced subsequently with a tapering regimen over a period of 13 months. The ORR was sealed 2 weeks later while vision improved to 6/15 (near vision of J2) 5 months later (Figure 3). The angiitis with mild frosting and retinal hemorrhages also resolved by 5 months post-treatment (Figure 4). Treatment with oral colchicine was reintroduced. No recurrence was observed over a follow-up period of 5 years.

Discussion

We report a rare manifestation of acute ORR developing in a young female with FMF who presented with FBA-associated HCRVO. Complete closure of ORR was attained and vision was recovered after the use of high-dose steroids.

Retinal involvement in FMF is rare, with a few reported cases of exudative retinal detachment, epiretinal membrane (ERM),[4] retinal tears requiring barrier laser,[7] neovascularization elsewhere requiring panretinal photocoagulation,[4] and vasculitis manifesting as FBA and retinal artery and vein occlusion.[4,8,13,14,15] Two previously reported cases of retinal vein occlusion (RVO) showed visual improvement, similar to the index case, following steroid treatment. The first case was of a 39-year-old man

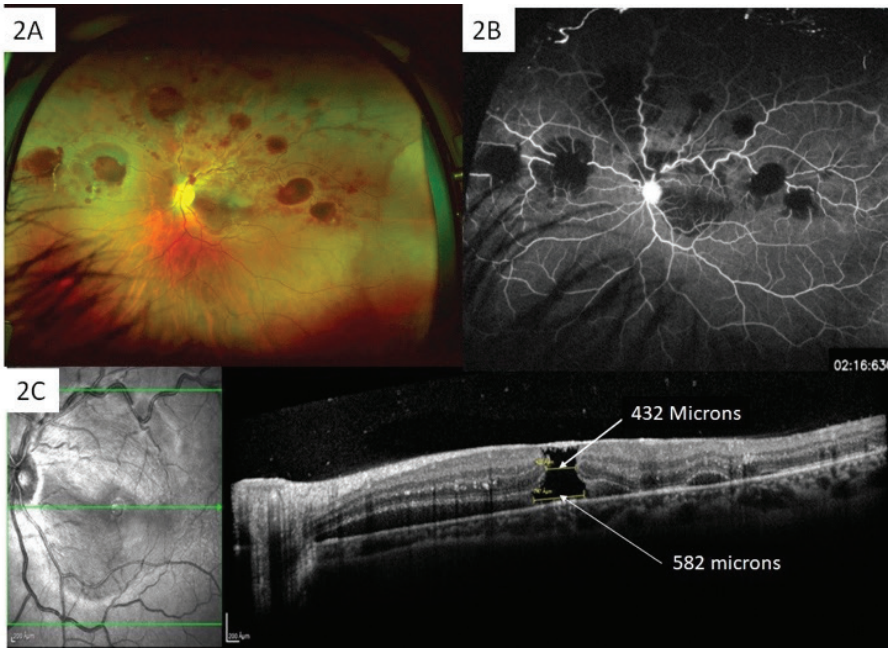

Figure 2. Multimodal imaging of the left eye fundus at presentation. A) Wide-field pseudo-color picture shows multiple foci of retinal hemorrhages mostly in the superior retina. B) Late-phase wide-field fluorescein angiography shows hyperfluorescence of the optic disc and areas of blocked fluorescence in the superior half of the retina and macular hypofluorescence. C) Optical coherence tomography cross-sectional scan across the fovea shows rupture of outer retina layer (measures 432 µm wide at its narrowest point) with the typical "anvil-shaped" deformity of the edges, overlying the internal limiting membrane, nerve fiber layer, and subretinal fluid.

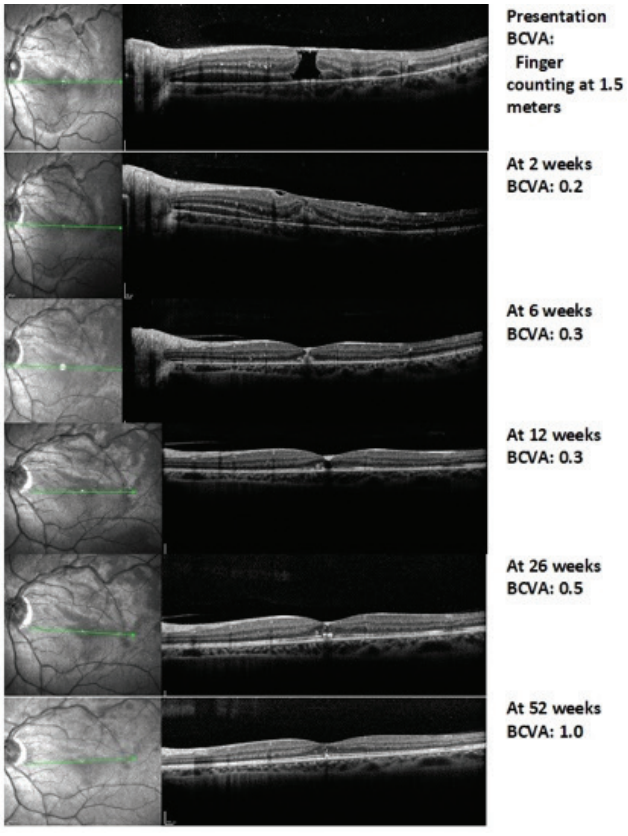

Figure 3. Optical coherence tomography cross-sectional macula scans through the fovea show the progressive closure of outer retina rupture over time, with concomitant visual improvement.

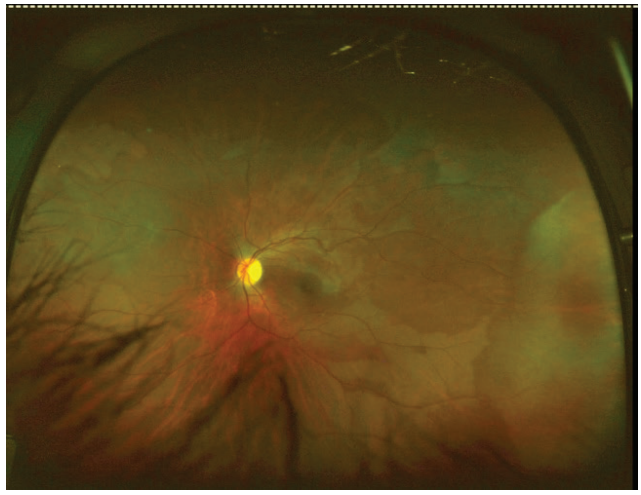

Figure 4. Wide-field pseudo-color fundus image of the left eye 5 months after starting treatment shows resolution of vasculitis and retinal hemorrhages in the superior retina.

who presented with unilateral FBA-associated central RVO. This was the first reported case of FBA associated with FMF in the literature, and vision improved to 6/6 within 7 months after starting immunosuppressants. He was treated with oral methylprednisolone (64 mg/day) with gradual tapering and concomitant azathioprine (150 mg/day) as he developed "moon face" due to corticosteroid use.[8] The second case was of a 53-year-old man who had bilateral vitritis and recurrent retinal vasculitis with resultant cystoid macular edema, ERM, and

branch RVO. Final VA improved to 6/6 after treatment with 3 days of intravenous pulse methylprednisolone (1 g/day) followed by oral prednisolone starting at 1 mg/kg with gradual tapering.[4] A recent article describing vasculitis in 16 patients with FMF also reported good visual recovery after long-term use of corticosteroids and other immunosuppressants.[13] Patients with chronic ocular inflammation often benefit from long-term management with steroid-sparing therapy. Immunomodulators should be considered in patients intolerant to steroid therapy, and they are particularly important because they carry far less risk of causing long-term complications and offer great potential in altering the immune system to induce durable remission.[17] The immediate and progressive favorable response without recurrence or complications observed in our patient under corticosteroid therapy tapered over 13 months made the need to add steroid sparing agents to her therapy less compelling. Moreover, she was restarted on colchicine, which is known to exert an anti-inflammatory effect in FMF.[18]

As a systemic proinflammatory condition, FMF would be expected to trigger hypercoagulability.[19] However, thrombotic events have rarely been reported in FMF. In the few case reports of thrombotic events, extensive work-up usually revealed concomitant multiple inherited and acquired risk factors for thrombosis.[20,21] Possible explanations for this advanced by Tayer-Shifman and Ben-Chetrit[22] include disruption of the balance between coagulation and fibrinolysis, the possibility that proinflammatory factors produced during attacks that would promote hypercoagulability are being consumed in the inflammatory process, and the possible impact of continuous colchicine use by FMF patients on the coagulation pathway. Our patient was not on colchicine treatment, and she had elevated lupus anti-coagulant and anti-cardiolipin levels. These factors may have predisposed to a thrombotic event.[23] On the other hand, anti-thrombin activity, which is supposed to limit clot formation, was borderline high.

To our knowledge, this is the first case of an acute rupture in the outer retina layers developing in the context of retinal vasculitis in a patient with FMF. Our patient had exudative retinal detachment, thus leading to tension and rupture of the outer retina. This mechanism of rupture is extremely rare, with most cases leading to full-thickness macular hole.[24] A similar pattern of healing without surgical intervention was observed in patients with macular holes, especially among young people, trauma patients, and those with deviations of less than 200 µm, as shown in a large series by Uwaydat et al.[24] Though our patient was young, the ORR spanned over 400 µm. However, it closed quickly, within 2 weeks of initiating corticosteroid therapy, with subsequent near-complete restoration of foveal anatomy and contour (Figure 3). No recurrence was observed over a follow-up period of 5 years.

Uveitis recurrence in FMF patients being tapered off steroids has been reported frequently in the literature,[4,7,11] though it is still unclear which factors influence this recurrence. It is possible that certain *MEFV* polymorphisms may be involved; for example, patients who are homozygous for the M694V polymorphism are more likely to manifest severe disease.[25,26]

Behçet's disease is an important differential diagnosis in this case and has even been shown to coexist in patients with FMF.[4] However, the patient's clinical findings did not meet the criteria of the International Uveitis Study Group of Behçet's disease.[27] Extensive laboratory and radiological work-up did not reveal any other pathology or coexistent disorder.

The peculiarity of this case was the presence of a large outer retina layer disruption which eventually self-sealed within 2 weeks of starting steroid therapy. The sudden nature of FBA with concomitant RVO associated with sudden drastic visual loss was also remarkable. This underscores the fact that ophthalmologists working amongst these populations at risk should maintain a high index of suspicion to avoid delays in the diagnosis and treatment of such patients with fulminant presentation.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Peer-review: Externally peer reviewed.

Yazarlık Katkıları

Concept: B.N.V., R.A., Design: B.N.V., R.A., Data Collection or Processing: B.N.V., R.A., Analysis or Interpretation: B.N.V., R.A., Literature Search: B.N.V., R.A., Writing: B.N.V., R.A.

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