



Multimodal treatment of Coats-like exudative vitreoretinopathy in Goldmann-Favre syndrome

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ABSTRACT

Purpose: To report a Coats-like exudative vitreoretinopathy in Goldmann-Favre syndrome.

Observations: A 64 year-old woman with prior diagnosis of retinal dystrophy presented with decreased vision in the right eye (OD). Ophthalmologic examination was remarkable for bilateral arteriolar attenuation, mid-peripheral bony-spicules, and waxy disc pallor. Coats-like exudative vitreoretinopathy and cystoid macular edema were present OD. Genetic testing showed a homozygous pathogenic mutation in gene *NR2E3*, variant c.932G>A (p.Arg311Gln), consistent with Goldmann-Favre syndrome. Targeted laser ablation and combination intravitreal therapy were effective in decreasing macular edema.

Conclusions and Importance: A Coats-like exudative vitreoretinopathy may occur in the setting of Goldmann-Favre syndrome. Targeted laser ablation in combination with intravitreal therapy can be efficacious in select patients.

1. Introduction

Goldmann-Favre syndrome (GFS) is a rare (1:1000000) progressive vitreoretinal degeneration phenotypically similar to retinitis pigmentosa (RP) that was first described in 1957–1958 by Goldmann and Favre in a pair of adolescent siblings.^{1–3} GFS is characterized by degenerative vitreous changes, macular or peripheral retinoschisis, retinal pigmentary changes and early cataracts.^{4,5} Similar to RP, the disease has been characterized by the appearance of peripheral pigment in the retina secondary to photoreceptor loss.⁶ While RP pigmentation is characterized by a bone spicule pattern, pigmentation in GFS is mostly of the clumped nummular type with little or no bone spicules.^{7,8} The initial symptoms include night blindness, tunnel vision and gradual loss of central vision.⁶ Progression of the disease may also lead to severe visual loss and blindness.^{6,7} Mutations in the *NR2E3* gene lead to the clinical spectrum of GFS and enhanced S-cone syndrome (ESCS).^{4,7} GFS may have a heterogenic presentation and it can be difficult to distinguish GFS/ESCS among other retinal degenerative disorders, such as RP.⁹ We report the first known case in the literature of a patient with Goldmann-Favre syndrome and Coats-like exudative vitreoretinopathy

that was managed successfully with multimodal therapy.

2. Case report

A 64-year-old woman with controlled essential hypertension was referred due to visual loss in the right eye (OD). Prior ocular history included a prior clinical diagnosis of retinitis pigmentosa and cataract surgery in both eyes (OU).

A complete ophthalmological exam was performed. Best-corrected visual acuity was counting fingers at 1 feet OD and 20/200 in the left eye (OS). Intraocular pressure was 9 mmHg OU. External and anterior segment examination was unremarkable except for pseudophakia OU. Pupils were equally round and equally reactive to light. Fundoscopic examination revealed waxy optic disc pallor, attenuated vessels, diffuse retinal pigment epithelium mottling, pigment clumps, and peripheral bony spicules OU (Fig. 1). Extensive macular edema and hard exudates were present OD.

Fluorescein angiography was performed and showed late hyperfluorescence consistent with temporal aneurismal changes and telangiectasias OD (Fig. 2), and OS showed no evidence of exudative changes.

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Macular spectral domain optical coherence tomography (SD-OCT) demonstrated retinal thickening, retinoschisis and intraretinal fluid OD (Fig. 3) and OS showed atrophic retinal changes without intraretinal or subretinal fluid.

Gene sequencing and deletion/duplication analysis using next-generation sequencing (NGS) (Invitae Corporation, San Francisco, California) was then performed. Results were positive for a homozygous pathogenic mutation in gene *NR2E3*, variant c.932G>A (p.Arg311Gln), consistent with Goldmann-Favre syndrome. The patient denied consanguinity. Targeted 810 nm diode laser ablation (OcuLight SLx, Iridex Corp.) of telangiectasias was undertaken in combination with monthly intravitreal bevacizumab (Avastin, Genentech, Inc.) 1.25mg/0.05ml or triamcinolone acetonide (Triesence, Alcon Laboratories Inc.) 4.0 mg/0.10 ml at discretion of treating physician (VV). A total of 14 intravitreal treatments were performed: 5 bevacizumab and 9 triamcinolone acetonide.

The mean decrease in central foveal thickness 1 month after intravitreal bevacizumab was 27 μ m. The mean decrease in central foveal thickness 1 month after intravitreal triamcinolone acetonide was 88 μ m. After 23 months of therapy, the patient had improved anatomical outcomes without any deterioration in visual acuity. Intraocular pressure remained less than 20 mmHg throughout all evaluations without topical therapy. Macular SD-OCT upon last evaluation showed a significant decrease in central macular edema when compared to the initial evaluation (Fig. 4).

3. Discussion

Zamorani et al. first described the association between a retinal dystrophy and an exudative retinopathy in 1956 in a patient with RP.¹⁰ The Coats-like exudative vitreoretinopathy seen in conjunction with RP may include vascular ectasia, aneurysm formation, telangiectasia, capillary dropout, and profuse intraretinal and subretinal exudation. Advanced cases may be complicated by neovascularization in the retina and/or choroid.¹¹ Unlike Coats' disease, Coats-like exudative vitreoretinopathy in RP is more common bilaterally, shows no gender preference, almost exclusively affects the temporal retina, and most of the patients are diagnosed during the second and third decade of life.¹¹ We report the first case of Coats-like exudative vitreoretinopathy in a patient with GFS.

The etiological and pathophysiologic mechanisms that lead to a Coats-like exudative vitreoretinopathy in various retinal dystrophies remains unclear.¹² Early theories of the origin of the exudative vasculopathy include primary endothelial cell dysfunction with a secondary increase in vascular permeability.¹³ Other secondary changes include RPE dysfunction, subretinal fluid accumulation, chronic inflammation, hypoxia and neovascularization.¹³ Vasoproliferative tumors may also be present in eyes with advanced Coats-like exudative vitreoretinopathy and retinal dystrophy.¹⁴

Advances in genetic testing is allowing for specific diagnoses of

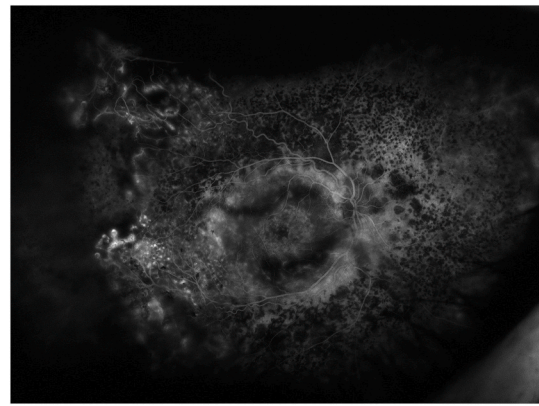


Fig. 2. Fundus fluorescein angiography of the right eye. Late phase hyperfluorescence consistent with temporal aneurismal changes, telangiectasias, and peripheral nonperfusion.

dystrophies with exudation. In this case, the patient had a presumptive diagnosis of RP based on phenotype, yet gene sequencing demonstrated a common pathological mutation associated with GFS, specifically a mutation in *NR2E3*, variant c.932G>A(p.Arg311Gln). In silico predictions (PolyPhen, SIFT, Mutation Assessor) classify the variant (OMIM#:604485.0005) as a likely benign and tolerated missense mutation. However, the variant has been reported in several affected individuals in a homozygous or compound heterozygous state and has therefore been classified as pathogenic.^{8,15–18} This diagnosis is compatible with the clinical findings in our patient who had early bilateral cataracts, retinal mottling and nummular pigmentary changes, and retinoschisis.

Recently, coats-like exudative vitreoretinopathy has been associated with X-linked RP, specifically RPGR and CRB1 mutations.^{19–23} A similar exudative response also been reported in association to Leber's congenital amaurosis and early-onset childhood retinal dystrophy.²⁴ These robust exudative changes may be a final common pathway regardless of the underlying dystrophic etiology,²⁴ although it is possible that environmental factors could play a role.^{19,20,25} Coats-like exudative vitreoretinopathy associated with dystrophies may have a worse prognosis when compared with pediatric Coats' disease.^{13,19} Even though early intervention may decrease the degree of vision loss, there is limited evidence of complete disease resolution post treatment.¹²

A myriad of treatments have been utilized for Coats-like exudative vitreoretinopathy including laser photocoagulation, cryotherapy, vitrectomy, and periocular/intravitreal agents.^{19,26}

Laser photocoagulation has been reported as the most effective alternative by some authors.^{12,26–29} However, no randomized prospective studies evaluating treatment for Coats-like exudative vitreoretinopathy has been performed. Intravitreal anti-vascular endothelial growth factors (anti-VEGF) agents have been recently utilized as

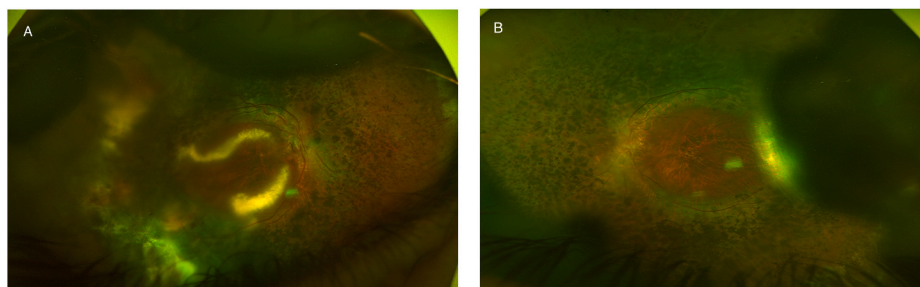


Fig. 1. Color fundus photography. A. Right eye, vascular attenuation, peripheral bony spicules, diffuse retinal pigment epithelium mottling, macular pigmentary changes and exudation along the major vascular arcades. B. Left eye, vascular attenuation, peripheral bony spicules, macular pigmentary changes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

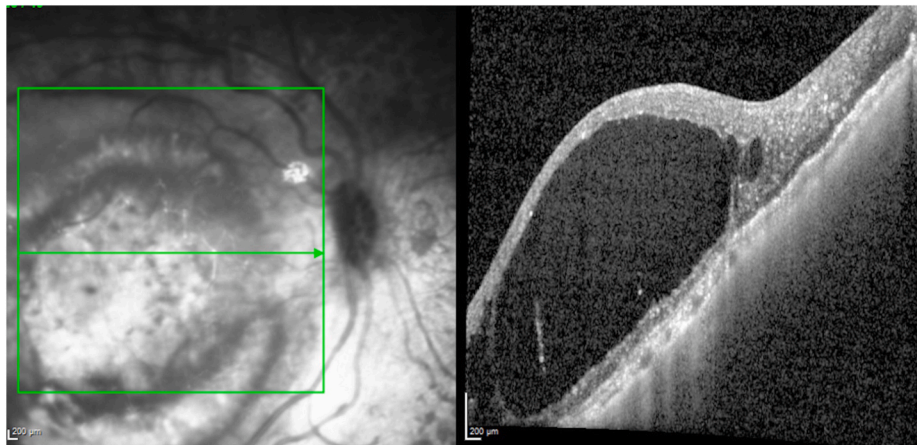


Fig. 3. Macular spectral domain optical coherence tomography (SD-OCT) of the right eye. Retinal thickening, retinoschisis, disorganized retinal layers, intraretinal fluid, and hard exudation are present.

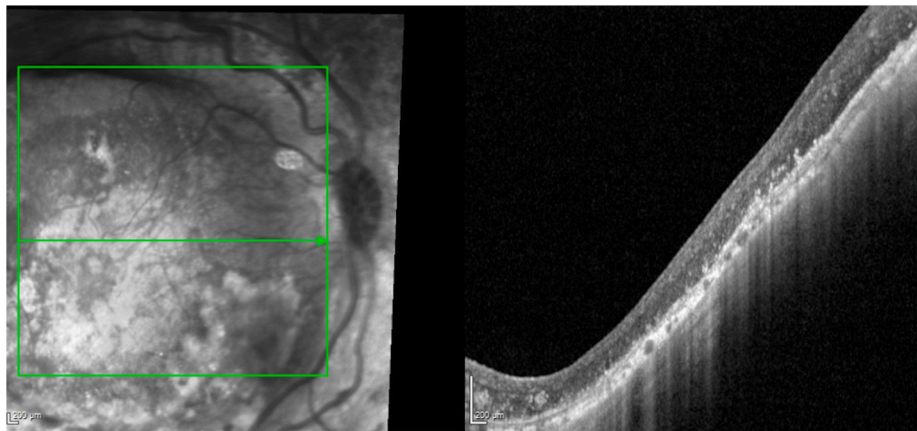


Fig. 4. Post treatment macular spectral domain optical coherence tomography (SD-OCT) of the right eye. Retinal atrophy and disorganization of the retinal layers (both inner and outer) with marked resolution of the intraretinal exudate are shown.

adjuvant treatment to modulate the acute exudative response seen after primary therapy.^{30–32} Most recently Patel et al.³⁰ have suggested that some anti-VEGF agents may have superior efficacy for this condition. Periocular and intravitreal corticosteroids have also been used by multiple authors as adjuvant therapy to minimize the concentration of several inflammatory cytokines -such as IL-6, IL-8 MCP-1- that have been found in eyes with Coats' disease.³³ Despite increasing availability of intravitreal agents, management continues to be an ongoing challenge with heterogeneous visual and anatomical outcomes.³⁴ In our report, disease control was achieved with laser photocoagulation in combination with intravitreal therapy. Interestingly, macular edema in our patient seemed to respond better when treated with triamcinolone than when bevacizumab was used. Perhaps treatment response may correlate to the underlying genetic mechanism that leads to the Coats-like exudative response. Further research needs to be performed to explore this finding.

4. Conclusion

This case demonstrates that Goldmann Favre Syndrome (*NR2E3* mutation) is associated with a Coats-like exudative vitreoretinopathy. Laser photocoagulation in combination with intravitreal anti-VEGF and corticosteroids provided control of the retinal exudation and edema. Further research on the underlying mechanisms of exudative retinopathies associated with retinal dystrophies is required to guide the development of appropriate standardized therapy.

Patient consent

Consent to publish this case was not obtained from the patient. The case report does not contain any identifying information.

Declaration of competing interest

No conflict of interest exists.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with

the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Authorship

All listed authors meet the ICMJE criteria.

We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the manuscript has been read and approved by all named authors.

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