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Bilateral exudative retinal detachments after subretinal gene therapy with voretigene neparvovec-rzyl for RPE65 Leber Congenital Amaurosis

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ABSTRACT

Purpose: To report panuveitis with exudative retinal detachments in a healthy 27-year-old woman with biallelic mutations in the RPE65 gene, who underwent bilateral sequential gene therapy with subretinal administration of voretigene neparvovec-rzyl.

Observations: Visual acuity improved for 30 days after surgery as oral corticosteroids were tapered. At post-operative week 6, vision declined due to sudden onset uveitis and exudative retinal detachments in both eyes. HLA Class II typing revealed the haplotype associated with sympathetic ophthalmia and Vogt-Koyanagi-Harada (VKH). The inflammation improved after corticosteroid, mycophenolate mofetil, and adalimumab therapy while vision remained poor.

Conclusions and Importance: Surgically-induced sympathetic ophthalmia is a plausible explanation for the clinical findings; surgery of both eyes within one week would conceal the inciting eye. VKH or inflammation related to the gene therapy are other possible etiologies but severe bilateral panuveitis has not been reported with voretigene neparvovec-rzyl. Informed consent for gene therapy surgery should include a discussion of the rare complication of sympathetic ophthalmia following vitrectomy surgery.

1. Introduction

RPE65 codes for all-trans retinyl ester isomerase, an enzyme essential to the retinoid cycle. A deficiency in RPE65 leads to severe progressive retinal degeneration beginning in childhood described clinically as Leber Congenital Amaurosis type 2 (LCA2) or recessive early-onset retinitis pigmentosa, which were the earliest targets of retinal gene therapy.[1] Voretigene neparvovec-rzyl, a recombinant adeno-associated virus (AAV) vector containing an RPE65 transcript, was approved by the FDA in 2017 after an open-label, randomized, controlled phase 3 trial showed improved multi-luminance mobility testing compared to control patients at one year.[2] Eye inflammation occurred in 3 of 40 patients (7.9%) who received gene therapy in the clinical trials and the investigators reported "no deleterious immune responses" two to four years after treatment.[3] There have been post-approval reports of foveal thinning and retinal or chorioretinal atrophy following surgery, but no major adverse events.[4–6]

We report severe intraocular inflammation in a 27-year-old woman that led to worsened vision after an initial promising response to gene therapy with voretigene neparvovec-rzyl.

2. Case report

A 27-year-old woman of Puerto Rican and Trinidadian descent (white, Hispanic ethnicity) presented in November 2019 with best corrected visual acuity of 20/250 bilaterally with a myopic correction of −10 D in the right eye and −8 D in the left eye. There were extensive bilateral retinal pigment epithelium (RPE) changes with bone spicules, arteriolar attenuation, and optic nerve pallor. Her younger sister had the same fundus appearance and reduced vision. There were no other affected family members. Genetic testing confirmed identical biallelic pathogenic variants in the RPE65 gene in both sisters: c.1022T > C (p.Leu341Ser) and c.1205G > A (p.Trp402*).

In June 2020, both the patient and her sister underwent bilateral sequential subretinal administration of voretigene neparvovec-rzyl to the right eyes on the same day and, one week later, to the left eyes on the

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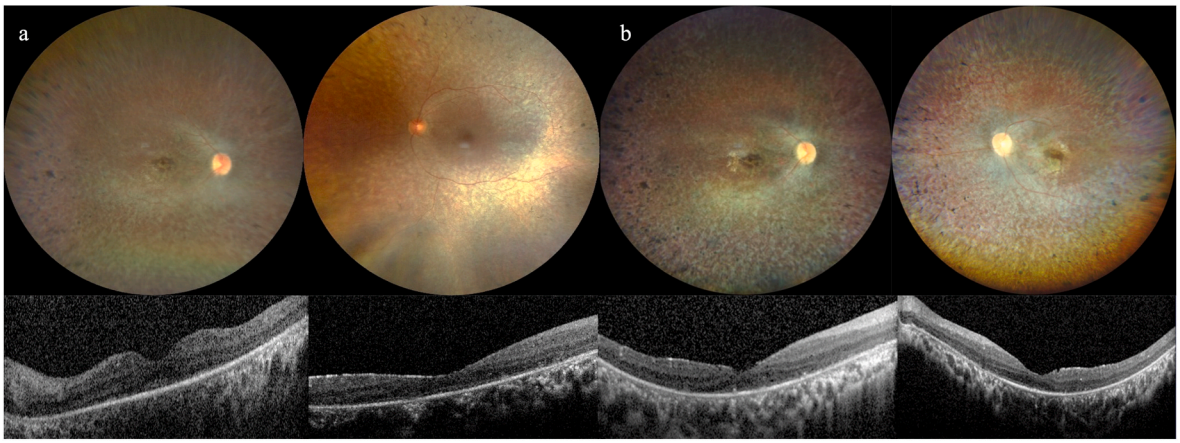

Fig. 1. A. Right eye and left eye fundus photos and macular OCT examinations prior to subretinal surgery. There is extensive pigmentary change with vascular attenuation. Central macular atrophic changes are present in both eyes. OCT examination shows preservation of a small area of subfoveal ellipsoid zone and severe outer nuclear layer thinning. **B**. Right eye and left eye fundus photos and OCT examinations four and three weeks after subretinal injection of gene therapy with voretigene neparvovec-rzyl in the right eye and left eye, respectively. There is trace cell in the vitreous in both eyes. There is a subtle increase in the macular pigmentary changes with stable peripheral pigmentary changes.

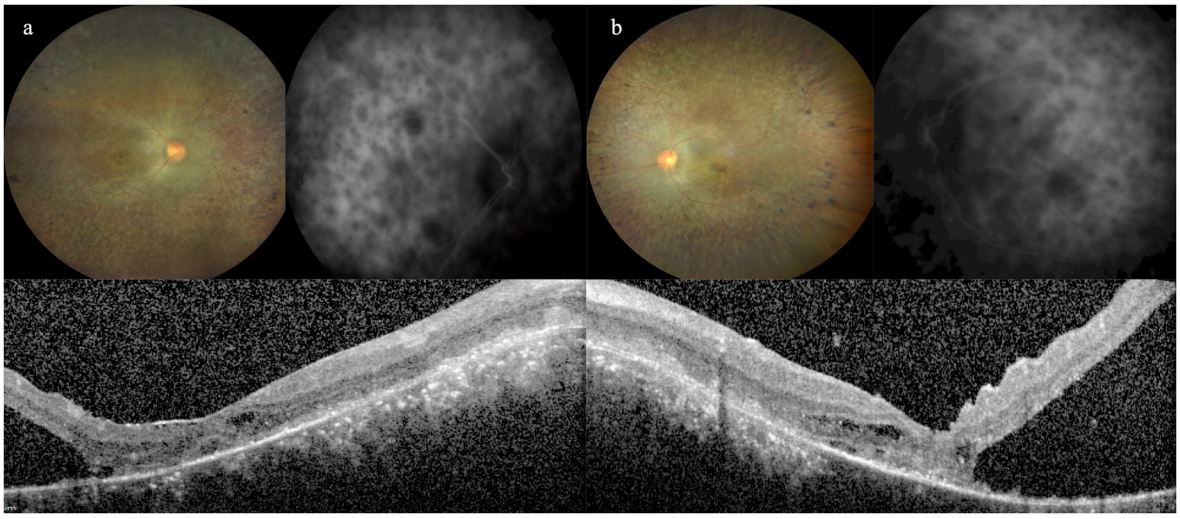

Fig. 2. A. Right eye, 5 days after the onset of bilateral eye redness with progressive decrease in vision. Top left, color fundus photograph demonstrating posterior subretinal fluid sparing the peripheral areas of pigmentary degeneration. Top **right**, mid-phase indocyanine green angiogram shows multiple focal hypofluorescent choroidal infiltrates. Bottom, macular OCT showing subretinal fluid temporal to the fovea with nasal subretinal hyperreflective deposits and trace intraretinal fluid. Choroidal thickness cannot be measured. **B**. Left eye, 5 days after the onset of bilateral eye redness with severe decrease in vision. Top **left**, color fundus photograph showing subretinal fluid in the posterior pole sparing the areas of severe pigmentary degeneration in the retinal periphery. Top right, mid-phase indocyanine green angiogram showing multifocal hypofluorescent choroidal infiltrates. Bottom, macular OCT confirms subretinal fluid temporal to the fovea with nasal subretinal hyperreflective material and trace intraretinal fluid. The posterior extent of the choroid is poorly visualized. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

same day, by the same surgeon and operating room team in Miami, Florida. There were no surgical complications. Oral prednisone 40 mg daily had been started three days prior to the first surgery and continued until 4 days after the second surgery and then tapered off over 10 days for a total 24-day course according to the suggested protocol in the manufacturer's brochure. Four weeks after surgery, both sisters were off corticosteroids and reported subjectively clearer vision.

The patient of this report improved initially to 20/200 in each eye. Her early post-operative macula optical coherence tomography (OCT) findings were similar to the preoperative findings showing outer nuclear layer loss in both eyes (Fig. 1A and 1B). In August 2020, 6 weeks after her last surgery, she developed mild conjunctival injection, slight headache, and occasional pain in the right eye. Three days later, she was seen in New York City with complaints of blurred vision. Anterior vitreous cell was present. OCT of macula showed central serous elevations in each eye. She was started on oral prednisone 50 mg daily. Three days later, vision was hand motions right eye and light perception left eye with bilateral exudative retinal detachments affecting the posterior poles. Macular OCT showed bilateral bacillary layer detachments, undulations in the RPE, and subretinal fluid. Indocyanine green angiography (ICGA) revealed multifocal early phase hypofluorescent spots that persisted into the late phase (Figs. 2A and B). The imaging was felt to be classic for VKH and sympathetic ophthalmia. She was hospitalized and received intravenous methylprednisolone 1 g daily for 3 days. Syphilis antibody and Quantiferon testing for tuberculosis exposure were negative, as were routine labs. Three days later, lumbar puncture and cerebrospinal fluid analysis were performed. There were 60–67 nucleated cells per cubic ml in each of two tubes, of which 93-97% were lymphocytes. On flow cytometry 7.4% of the lymphocytes could be characterized as small T cell lymphocytes with a CD4:CD8 ratio of 5:1. CSF

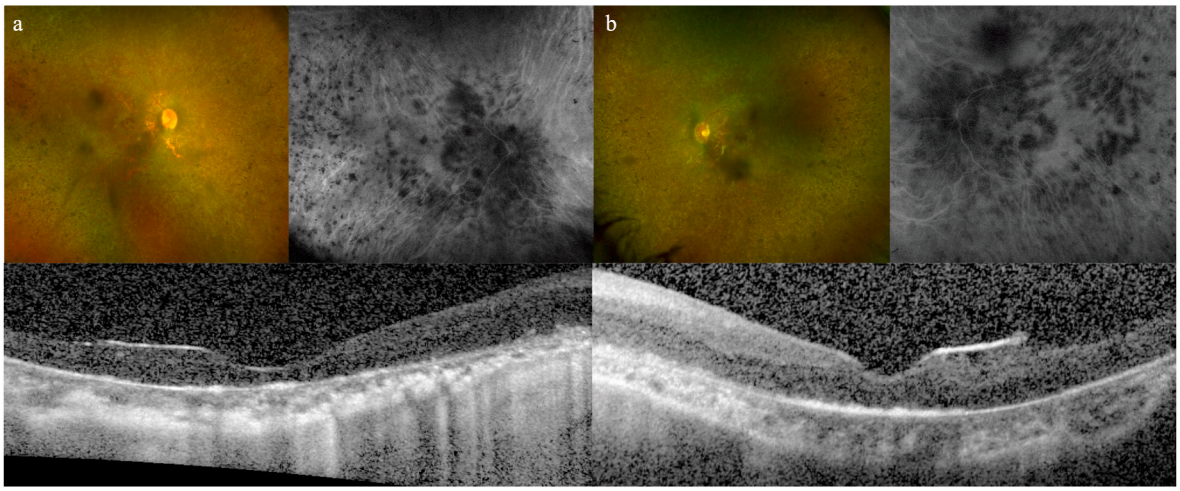

Fig. 3. A. Right eye, one year after onset of the acute ocular symptoms. Top left, color fundus photograph showing resolution of the subretinal fluid. Top **right**, mid-phase indocyanine green angiogram shows a few remaining choroidal infiltrates as well as blockage from overlying pigment. The choroid is no longer hyperfluorescent. Bottom, macular OCT shows disorganization of the laminations of the retina with poor identification of the ellipsoid zone. The choroid is now normal thickness. **B.** Left eye, one year after onset of the acute ocular symptoms. Top left, color fundus photograph shows resolution of subretinal fluid with extensive pigmentary changes. Top right, mid-phase indocyanine green angiogram. The choroidal infiltrates are better defined with less choroidal hyperfluorescence. Bottom, macular OCT confirms resolution of the retinal detachment. The ellipsoid zone is fully attenuated. Choroidal thickness is now normal. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

glucose and protein were in the normal range. She was discharged on oral prednisone 80 mg daily with ophthalmic difluprednate drops.

In September 2020, 4 weeks after the onset of her eye symptoms, a consulting rheumatologist prescribed mycophenolate mofetil 500 mg by mouth twice daily and decreased the oral prednisone to 60 mg daily. Two weeks later, mycophenolate mofetil had been increased to 1 g twice daily. Her visual acuity was hand motions in both eyes and she complained of a visual disturbance similar to static on a television screen. Subretinal and intraretinal fluid had improved and the choroidal thickening had improved on B scan ultrasound. The rheumatologist initiated a slow taper of the oral prednisone.

In January 2021, 5 months after the onset of inflammation, her visual acuity had improved to counting fingers in both eyes on mycophenolate 1 g twice daily and prednisone 7.5 mg daily. No intraretinal or subretinal fluid was present on OCT (Figs. 3A and B). She reported that the visual disturbance resembling static had increased her dependency on a white cane for ambulation. Bilateral 2+ posterior subcapsular cataracts were present. Ocular hypertension was treated by discontinuing difluprednate topical drops. Adalimumab was started due to persistent hypofluorescent lesions on ICG angiography.

High resolution Sanger-sequencing-based HLA typing (SBT) was performed by the Transplantation Lab at the University of Miami to determine if risk alleles for VKH and sympathetic ophthalmia were present.[7–10] The affected sister had two high risk haplotypes: 1) DRB1*04:04 + DQB1*03:02 + DQA1*03:01, and 2) DRB1*04:05 + DQB1*03:02 + DQA1*03:03. The unaffected sister inherited the DRB1*04:05 and DQB1*03:02 risk alleles; her other haplotype was DRB1*10:01 + DQB1*05:01 with recombination at the DQA1 locus. Assays for T cell and antibody responses to the AAV2 capsid antigens were attempted but unsuccessful.

Two and a half years after surgery she retained counting fingers vision in each eye, had been tapered off of mycophenolate mofetil and prednisone by the rheumatologist and had no signs of active inflammation on adalimumab 40 mg subcutaneous injection every 14 days.

3. Discussion

Panuveitis due to VKH or sympathetic ophthalmia fits the clinical features of our case. Prodromal headache has been reported in sympathetic ophthalmia but is more common in VKH. Lymphocytic meningitis can occur in both VKH and in sympathetic ophthalmia.[11] No integumentary findings typical for VKH occurred during follow-up. Standardization of Uveitis Nomenclature (SUN) classification criteria for VKH[12] exclude patients with prior trauma or vitreoretinal surgery for research purposes but do not restrict diagnoses of individual patients on clinical grounds.[13] Similarly, the classification criteria for sympathetic ophthalmia require unilateral trauma or surgery as the inciting event.[14] Bilateral surgery complicates the identification of a clear inciting and sympathizing eye. The patient was genetically predisposed to both VKH and sympathetic ophthalmia based on two high risk HLA haplotypes compared to her unaffected sister who inherited some of the high-risk alleles, but neither complete haplotypes. It is unknown whether this genetic difference determined the outcomes in these two sisters.

Lack of prior severe uveitis after voretigene-neparvovec gene therapy[3] supports a diagnosis of either incidental VKH or sympathetic ophthalmia incited by surgery. In addition to vitrectomy, a known cause of sympathetic ophthalmia, the patient also underwent retinotomy with injection of gene therapy in the subretinal space, a new procedure. Ocular inflammation temporally related to gene therapy surgery is common[15] but more so with intravitreal than with subretinal injection of vector due to greater biodistribution of the vector to the systemic compartment.[16] Timing and presence of cellular infiltrates in the choroid support a T cell mediated immune response to intrinsic ocular antigens or to the vector of transgene.[15] To our knowledge, no other cases of sympathetic ophthalmia have been reported after vitrectomy for gene therapy surgery nor has panuveitis with exudative retinal detachment and choroidal inflammation. Either is a potential complication of subretinal gene therapy with significant ocular morbidity.

4. Conclusions

Clinicians should inform patients about the rare risk of sympathetic ophthalmia as well as other types of severe inflammation that may require prolonged treatment during the consent process prior to gene therapy surgery. The HLA typing data are suggestive that some patients may be at higher risk of sympathetic ophthalmia after eye surgery.

Patient consent

The patient provided verbal consent to allow the authors to prepare

and submit the associated case report on her clinical history and treatment course.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. BLL, NZG, and JLD have participated in clinical trials of gene therapy funded by NightStar, Biogen, AGTC, Nanoscope, Ocugen. NZG has participated in clinical trial and has consulted for Gyroscope Therapeutics.

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