Iatrogenic choroidal neovascularization associated with subretinal gene therapy surgery

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ABSTRACT

Purpose: To report a case of iatrogenic choroidal neovascularization (CNV) developing one month after subretinal gene therapy surgery.

Observations: A 16-year-old male with biallelic RPE65 mutation associated retinal dystrophy was treated with subretinal voretigene neparvovec in the left eye. During initiation of a balanced salt solution pre-bleb, a faint and transient subretinal hemorrhage was observed at the retinotomy site. One month post-operatively, multi-modal imaging detected a CNV and a break in Bruch’s membrane at the retinotomy site. The asymptomatic CNV was observed without treatment and resolved spontaneously.

Conclusions & importance: As subretinal gene therapy surgery becomes more common, clinicians should monitor for possible trauma induced CNV associated with retinotomy formation and subretinal injection.

1. Introduction

The advent of subretinal gene therapy has revolutionized the treatment trajectory of inherited retinal diseases. While still in the early years of development, new surgical techniques are being employed to allow delivery of therapeutics to the subretinal space. The safety profiles of subretinal viral vectors are encouraging and the theoretical risks of retinal manipulation are well known. There is no report, to our knowledge, of traumatic choroidal neovascularization (CNV) caused by subretinal delivery of genetic therapy.

2. Case report

A 16 year-old male is referred to the genetics clinic due to a biallelic mutations in RPE65 retinal dystrophy. His visual acuity was 20/70 and 20/50 in the right and left eye respectively, with dilated exams in both eyes showing waxy pallor of the optic nerve heads, pigmented changes throughout the macula, and coarse granular hypopigmentation throughout the periphery. Both eyes were treated with subretinal voretigene neparvovec gene therapy, first the right eye followed by the left eye one week later. After pre-treatment with three days of 40 mg of oral prednisone, he underwent an uneventful surgery in the right eye. One week later, he underwent surgery on the left eye. Prior to initiation of a balanced salt solution (BSS) pre-bleb, the subretinal cannula was trimmed with Vannas scissors to create a beveled tip. This was done twice because initial bevel angle was too acute. During propagation of BSS pre-bleb, with a preset injection pressure limit set at 16 pounds per square inch, a faint subretinal hemorrhage (SRH) was noted beneath the retinotomy site (Fig. 1). The SRH quickly became diluted due to BSS and was visually imperceptible. However, intraoperative optical coherence tomography (OCT) showed focal subretinal hypo-reflective material and possible break in Bruch’s membrane. Subretinal voretigene neparvovec was delivered and the entire macula was treated. One month after surgery, an asymptomatic CNV was detected at retinotomy site with OCT and fluorescein angiography (Fig. 2). Given the location was outside the macula, the CNV was observed without treatment and was noted to spontaneously regress. A persistent break in Bruch’s membrane was noted at the site of regressed CNV (see Fig. 3).

3. Discussion/conclusions

Traumatic CNV has been reported as a rare complication associated with vitreo-retinal surgical techniques. This is the first published report of a traumatic CNV associated with subretinal gene therapy procedure and this is the first case we have experienced at the Casey Eye Institute after performing over 120 subretinal gene therapy surgeries. This is a rare occurrence and it is related to the subretinal surgical technique and not to the gene therapy product. In our experience, creating a beveled
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subretinal cannula is helpful to initiate a subretinal bleb. However, in this case, we suspect the subretinal cannula was cut too short resulting in increased cannula stiffness and/or possibly reducing resistance to flow and therefore increasing the pressure gradient leading to traumatic injury to Bruch’s Membrane. Because SRH develops simultaneously with subretinal injection of either BSS or gene therapy product, SRH may become diluted and dissipate quickly making it difficult to detect. If SRH is suspected during subretinal bleb formation, careful intra-operative inspection and use of intra-operative OCT can be used to assess for possible break in Bruch’s Membrane (Fig. 1B) or for possible inadvertent injection into the sub-retinal pigment epithelium (RPE) space. In the hypothetical scenario of significant SRH or a new pigment epithelial detachment (PED), a surgeon may consider moving to a different location for delivery of gene therapy. In this case, the SRH was minimal and there was no evidence of a PED and the gene therapy product was successfully injected into the subretinal space.

The CNV did not affect visual acuity because of its location outside the macula and it was found spontaneously regress one month later. For those gene therapy surgical protocols calling for retinotomy within the macula, identification of intraoperative break in Bruch’s Membrane may carry greater importance given higher risk of vision loss associated with CNV. In this scenario, close post-operative monitoring is important for early CNV detection and treatment with anti-vascular endothelial growth factor to prevent vision loss would likely be beneficial.

In summary, subretinal gene therapy procedure may induce traumatic CNV. Presence of intraoperative subretinal hemorrhage or a suspected break in Bruch’s Membrane should be monitored closely for early detection of traumatic CNV.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.
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Authorship

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

Declaration of competing interest

Steven Bailey and Kenneth Price report no pertinent conflicts of interest.

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References

1. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber’s congenital amaurosis. N Engl J Med. May 22 2008;358(21):2231–2239. https://doi.org/10.1056/NEJMoa0802268.

2. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber’s congenital amaurosis. N Engl J Med. May 22 2008;358(21):2240–2248. https://doi.org/10.1056/NEJMoa0802315.

3. Maguire AM, High KA, Auricchio A, et al. Age-dependent effects of RPE65 gene therapy for Leber’s congenital amaurosis: a phase 1 dose-escalation trial. Lancet. Nov 7 2009;374(9701):1597–1605. https://doi.org/10.1016/S0140-6736(09)61836-5.

4. Bainbridge JW, Mehat MS, Sundaram V, et al. Long-term effect of gene therapy on Leber’s congenital amaurosis. N Engl J Med. May 14 2015;372(20):1887–1897. https://doi.org/10.1056/NEJMoa1414221.

5. Ng EW, Bressler NM, Boyer DS, de Juan Jr E. Iatrogenic choroidal neovascularization occurring in patients undergoing macular surgery. Retina. Dec 2002;22(6):711–718. https://doi.org/10.1097/00006982-200212000-00005.