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Persistent corneal edema associated with subconjunctival 5-fluorouracil in an infant with primary congenital glaucoma

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Abstract

A 3-month-old boy with primary congenital glaucoma developed a transient corneal endothelial opacity after needle bleb revision with adjunctive 5-fluorouracil (5-FU). This case presents a rare toxicity that, although transient, is concerning due to the potential of amblyopia. We review prior cases of corneal opacity associated with 5-FU.

Keywords

Congenital Glaucoma; 5-Fluorouracil; Trabeculectomy; Cornea; Antifibrotic

Introduction

Glaucoma filtration surgery is often augmented with antifibrotics to minimize scar tissue formation and thus increase chances for long term surgical success¹. Pediatric patients in particular are known to have aggressive healing responses which place them at greater risk for surgical failure². However, use of antifibrotics in the pediatric population remains controversial with respect to both efficacy and safety. While studies have shown mitomycin C (MMC) to be more effective than 5-fluorouracil (5-FU) in lowering intraocular pressure, it is also associated with more severe complications^{1,3,4,5}. 5-FU is thought to be less toxic to the corneal endothelium. We report a case of an infant with primary congenital glaucoma who developed a transient corneal opacity lasting 2 weeks following trabeculectomy revision with adjuvant 5-FU. We also review the literature on endothelial dysfunction attributed to 5-FU.

Case

A 3-month-old African-American male infant with bilateral primary congenital glaucoma presented to University of Maryland Department of Ophthalmology in Baltimore, MD with marked corneal edema four days after bleb needling with 5-FU in the right eye. His previous

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Conflicts of Interest: none

surgical history in the affected eye includes goniotomy and combined trabeculotomy and trabeculectomy, notably without the use of any antifibrotics. The left eye stabilized after initial angle surgery. The patient was otherwise healthy. There was no family history of glaucoma or ocular disease.

The patient underwent bleb needling with suture lysis and subconjunctival injection of 0.25 milliliters of 50 mg/ml 5-FU superonasally and away from the superotemporal bleb. On post-operative day 1, the anterior chamber was formed and the cornea was grossly clear with no significant opacity noted. The patient was prescribed prednisolone acetate 1% four times daily with reportedly strong adherence. On post-operative day 4, the patient was noted to have epiphoria, photophobia, and blepharospasm. His parents noticed that the operative eye started to look “cloudy” the day before. His visual acuity was central, steady, and unmaintained in the affected right eye and central, steady, and maintained in the left eye. He demonstrated a preference for the left eye. Pressure in the right eye, measured with Icare tonometry (Icare Finland Oy, Helsinki, Finland), was 23 mmHg. Anterior segment examination was significant for a focal nasal corneal opacity involving 40% of the cornea in the operative eye (Figure 1). The opacity was found to involve the endothelium and deep stromal layers on portable slit lamp examination. There were no tears in Descemet’s membrane. The temporal side of the cornea was clear. Anterior chamber examination had appropriate post-operative inflammation. The lens and posterior segment examinations were unremarkable.

The patient was followed closely over the next two weeks and prescribed prednisolone acetate 1% eight times daily, oral acetazolamide taper, and phenylephrine 2.5% in his right eye immediately followed by 2 hours of patching. His intraocular pressure (IOP) improved and remained stable in the mid-teens as measured by Perkins tonometry (Haag Streit, Mason, OH) and Tono-Pen (Reichert Technologies, Depew, NY). There were no signs of infection. This patching regimen with pharmacologic dilation was chosen to prevent amblyopia; the patient’s undilated pupil was completely obscured by the corneal clouding but his dilated pupil allowed for a clear view through the temporal cornea. Corneal clarity gradually improved and the clouding completely resolved after 13 days without recurrence (Figure 2).

The patient subsequently required implantation of a Baerveldt tube shunt (Abbott Medical Optics, Abbott Park, IL) placement in his right eye. Six months post-operatively, IOP was measured at 12 in the affected eye by both Tono-Pen (Reichert Technologies, Depew, NY) and Perkins tonometry (Haag Streit, Mason, OH). Notably, his vision is central, steady and maintained in both eyes with no sign of amblyopia.

Discussion

Surgical management is the mainstay of treatment for congenital glaucoma². Whereas angle surgery is the preferred and most common approach, trabeculectomy is used in patients with refractory congenital glaucoma. The main mechanism of trabeculectomy failure is scarring of the surgical site³. Filtration surgery in pediatric patients has been associated with lower success rates as compared to adult populations due to rapid healing response and thick

Tenon's capsule in children². For this reason, antifibrotics are commonly used to augment trabeculectomy in this population².

In this particular case, the differential diagnosis for corneal clouding after trabeculectomy revision surgery includes infection, elevated IOP, Descemet's membrane tear, and intracorneal drainage of aqueous. Examination effectively ruled out these etiologies. We believe that the corneal clouding was a potential complication of 5-FU injection.

MMC may be more effective at lowering IOP than 5-FU, but is believed to have a higher potential for corneal endothelial toxicity. This case report illustrates the potential toxic effect of 5-FU to the corneal endothelium in pediatric glaucoma patients. In two separate meta-analyses, Lin et al. and De Fendi et al. compared the efficacy of 5-FU and mitomycin C and found intraoperative MMC to be more effective in lowering IOP, though they disagree whether 5-FU is comparable to MMC for overall success rate^{1, 3}. MMC is also associated with more severe complications such as hypotony, leakage of ischemic blebs, endophthalmitis, and corneal toxicity^{4, 5}. Clinical studies and case reports documented significant corneal endothelial loss and corneal edema associated with MMC treatment in photorefractive keratectomy, as well as irreversible corneal decompensation following filtration surgery⁵. MMC has additionally been shown to cause corneal swelling, transcellular vacuole formation, and intercellular junction effacement *in vitro*⁶. The fact that MMC is considerably more potent than 5-FU relative to their antifibrotic activity may explain these findings³. Whereas 5-FU is known to cause corneal epithelial toxicity³, only four prior cases of 5-FU causing endothelial toxicity or stromal opacity in humans⁷⁻⁹ have been reported to our knowledge (Table 1), and only one of these cases was in a child.

Mazey et al. described two adult cases of corneal edema within one day of trabeculectomy bleb needling revision with subconjunctival 5-FU injection⁷. This spontaneously resolved over the course of 3–7 weeks. In one of the cases, the patient was also found to have 4+ corneal pleomorphism by specular microscopy of the involved eye at 7 weeks post-injection; however, this had completely resolved at 6 months. In another adult patient, Hirji reported snailtrack-like corneal changes thought to signify corneal endothelial cell damage one week following bleb needling augmented with 5-FU⁸. This persisted even at 6 months after bleb modulation. Jalil et al. described a 1-week-old infant with congenital glaucoma who developed bilateral corneal stromal scarring after failed combined trabeculotomy and trabeculectomy augmented with 5-FU⁹, though it is unclear whether the corneal scarring was related to the surgery or the adjuvant. Unlike our case, the toxicity in this instance was permanent, requiring multiple diode laser cycloablations in one eye and a glaucoma drainage implant in the other.

This case illustrates the potential toxic effects of 5-FU to the corneal endothelium. This is an important consideration in pediatric glaucoma patients undergoing filtration surgeries augmented with antifibrotics as media opacity can potentially cause deprivation amblyopia. While this patient's corneal clouding entirely resolved within 13 days without any long-term consequences, even short-term visual deprivation at this critical developmental age may result in some degree of amblyopia¹⁰. Surgeons using adjuvant 5-FU in combination with

glaucoma surgery in pediatric patients should consider the potential toxic effects to the corneal endothelium.

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Figure 1.
Digital photograph of patient's right eye demonstrating substantial nasal corneal clouding on post-operative day 4 after trabeculectomy revision with subconjunctival injection of 5-fluorouracil.

Figure 2.
Digital photograph of patient's right eye with full resolution of corneal clouding noted 13 days later.

Table 1

Literature review: reports of 5-FU associated with corneal endothelial toxicity

Author	Patient Age	Surgery	[5-FU] (mg/mL)	Corneal Toxicity	Post-Operative Day	Toxicity Duration
Mazey et. al. (1994)	52 yrs.	Bleb needling with 5-FU	50	Edema	1	6 mo.*
Mazey et. al. (1994)	68 yrs.	Bleb needling with 5-FU	--	Edema, Pleomorphism	0 (2 hours)	6 mo.*
Jalil et. al. (2011)	1 wk.	1. Combined trabeculectomy and trabeculectomy with 5-FU soaked sponges 2. Peribleb 5-FU injection	25	Stromal scarring	Unspecified	Unspecified [†]
Hirji (2012)	50 yrs.	Bleb needling with 5-FU	--	Snailtracks	7	>6 mo.
Fu et. al. (2015)	3 mo.	Bleb needling with 5-FU	50	Opacity	4	2 wks.

5-FU = 5-fluorouracil; MMC = Mitomycin C

* In both of Mazey's reported cases, increased corneal clarity was noted beginning one week after the edema, with complete resolution at 6 month follow-up.

[†] Patient was followed for 59 total months and required multiple diode laser cycloablations in one eye, and a glaucoma drainage implant in the other.