American Journal of Ophthalmology Case Reports 19 (2020) 100812

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Successful pediatric DMEK facilitated by intracameral tissue plasminogen activator to mitigate anterior chamber fibrin reaction

Tanner J. Ferguson *, Elias I. Traboulsi, Jeffrey M. Goshe

Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

ARTICLE INFO

Keywords:
DMEK
Endothelial keratoplasty
Fibrin
Surgical complications

ABSTRACT

Purpose: To report a case of a successful Descemet's membrane endothelial keratoplasty (DMEK) facilitated by the use of intracameral tissue plasminogen activator (tPA) in a 4-year old with posterior polymorphous corneal dystrophy (PPCD).

Observations: A 4-year old male was referred for bilateral corneal haze and blurry vision. Patient's exam and genetic testing were consistent with a diagnosis of PPCD. Patient was successfully treated with DMEK augmented by the use of intracameral tPA intraoperatively to combat the anterior chamber fibrin formation that can occur in DMEK.

Conclusions: To our knowledge, this case represents the youngest reported successful DMEK procedure and the first case describing the use of intracameral tPA intraoperatively to attenuate the anterior chamber fibrin formation that can occur in DMEK.

1. Introduction

Posterior polymorphous corneal dystrophy (PPCD) is a rare corneal dystrophy characterized by irregular differentiation of endothelium into epithelial-like cells.[1,2] This leads to sectoral or diffuse thickening of Descemet membrane and progressive corneal edema.[3] In severe cases, extension of the irregular endothelium into the angle results in iridocorneal adhesions and increased intraocular pressure.[4–6]

PPCD is inherited in an autosomal dominant fashion, although clinical expression and severity is variable.[1,4] The disease can present at any age but often is detected around the second or third decade of life. Less commonly, symptoms can manifest in early childhood.[7] Although PPCD is typically diagnosed clinically by slit lamp examination, genetic testing may be helpful to confirm the diagnosis.[8,9]

The management of PPCD is dependent on the severity of the disease at presentation. Prior to the advent of endothelial keratoplasty (EK) procedures, penetrating keratoplasty was the gold-standard for visually significant PPCD. More recently, Descemet stripping automated endothelial keratoplasty (DSAEK) has been shown to be an effective option in PPCD, avoiding the slower visual rehabilitation of full-thickness corneal transplants.[10]

In the last decade, Descemet membrane endothelial keratoplasty (DMEK) has emerged as an alternative to DSAEK, offering more rapid visual rehabilitation, improved visual outcomes, and decreased risk of rejection.[2,11,12] However, DMEK may be more challenging in pediatric patients. Specifically, surgery may be complicated by difficulty stripping the host endothelium, aggressive intraocular inflammation (including fibrin formation), and challenges with postoperative compliance and positioning.[13,14]

Few previous reports exist regarding DMEK surgery in pediatric patients. At present, the youngest reported patient to successfully undergo DMEK surgery was twelve years old.[15] Strungaru et al.[1] described an unsuccessful DMEK in a 4-month-old infant with PPCD who required subsequent DSAEK.

We describe successful, bilateral DMEK surgery in a 4-year-old with PPCD facilitated by the use of intracameral tissue plasminogen activator (tPA). To our knowledge, this case represents the youngest reported successful DMEK procedure and the first case describing the use of intracameral tPA intraoperatively to combat the fibrinoid inflammatory reaction that can occur in DMEK.

2. Case presentation

A 4-year-old male was referred for evaluation of bilateral corneal haze. He was photophobic and had difficulties with vision and reading over the past six months. The patient had no other medical or

* Corresponding author.
E-mail address: tannerferg@gmail.com (T.J. Ferguson).

https://doi.org/10.1016/j.ajoc.2020.100812
Received 24 August 2019; Received in revised form 13 April 2020; Accepted 28 June 2020
Available online 30 June 2020

ophthalmic problems. Several family members on the maternal side had previously undergone corneal transplantation but the exact diagnosis of their corneal disease was unknown.

On initial exam, cycloplegic refraction revealed mild, hyperopic astigmatism with best-corrected visual acuity (BCVA) of 20/150 OD and 20/400 OS. Baseline intraocular pressures were 19 mmHg OD and 18 mmHg OS. Pupillary responses, extraocular motility and ocular alignment were all normal. Slit-lamp biomicroscopy revealed broad areas of thickened, irregular endothelium in both eyes with overlying edema and posterior corneal haze, slightly worse in the left eye. Additionally, endothelial cystic changes and "snail tracks" were present bilaterally (Fig. 1). Both pupils were round and there was no iris synechiae. Posterior segment exam was unremarkable.

The patient's mother was also examined and had corneal findings similar to those of her son, in addition to focal regions of peripheral anterior synechiae. Based on the clinical findings and family history, a presumptive diagnosis of PPCD was made. Due to the presence of symptomatic cornea edema and the concern for progressive amblyopia, the family elected to proceed with DMEK surgery, left eye (OS) followed by right (OD).

Genetic testing was performed which revealed a frameshift mutation (c.2243_2246del) in *ZEB1*, which has previously been reported to be associated with PPCD,[9,16] confirming the diagnosis.

DMEK surgery was performed under general anesthesia utilizing a previously published standardized technique with several modifications.[17] Prestripped donor tissue was utilized and was prepared by the surgeon in both cases. To prevent pupillary block, an inferior peripheral iridectomy was created by excising a small segment of peripheral iris through a separate 1 mm limbal incision. Continuous descemetorrhexis was not possible owing to the densely adherent, friable Descemet membrane necessitating gentle scraping of the endothelium with a semi-sharp Terry Scraper (Bauch and Lomb Storz, Bridgewater, NJ). Owing to equipment availability, graft orientation was confirmed using different methods for the two surgeries and tissue preparation was modified. For the left eye, pre-stripped donor tissue with an S-stamp for graft orientation was utilized and was prepared by the surgeon. For the right eye, the donor tissue was pre-stripped and pre-loaded and graft orientation was confimred via intraoperative OCT (iOCT) using a microscope integrated system (RESCAN 700; Carl Zeiss Meditec, Oberkochen, Germany). After unscrolling of the tissue, 20% sulfur hexafluoride was injected to promote elevation of the graft to the host cornea. The anterior chamber was left with 80–90% gas fill following a gas-fluid exchange to permit passage of aqueous through the peripheral iridectomy for avoidance of pupillary block. A compounded solution of intracameral tPA (0.1 mL of 12.5 μg/0.1 mL) was also prepared in anticipation of a possible anterior chamber fibrinoid reaction.[14]

For the left eye, despite insertion of the DMEK tissue in an optimal configuration ("double scrolls on top"), the graft could not be unscrolled by standard external "tapping" and "sweeping" maneuvers. The presence of fibrin in the anterior chamber was confirmed by visible adherence of the graft to the iris and focal areas of fibrinoid stranding. To address the fibrinoid reaction, 0.1 mL of tPA (12.5 μg/0.1 mL) was injected into the anterior chamber. After approximately 15 minutes, the fibrinoid reaction had significantly diminished and the tissue could be manipulated via external maneuvers. Graft orientation was confirmed by visualizing the pre-placed "S-stamp." The unscrolling duration (from tissue insertion to complete attachment with a gas-filled anterior chamber) was 21 minutes.

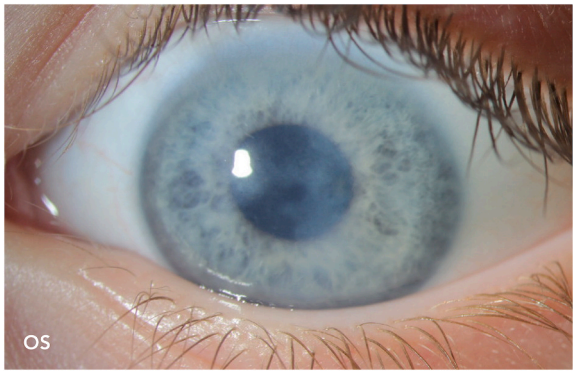

Fig. 1. Slit-lamp photo from initial visit depicts the visually significant corneal edema present pre-operatively in the left eye, the first operative eye.

For the left eye, postoperative day 1 examination was remarkable for normal intraocular pressure, a fully attached DMEK graft, and a deep anterior chamber with a 60% gas bubble. Topical neomycin-polymyxin-dexamethasone drops were started every 2 hours while awake and supine positioning was encouraged as much as possible for the first 5 days postoperatively. The patient was re-examined at one week and one month postoperatively. The graft remained attached at all subsequent postoperative visits with successful resolution of the patient's photophobia and corneal edema, although areas of posterior corneal haze remained visible (Fig. 2).

Based on the response of the left eye, a preventative strategy was employed for the right eye. After Descemet stripping, 0.1 mL of tPA was injected into the anterior chamber 10 minutes prior to graft insertion. No fibrinoid reaction occurred and the DMEK graft was unscrolled without difficulty in less than 3 minutes. Graft orientation was confirmed by scrolling behavior via intraoperative OCT.

The postoperative course for the right eye was complicated by a shallow temporal graft detachment with symptomatic edema visible at the one week visit (Fig. 3). The graft was successfully re-bubbled with air injection on postoperative day 10 and the graft remained attached at all subsequent visits. At the most recent visit (2 and 3 months postoperatively for OD and OS respectively), best-uncorrected visual acuity was 20/125 (OD) and 20/100 (OS), both improved from baseline.

There was no significant IOP increase that necessitated medical or surgical management in the left eye. There was a mild postoperative IOP spike (31 mmHg) in the right eye 1 month postoperatively, which responded to topical therapy.

3. Discussion

The adoption of DMEK for the surgical treatment of pediatric corneal endothelial disease has been slow, likely attributable to the rarity of surgical candidates and the technical difficulty of DMEK surgery in pediatric eyes. One specific concern is the tendency of pediatric eyes to develop a rapid, aggressive intraoperative fibrinoid reaction that may impede or prevent the requisite maneuvers necessary to unscroll DMEK tissue.

Tissue plasminogen activator (tPA) is a naturally occurring serine protease with fibrinolytic action. As an intraocular injection, it has demonstrated efficacy for treating fibrin exudates in patients with uveitis.[13] Moreover, it has been reported to be of value in the postoperative setting in treating severe, fibrinoid anterior chamber reactions in numerous studies.[18–20] In addition, studies have also described the use of intracameral tPA postoperatively in pediatric cataract surgery as an avenue to combat inflammation.[21] However, to our knowledge, there have been no previous reports describing its use in the intraoperative setting, nor any applications to DMEK surgery. Our case highlights the potential value of intracameral tPA intraoperatively to treat, or, optimally prevent, the spontaneous fibrinoid reaction that may complicate DMEK surgery in pediatric eyes. The notable absence of fibrin formation in the right eye highlights the potential benefit of pre-treating eyes at high risk for intraoperative fibrin.

Fibrinoid anterior chamber reactions in adults, albeit less common, have also been reported during DMEK surgery.[14] A recent study by Benage et al.[14] reviewed a large series of DMEK cases and described the spontaneous, intraoperative fibrin formation complicating DMEK

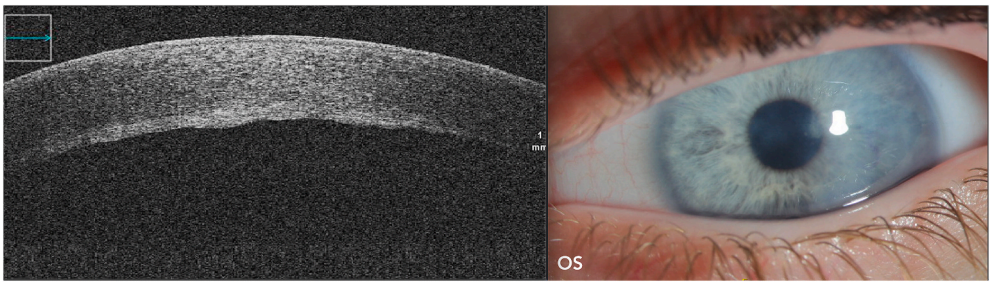

Fig. 2. Anterior segment OCT photo taken 5 days postoperatively in the first operative eye (OS). Image demonstrates a fully attached DMEK graft with posterior hyperreflectivity corresponding areas of posterior corneal haze. Postoperative slit-lamp photo from the first eye (OS) demonstrating significant improvement corneal edema and reduced corneal haze.

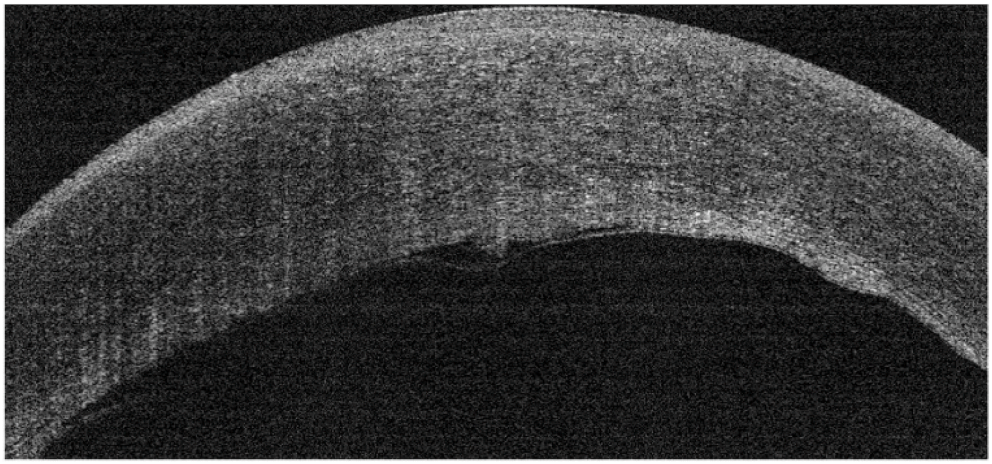

Fig. 3. Anterior segment OCT photo captured at 1-week postoperative in the second eye (OD). Image demonstrates a thin, temporal detachment with symptomatic edema overlying a region of irregular, residual fibrillar material that was unable to be completely removed during descemetorrhexis.

procedures. They proposed that minimizing the intraoperative bleeding could potentially reduce the risk of a fibrinoid reaction. Thus, while there is no data comparing the rate of fibrin formation for iridectomy types or techniques, the fibrin formation could be related to the surgical iridectomy performed intraoperatively. Nonetheless, the etiology of fibrin formation in these patients remains unclear but its potential impact on surgical outcomes is noteworthy. Akin to pediatric patients, a fibrinoid reaction can greatly escalate the difficulty of DMEK in adult patients by causing the graft to become adherent to itself and the iris. The resultant inability to unscroll or position a graft may lead to increased incidence of postoperative complications, including graft detachment or primary graft failure. The favorable use of tPA to mitigate fibrin formation in our patient suggests that its use may provide similar value in adult patients and warrants further exploration.

Given that this is an isolated case report, additional research is needed to further investigate the safety and efficacy of intracameral tPA during intraocular surgery. For risk of corneal toxicity, a prior study by Dotan et al.[22] collected mean endothelial cell count (ECC) 1 week after injection of intracameral tPA and demonstrated there was no change from baseline. While this study suggests there is no short-term change in mean ECC, long-term data would be valuable for evaluating whether tPA has a deleterious effect on endothelial cells. In addition, although we observed improvement of the fibrinoid reaction <15 minutes after intracameral injection, the onset of action for intracameral tPA remains unclear. When given systemically, the half-life of tPA is < 5 minutes. Prior studies reporting the intracameral use of tPA have observed timing similar to our case with reports of onset of action within minutes.[13] Another consideration is cost and availability, which may be dependent on the institution. In this present case, the unit cost for the tPA was $28.75 and was available in single-use vials from an on-site compounding pharmacy which can be preserved frozen for up to 45 days. Smaller institutions may not have access to an on-site compounding pharmacy, which could limit their ability to get the agent at a similar cost. Use of an alternative, lower cost fibrinolytic such as heparin may circumvent some of these issues but it has primarily been studied[23] as a continuous infusion during pediatric cataract surgery. To our knowledge, a single injection of intracameral heparin has not previously been described to reduce or eliminate anterior chamber fibrin. Continuous heparin irrigation may be impractical for DMEK surgery owing to the necessary anterior chamber fluid dynamics during DMEK surgery. Finally, although it was not observed in this present case, it is important to acknowledge the risk of intraocular hemorrhage with the use of any anti-thrombotic agent.

In summary, to our knowledge, this case represents the youngest patient to undergo successful DMEK surgery. In addition, it also constitutes the first reported use of intracameral tPA intraoperatively to both treat, and prevent, anterior chamber fibrinoid reaction during DMEK surgery. Although further investigation is warranted, this case reports supports the use of intracameral tPA to facilitate DMEK surgery for patients at high risk for intraoperative fibrinoid reaction.

Patient consent

The patient's legal guardian consented to publication of this case orally.

Funding

There were no funding sources or grant support.

Authorship

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

Declaration of competing interest

The following authors have no financial disclosures: TF, ET, JG.

Acknowledgments

None.

References

1. Hermina Strungaru M, Ali A, Rootman D, Mireskandari K. Endothelial keratoplasty for posterior polymorphous corneal dystrophy in a 4-month-old infant. *Am J Ophthalmol Case Rep*. 2017;7:23–26. https://doi.org/10.1016/j.ajoc.2017.05.001.
2. Sorkin N, Einan-Lifshitz A, Boutin T, et al. Descemet membrane endothelial keratoplasty in iridocorneal endothelial syndrome and posterior polymorphous corneal dystrophy. *Can J Ophthalmol J Can Ophtalmol*. 2019;54(2):190–195. https://doi.org/10.1016/j.jcjo.2018.05.012.
3. Studeny P, Jirsova K, Kuchynka P, Liskova P. Descemet membrane endothelial keratoplasty with a stromal rim in the treatment of posterior polymorphous corneal dystrophy. *Indian J Ophthalmol*. 2012;60(1):59–60. https://doi.org/10.4103/0301-4738.91350.
4. Krachmer JH. Posterior polymorphous corneal dystrophy: a disease characterized by epithelial-like endothelial cells which influence management and prognosis. *Trans Am Ophthalmol Soc*. 1985;83:413–475.
5. Rodrigues MM, Phelps CD, Krachmer JH, Cibis GW, Weingeist TA. Glaucoma due to endothelialization of the anterior chamber angle. A comparison of posterior polymorphous dystrophy of the cornea and Chandler's syndrome. *Arch Ophthalmol*. 1980;98(4):688–696.
6. Henriquez AS, Kenyon KR, Dohlman CH, et al. Morphologic characteristics of posterior polymorphous dystrophy. A study of nine corneas and review of the literature. *Surv Ophthalmol*. 1984;29(2):139–147.
7. Oellerich S, Baydoun L, Peraza-Nieves J, et al. Multicenter study of 6-month clinical outcomes after Descemet membrane endothelial keratoplasty. *Cornea*. 2017;36(12):1467–1476. https://doi.org/10.1097/ICO.0000000000001374.
8. Laganowski HC, Sherrard ES, Muir MG. The posterior corneal surface in posterior polymorphous dystrophy: a specular microscopical study. *Cornea*. 1991;10(3):224–232.
9. Chung DD, Zhang W, Jatavallabhula K, Barrington A, Jung J, Aldave AJ. Alterations in GRHL2-OVOL2-ZEB1 axis and aberrant activation of wnt signaling lead to altered gene transcription in posterior polymorphous corneal dystrophy. *Exp Eye Res.*. 2019 https://doi.org/10.1016/j.exer.2019.107696, 107696.
10. Sella R, Rootman D, Bahar I. Descemet's stripping automated endothelial keratoplasty for posterior polymorphous corneal dystrophy in an 8-month-old boy. *J AAPOS Off Publ Am Assoc Pediatr Ophthalmol Strabismus*. 2013;17(1):94–96. https://doi.org/10.1016/j.jaapos.2012.09.009.
11. Bromley JG, Randleman JB, Stone D, Stulting RD, Grossniklaus HE. Clinicopathologic findings in iridocorneal endothelial syndrome and posterior polymorphous membranous dystrophy after Descemet stripping automated endothelial keratoplasty. *Cornea*. 2012;31(9):1060–1064. https://doi.org/10.1097/ICO.0b013e31823fb978.
12. Feng MT, Price MO, Price FW. Update on Descemet membrane endothelial keratoplasty (DMEK). *Int Ophthalmol Clin*. 2013;53(2):31–45. https://doi.org/10.1097/IIO.0b013e31827822b9.
13. Lerner LE, Patil AJ, Kenney MC, Minckler D. Use of intraocular human recombinant tissue plasminogen activator as an adjunct treatment of posterior synechiae in patients with uveitis. *Retin Cases Brief Rep*. 2012;6(3):290–293. https://doi.org/10.1097/ICB.0b013e31822a2f4f.
14. Benage M, Korchak M, Boyce M, et al. Intraoperative fibrin formation during Descemet membrane endothelial keratoplasty. *Am J Ophthalmol Case Rep*. 2020;18. https://doi.org/10.1016/j.ajoc.2020.100686, 100686.
15. Gonnermann J, Klamann MKJ, Maier A-KB, et al. Descemet membrane endothelial keratoplasty in a child with corneal endothelial dysfunction in Kearns-Sayre syndrome. *Cornea*. 2014;33(11):1232–1234. https://doi.org/10.1097/ICO.0000000000000252.
16. Frausto RF, Chung DD, Boere PM, et al. ZEB1 insufficiency causes corneal endothelial cell state transition and altered cellular processing. *PloS One*. 2019;14(6), e0218279. https://doi.org/10.1371/journal.pone.0218279.
17. Terry MA, Straiko MD, Veldman PB, et al. Standardized DMEK technique: reducing complications using prestripped tissue, novel glass injector, and sulfur hexafluoride (SF6) gas. *Cornea*. 2015;34(8):845–852. https://doi.org/10.1097/ICO.0000000000000479.
18. Hong BK, Francis BA. Intracameral injection of tissue plasminogen activator to treat severe postoperative fibrinous reaction in iridocorneal endothelial syndrome. *Digit J Ophthalmol DJO*. 2013;19(2):21–23. https://doi.org/10.5693/djo.02.2013.02.002.
19. Wedrich A, Menapace R, Ries E, Polzer I. Intracameral tissue plasminogen activator to treat severe fibrinous effusion after cataract surgery. *J Cataract Refract Surg*. 1997;23(6):873–877.
20. Ozveren F, Eltutar K. Therapeutic application of tissue plasminogen activator for fibrin reaction after cataract surgery. *J Cataract Refract Surg*. 2004;30(8):1727–1731. https://doi.org/10.1016/j.jcrs.2004.02.042.
21. Mehta JS, Adams GG. Recombinant tissue plasminogen activator following paediatric cataract surgery. *Br J Ophthalmol*. 2000;84(9):983–986. https://doi.org/10.1136/bjo.84.9.983.
22. Dotan A, Kaiserman I, Kremer I, Ehrlich R, Bahar I. Intracameral recombinant tissue plasminogen activator (r-tPA) for refractory toxic anterior segment syndrome. *Br J Ophthalmol*. 2014;98(2):252–255. https://doi.org/10.1136/bjophthalmol-2013-304294.
23. Bayramlar H, Totan Y, Borazan M. Heparin in the intraocular irrigating solution in pediatric cataract surgery. *J Cataract Refract Surg*. 2004;30(10):2163–2169. https://doi.org/10.1016/j.jcrs.2004.07.003.