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Case report

Trans-stromal epithelial cyst after multiple lamellar keratoplasties - Case report and review of literature

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ABSTRACT

Design: Single Observational Case Report.
Setting: A 67-year-old male of Persian descent had a complex systemic and ocular history prior to a right penetrating keratoplasty (PK) reported here. The clinical diagnoses leading to the PK included Cogan's syndrome, chronic uveitis, secondary glaucoma, and corneal stromal scarring, presumed secondary to a corneal ulcer diagnosed on the second visit to our clinic. The specimen described here had been in place for 11 months and 17 days after the third failed Descemet stripping endothelial keratoplasty (DSEK). Visual acuities had ranged from 20/100 to 20/400 in both eyes. Visual acuity in the right eye just before surgery was 20/400. Intraocular pressures were 22 mmHg in both eyes with functioning Ahmed glaucoma shunts. The stromal cyst was not suspected preoperatively and no clinical imaging was performed.
Study Methods: Histopathology including serial sections and immunohistochemistry.
Results: Histologic study demonstrated a *trans*-stromal corneal epithelial cyst without goblet cells that extended through a 500 μm gap in the donor tissue surface and edge.
Conclusions: This large stromal cyst was an unusual complication of serial posterior lamellar keratoplasties and we postulate that multiple prior posterior lamellar grafts may have been a risk factor for this complication. Anterior segment imaging with either anterior segment optical coherence tomography or high-resolution ultrasound would likely have detected this stromal cyst.

1. Introduction

Corneal cysts can be congenital or may develop as a complication of penetrating trauma or surgical wounds after inadvertent implantation of epithelium from contaminated instruments. Epithelial ingrowth can present as a sheet-like layer of cells on the endothelium, an anterior chamber cyst, or an iris pearl tumor. Anterior chamber epithelial cysts extending from a corneal wound or iris stroma may demonstrate progressive growth with associated complications, including visual axis obstruction, iridocyclitis, secondary glaucoma, intractable pain and corneal decompensation.[1]

Intrastromal corneal epithelial cysts are rare. In a review by Mifflin et al., only 16 cases were reported in the ophthalmic literature from 1971 to 2001.[2] Such cysts may infrequently resolve on their own, perhaps by spontaneous drainage into the anterior chamber. However, in cases of progressively enlarging cysts that threaten the visual axis, interventions ranging from simple drainage to cyst wall excision to lamellar or penetrating keratoplasty (PK) may be required.[3] Methods to prevent cyst formation include cryotherapy prior to PK and irrigation of any accidently implanted epithelial cells after PK. Repeated irrigation of the corneal bed following cyst removal may also help to prevent entrance of epithelial cells into the anterior chamber, and reduce the risk of cyst recurrence.[3]

We report a *trans*-stromal corneal epithelial cyst studied by histopathology in a PK specimen following multiple Descemet stripping endothelial keratoplasties (DSEKs).

2. Case report/findings

A 67-year-old male of Persian descent with a history of Cogan's syndrome, severe chronic uveitis and secondary glaucoma bilaterally presented with complaints of blurry vision in his right eye.

Past non-corneal ocular surgeries in the right eye included trabeculectomy in March 2007 and subsequent revision in May 2007, as well as

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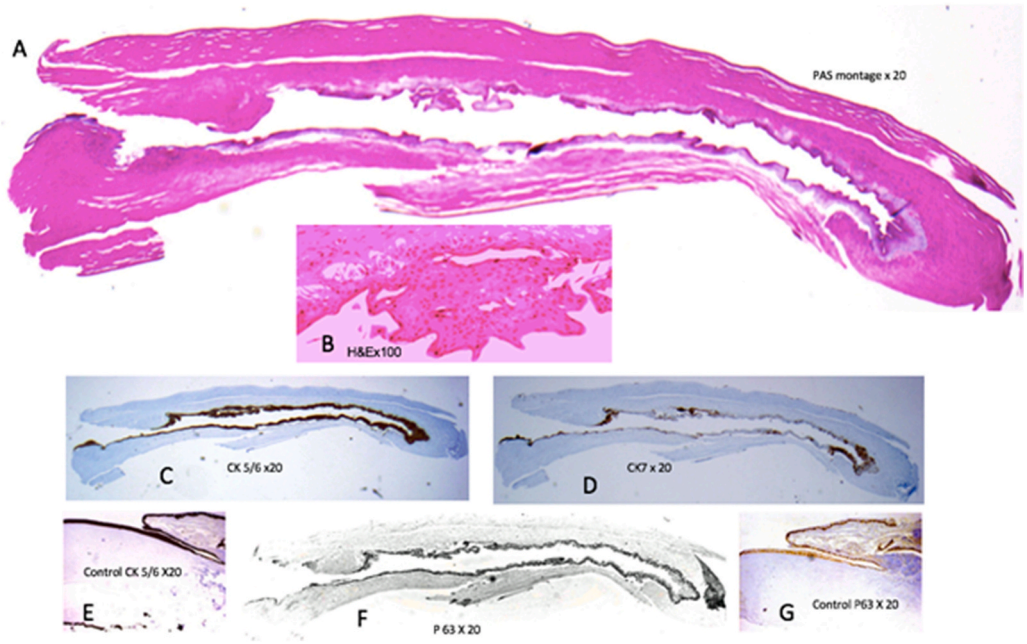

Fig. 1. **(A)** Trans-stromal corneal cyst with one open end (PAS stain original magnification ×20); **(B)** Higher magnification of squamous epithelium (H&E original magnification ×100); **(C)** Immunostains CK 5/6 highlighting corneal epithelium (original magnification ×20); **(D)** CK 7 (original magnification ×20); **(E)** Control CK 5/6 in normal surface epithelium of cornea and adjacent conjunctiva from normal eye of similar age (original magnification ×20); **(F)** Immunostain P63 demonstrating expected positivity in stromal cyst lining for corneal squamous epithelium; (original magnification ×20); **(G)** P63 in similarly aged eye as control for stromal cyst lining (original magnification ×20).

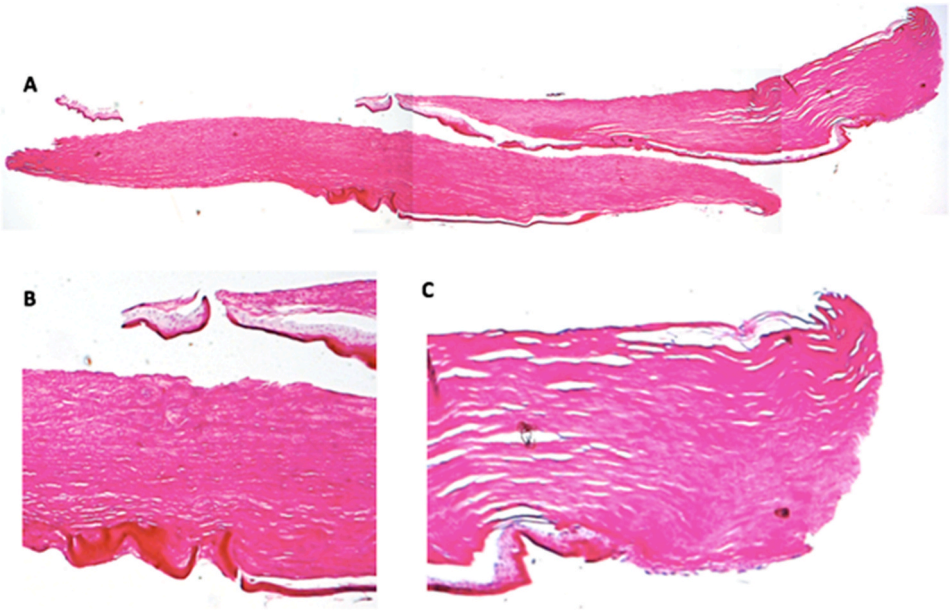

Fig. 2. **(A)** Surface epithelium extending into surface gap stroma between anterior and posterior portions of PK specimen (H&E, original magnification ×31.25); **(B)** Higher magnification of paracentral end of gap in PK specimen (PAS, original magnification ×125); **(C)** Higher magnification of deep end of specimen (PAS, original magnification ×125).

Trabectome and cataract extraction in the right eye in November 2007. An Ahmed shunt was placed in the right eye in October 2008. Conjunctival leak over the Ahmed shunt in the right eye was repaired in June 2014 and a subsequent extrusion of the same shunt was repaired in June 2017.

Corneal surgeries in the right eye included three DSEKs in 2013, 2014, and 2018. The initial DSEK was performed in the right eye in May 2013 utilizing an 8.5 mm graft placed through a 3 mm temporal corneal incision. The graft gradually failed and was replaced in October 2014, failing again after tube revision in 2017. The third DSEK occurred in January 2018. All three posterior lamellar grafts utilized the same general incision area and all three were uncomplicated.

Past non-corneal ocular surgeries in the left eye included trabeculectomy in November 2006, Trabectome in November 2007, and another trabeculectomy in June 2008. Cataract extraction in the left eye occurred in October 2009. A Baerveldt shunt was placed in the left eye in October 2010.

At initial presentation to the eye clinic at UCI (University of California, Irvine) in August 2018, visual acuity was 20/300 in the right eye and 20/150 in the left eye. Intraocular pressures were 22 mmHg in both eyes with a functioning Ahmed glaucoma shunt in the right eye. On slit lamp examination of the right eye, corneal edema, a covered tube shunt, peripheral anterior synechiae and a shallow anterior chamber were noted. The posterior pole of the right eye was difficult to visualize due to corneal edema. By three months later, the patient had developed a new right corneal ulcer that was culture-positive for *Klebsiella pneumoniae*.

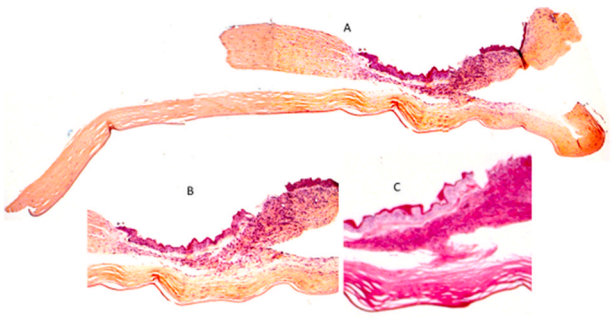

Fig. 3. (A) Weld-like stromal scar holding anterior and posterior corneal lamellae together across gap in serial sections adjacent to moderate chronic inflammatory infiltrate most obvious in the anterior portion (H&E original magnification ×31.25); **(B)** Same weld-like scar between anterior and posterior lamellae slightly enlarged from same plane and magnification slightly enlarged from A; **(C)** Slightly different plane with same magnification as A (PAS original magnification X31.25).

The ulcer was debrided with a cotton tipped applicator and treated with ciprofloxacin and difluprednate. The ulcer resolved with residual anterior stromal scarring. PK was recommended and performed in the right eye without complications in January 2019. The specimen described in this report was accessioned in Pathology at UCI on the same day. The posterior lamellar graft had been in place for 11 months and 17 days. Subsequent right fundus exam revealed a cup-to-disc ratio of 0.85, posterior vitreous detachment, macular cystoid edema with intraretinal fluid, and an epiretinal membrane with pseudomacular hole.

3. Pathology findings

Histopathology included serial sections of the full-thickness corneal specimen and staining with Hematoxylin and Eosin (H&E), Periodic Acid-Schiff (PAS) and immunohistochemistry (IHC), including P63, CK 7, and CK 5/6 (Fig. 1). Histology demonstrated a huge *trans*-stromal corneal epithelial cyst without goblet cells, extending through an approximately 500 μm gap in the surface of the corneal specimen (Fig. 2). PAS staining of the specimen identified Descemet's membrane but no goblet cells in the cyst lining (Fig. 1A). CK 5/6 was positive, diffusely staining the entire epithelium of the cyst (Fig. 1C). CK 7 was also positive but less intense and patchy in the epithelium of the cyst compared to CK 5/6 (Fig. 1D). Finally, P63 was positive and intensely stained the basal layer of the epithelium lining the cyst, possibly consistent with stem-cell origin (Fig. 1F). All these staining results were consistent with corneal epithelial origin of the cyst.

In early serial sections the cyst extended from one end of the full-thickness corneal specimen to the other between closed thin edges of surrounding stroma. The original corneal graft was 7 mm in diameter and the stromal cyst estimated at 6.8 mm in diameter. The epithelium of the cornea was largely absent, due to surgical removal, and the endothelium was also largely absent, with the exception of a few fragments of cytoplasm. Descemet's membrane and Bowman's membrane were both intact. The anterior corneal stroma was more clefted than usual in paraffin-processed corneas and chronic inflammatory infiltrate was prominent focally in the anterior lamellae of the posterior stroma and posterior lamellae of the anterior stroma, the two separated by what was initially assumed to be a processing artifactitious cleft (Fig. 3). Artifacts can be meaningful, however, and the large separation between anterior and posterior corneal lamellae may have reflected poor adhesion related to multiple prior posterior lamellar grafts. We also reviewed two sets of pathology slides of the first two failed lamellar grafts, performed in May 2013 and October 2014 at a separate facility, which revealed only minimal posterior stromal scarring without significant inflammation or thickening of Descemet's membrane, and endothelial absence.

4. Discussion/Conclusions

This report presents a *trans*-stromal epithelial cyst discovered after PK that was not suspected preoperatively. To our knowledge, this is the first report of a corneal stromal epithelial cyst of this size that most likely grew into the corneal stroma through a gap in the graft's surface and edge.

Historically, the most common source of epithelial ingrowth has been defective wound closure following large incision cataract surgery. Ingrowth of epithelium following cataract surgery is well known to occur in three main forms: 1. Sheets covering the endothelial surface, angle structures and iris surface rarely extending through the pupil into the vitreous; 2. cysts expanding into the anterior chamber from inadequately closed wounds; and 3. iris pearl tumors.[4] Intracorneal cysts may follow ocular trauma[5–7] and prior ocular surgeries including keratoplasty (both penetrating and lamellar),[8–10] glaucoma surgeries,[11] and strabismus surgeries.[2,12] Stromal cysts have reportedly ranged from 2 mm to 9 mm in diameter, occupying one or more lamellar planes (Table 1).

Proposed mechanisms for stromal cyst formation include epithelial migration into the anterior chamber through a limbal paracentesis or stromal puncture.[4,9,13] Injuries to the limbus, such as those associated with limbal paracentesis or needle used to place a traction suture, can also allow epithelial cell entrance into the anterior chamber.[12] Sequestration of these cells in the stroma and their subsequent proliferation likely account for cyst growth. Serial sections and IHC studies of our specimen established that the cyst likely originated from the patient's corneal epithelium, specifically basal or possibly corneal epithelial stem cells identified by P63 IHC.[14] In our case, the patient had initially presented with a corneal ulcer treated with debridement with a moistened cotton tipped applicator. We doubt that debridement would lead to epithelial invasion and cyst formation. Alternative etiologies of the cyst also include accidental corneal epithelial implantation during the patient's prior endothelial keratoplasty procedures. While there are multiple plausible explanations for stromal epithelial ingrowth that are consistent with the serial section pathology obtained, we suspect the multiple prior posterior lamellar surgeries may have increased the patient's risk for developing epithelial ingrowth between posterior and anterior corneal lamellae secondary to the trauma and inflammation following the three prior dissections.

Li et al. reported a case of an intrastromal epithelial corneal cyst following corneal laceration suturing surgery that was successfully treated with deep anterior lamellar keratoplasty (DALK). The authors reported that DALK was required to treat the cyst, which had extended deep into the central corneal stroma and occupied a significant portion of the visual axis.[15] In our case, the patient had corneal edema prior to developing the corneal ulcer, suggesting corneal endothelial cell failure that required a transplant of both Descemet's membrane and endothelium. Because of the scar that developed in the stroma after the ulcer, it was also necessary to replace the stroma to restore optical clarity. Thus, PK was indicated, as he would not have benefited from repeat lamellar transplantation.

An untreated large cyst invading the stroma has several potential visual consequences such as visual axis obstruction, iridocyclitis, secondary glaucoma, intractable pain and corneal decompensation. Therefore, it is desirable to diagnose large *trans*-stromal cysts early on when excision is still possible. Baseline and peri-operative anterior segment optical coherence tomography (AS-OCT) may aid early diagnosis and management of patients with complicated corneal surgical histories.[16,17]

In conclusion, we report a large corneal epithelial stromal ingrowth found incidentally by histopathology after PK that likely would have been detected by preoperative AS-OCT or high-resolution ultrasound. We speculate that multiple prior posterior lamellar keratoplasties may have led to corneal lamellar alterations that increased the likelihood of the large cyst occurrence.

Table 1
Selected previously reported cases of stromal cysts.

Author	Year	Journal	Patient Demographics	Size of Cyst	Stromal Layers Involved	Etiology of Cyst	Management	Outcome
Bloomfield et al.[6]	1980	*American Academy of Ophthalmology*	5yo M	2–3 mm	Posterior third of the corneal stroma	Ocular trauma from wire cable	PK	Graft failure at POM 3
Dhiman et al.[18]	2015	*BMJ Case Reports*	11yo M	4 × 4.2 mm	Mid- to posterior stroma	Suture removal following PK	1) Cyst aspiration with chemo-cytodestruction of the cyst cavity with povidone iodine 1% 2) Focal anterior stromal flap lift, deep lamellar dissection to excise the stroma containing the recurrent cyst, and donor corneal stromal lenticule lamellar placement beneath the flap and suturing of the flap	Small recurrence 1.5 years after last surgery.
Mifflin et al.[2]	2001	*Cornea*	5yo F	4–5 mm	Mid- to deep stroma	Iatrogenic seeding of corneal stroma from limbal traction suture (prior strabismus surgery)	Cyst incision and debridement	No recurrence at POM 21
Zare et al.[3]	2012	*Oman Journal of Ophthalmology*	10yo F	5 × 8 mm, progressing to 6 mm × 10 mm at 2-year follow-up after first operation	Anterior to deep stroma, near Descemet's membrane	Unknown	Multiple surgical interventions: 1) Cyst drainage, debridement, and mechanical curetting of the cyst wall through a 2.0mm partial-thickness limbal incision. 2) LK complicated by perforation of posterior corneal lamella, and subsequently converted to PK.	No recurrence of cyst in cornea and anterior chamber at POM 20
Bhatt et al.[12]	2007	*Eye*	10yo F	5 × 5.2 mm	Mid-stroma	Iatrogenic seeding of corneal stroma from limbal traction suture (prior strabismus surgery)	Cyst incision, irrigation, and drainage	No recurrence of cyst in cornea and anterior chamber at POM 6
Lazzaro et al.[11]	2012	*Eye & Contact Lens*	64yo M	5 × 7 mm	Anterior stroma	Prior ocular surgeries (glaucoma surgery, cataract extraction)	Serial monitoring	No change in size or appearance at 5-month follow-up
Li et al.[15]	2018	*Canadian Journal of Ophthalmology*	25yo M	6 mm	Anterior to deep stroma	Ocular trauma from an awl (small tool used for piercing)	DALK	No recurrence of cyst in cornea and anterior chamber at POM 6
Reed et al.[7]	1971	*Arch Ophthal*	1) 15yo M 2) 10yo M 3) 70yo M 4) 9yo M 5) 4yo F 6) 2yo M 7) 22mo F 8) 25yo M	1) 7 × 7 mm 2) 4 × 4 mm 3) 3 × 3 mm 4) 5 × 4 mm 5) 3 × 2 mm 6) 6 × 5 mm 7) 6 × 5 mm 8) 5 × 2 mm	1) Mid-stroma 2) Mid-stroma 3) Deep stroma 4) Deep stroma 5) Mid-stroma 6) Mid-stroma 7) Mid-stroma 8) Deep-stroma	1) Prior ocular surgery (congenital cataract extraction) 2) Traumatic hyphema irrigated at age 8 3) Cataract extraction at age 68 4) Unknown 5) Unknown 6) Unknown 7) Unknown 8) Unknown	1) Incision 2) Excision of anterior wall; conjunctiva sutured to posterior lip 3) None 4) 1 - aspiration, 2 - incision, posterior wall 5) None 6) 1 - aspiration, 2 - excision anterior wall, 10% acetic acid irrigation, 3 - excision anterior wall 7) 1 - excision anterior wall, electrocautery, 2 - excision anterior wall, iodide cautery, 3 - irrigation corneal portion with iodine and cocaine, sutured 8) None	1) Recurrence at POM 1 2) No recurrence at POY 4 3) Slight progression 4) Recurrent but no enlargement at POY 4 5) Spontaneous disappearance 6) No recurrence at POM 6 after third procedure 7) No recurrence at POY 1 after third procedure 8) None
Al-Towerki et al.[5]	2008	*Cornea*	17yo F	9 × 9 mm	Mid-stroma	Ocular trauma	Surgical excision	No recurrence at POY 2
Ali Javadi et al.[19]	2006	*Cornea*	1) 14yo F 2) 12yo M	NA	1) Anterior third of the	1) Prior strabismus surgery	Drainage of cyst contents, chemical cytodestruction with 96% ethanol for 1	1) No recurrence at POM 8 2) No recurrence at

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Journal	Patient Demographics	Size of Cyst	Stromal Layers Involved	Etiology of Cyst	Management	Outcome
					corneal stroma 2) NA	2) Ocular trauma and limbal laceration repair	minute in a closed system, and cyst wall excision	POM 3 but moderate interface haze was noted at the site of the removed cyst

yo: year-old; mo: month-old; F: female; M: male; PK: penetrating keratoplasty; DALK: deep anterior lamellar keratoplasty; POM: postoperative month; POY: post-operative year.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

Statement of ethics

The IRB at UCI does not require patient permission for clinicopathologic single case reports.

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Author contributions

Chen AC – designed study, analyzed data, wrote and revised manuscript, Nowroozizadeh S - designed study, analyzed data, Kedhar S - designed study, analyzed data, wrote and revised manuscript, Minckler D - designed study, analyzed data, wrote and revised manuscript.

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.

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