Managing epithelial downgrowth after clear corneal phacoemulsification

Lauro A. Oliveira, MD, Marco Bordón, MD, Edson S. Mori, MD, Norma Allemann, MD

We present a case in which epithelial downgrowth developed after uneventful clear corneal phacoemulsification. The diagnosis of epithelial downgrowth was confirmed by clinical features and anterior segment optical coherence tomography (OCT), high-frequency ultrasound (US), and confocal microscopy. Intracameral 5-fluorouracil (5-FU) was administered 3 times to control epithelial growth. Sixteen months after the last intervention, the epithelial layer did not appear to have increased. Although 5-FU seemed to be effective in preventing epithelial growth, we cannot be sure epithelial cell growth will not progress over time. Corneal melting is a potential complication of this treatment. Anterior segment OCT and high-frequency US were helpful tools in the diagnosis of epithelial downgrowth after clear corneal phacoemulsification.

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Sutureless phacoemulsification has become the surgery of choice for cataract extraction. Small wounds make the procedure safer, with decreased trauma to the ocular structures, lower induced astigmatism, less surgical time, and fewer complications. Downgrowth of epithelial cells into the anterior chamber is a rare complication of intraocular surgery. It occurs more readily when there is prolonged communication between the corneal epithelium and the anterior chamber, as in cases complicated by wound fistulas, iris incarceration, or vitreous in the wound, highlighting the importance of appropriate wound architecture and prompt repair of a leaking wound.

The incidence of epithelial downgrowth ranges from 0.08% to 0.12% after cataract surgery (extracapsular or intracapsular extraction or both) and up to 0.25% after penetrating keratoplasty (PKP). Epithelial downgrowth through the wound, as in phacoemulsification, onto the posterior surface of the cornea usually proliferates in opaque sheets that may extend across the iris and anterior chamber angle, inducing secondary glaucoma.

We present a case of epithelial downgrowth that progressed despite repeated intracameral injections of 5-fluorouracil (5-FU). We report corneal melting as a complication of 5-FU and emphasize the importance of an imaging study of the incisions to localize a possible fistula or wound defect.

CASE REPORT

A 74-year-old man was referred for painless progressive decrease of vision in the right eye 6 months after sutureless phacoemulsification through a clear corneal incision (CCI). On examination, the corrected distance visual acuity (CDVA) in the right eye was 20/40. The right cornea appeared to be transparent with no edema and the incisions were normal on biomicroscopy. The corneal stroma was clear, and a white membrane-like layer was present along the endothelial surface superiorly, consistent with epithelial downgrowth extending to the visual axis (Figure 1). The intraocular pressure (IOP) was 13 mm Hg (the same as in the left eye). No evidence of iris involvement was observed on slitlamp examination. Confocal microscopy (Confoscan 2, Fortune Technologies), ultrasound biomicroscopy (UBM) (840, Paradigm, 50 MHz transducer, immersion technique), and anterior segment optical coherence tomography (AS-OCT) (Visante, Carl Zeiss Meditec AG) were performed to help with the diagnosis and to evaluate the incisions (Figures 2...
to 4). The epithelial downgrowth diagnosis was confirmed. On confocal microscopy, the area presented hyperreflective nuclei at the endothelium level; UBM and AS-OCT demonstrated a posterior gap in the incision and a continuous hyperreflective line was observed at the incision level, progressing over the endothelial surface.

Debridement and revision of the surgical incisions were performed as well as an exchange of 0.1 mL of aqueous for 0.5 mg of 5-FU in 0.1 mL of a balanced salt solution. Three months later, the epithelial downgrowth did not show regression and another intracameral exchange of 0.1 mL of aqueous for 0.5 mg of 5-FU in 0.1 mL of a balanced salt solution was performed. On the third postoperative day, the patient complained of pain and decreased vision. The anterior chamber was shallow, and there was leaking from the incision. On the seventh day, the patient presented with stromal melting at the incision and was taken to the operating room twice to control the leak with sutures. A choroidal detachment resulted, and the leak was controlled with cyanoacrylate glue of the nasal incision. Two months later, the glue was removed and the cornea was healed with new vessels around the affected area (Figure 1, C). Three months later, the epithelial layer was again apparently increasing and the patient was submitted to a third exchange of 0.1 mL of aqueous for 0.5 mg of 5-FU in 0.1 mL of a balanced salt solution. Sixteen months after the last intervention, the eye remained quiet, the IOP was stable, and the epithelial layer appeared not to have increased. However, the patient complained of low CDVA (decreased to 20/70) and light sensitivity, and anterior synechia was present at the main incision.

After 2 years of follow-up, there was worsening of the CDVA (20/200) and progressive opacification of the upper third and nasal areas of the cornea without evidence of epithelial downgrowth. It was decided to perform a PKP with an intracameral injection of 5-FU before host cornea trephination.

The PKP was successful and at the 1-year follow-up, the cornea was clear and there were no signs of epithelial downgrowth in the donor cornea. The patient presented with ocular hypertension (35 mm Hg). Gonioscopy ruled out the suspicion of epithelial downgrowth at the angle, and specular microscopy did not show abnormalities on the corneal endothelium. The ocular hypertension was successfully controlled with topical hypotensive medication. Two years after corneal transplantation, the eye remained quiet, the

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**Figure 1.** Slitlamp photography of postoperative phacoemulsification with CCI presenting epithelial downgrowth. A: Diffuse illumination showing a white membrane-like layer in the endothelial surface (arrow). B: Retroillumination showing the epithelial layer in the upper half of the cornea (over the line highlighted by an arrow). C: Postoperative view of surgical intervention to control epithelial downgrowth, last visit. Leucoma and new vessels in the main CCI (after melting recovery).

**Figure 2.** Six-month postoperative view of phacoemulsification with epithelial downgrowth. Confocal microscopy shows the aspect of the cells presented at the endothelial level. A: The hyperreflective nuclei (arrow) corresponding to the epithelial cells. B: Transition zone (arrow) between the noninvolved (lower half) and involved (upper half) epithelial downgrowth area with hyperreflective nuclei.
IOP was stable, the epithelial layer did not appear to have increased, and there was a good endothelial pattern.

**DISCUSSION**

We report a patient with the sheet-like or diffuse form of anterior chamber epithelial downgrowth, which is known to be aggressive, difficult to diagnose, and tends to recur after treatment. Typical clinical signs are decreased vision, mild inflammation, and a white or transparent membrane-like layer on the posterior surface of the cornea. At the end stage, the eye may become severely inflamed and can be painful secondary to glaucoma. Treatment of increasing epithelial downgrowth has been controversial. Current treatment options include transcorneal cryotherapy and block excision with tectonic grafting. However, these treatments are invasive and potentially destructive; they are often declined in cases in which the eye presents some vision and is not severely painful and inflamed.

The patient had discrete vision decrease and no pain or inflammation, and the vision in the fellow eye was functional. Another treatment option for anterior chamber epithelial downgrowth is intracameral injection of antimetabolites such as 5-FU. Loane and Weinreb report a case in which subconjunctival 5-FU failed to resolve an epithelial downgrowth in an eye that had a trabeculectomy. Two papers report complete regression of an epithelial downgrowth in eyes that had corneal grafting using intracameral 5-FU. Wong et al. report a case of epithelial downgrowth after Descemet-stripping automated endothelial keratoplasty (DSAEK) successfully treated with 5-FU.

However, the case had a short follow-up. Tomlins et al. report a case of epithelial downgrowth after clear corneal cataract extraction in which intracameral 5-FU (5 injections) failed to prevent progression or to prevent angle closure. They reported no signs of toxicity to any ocular structure and questioned the use of higher doses of 5-FU in repeated intracameral injections as a possibility of slowing the progression or resolving the process. Instead of that, our patient who had 3 5-FU intracameral injections, did present with corneal melting where the injection was performed (through the main CCI). Our hypothesis is that there were epithelial cells in the incision that were injured by the 5-FU. Once the epithelial cells were injured, inflammatory cytokines such as transforming growth factor-$eta$ and interleukin-1 could trigger the adjacent stromal response. We cannot confirm this since it was not addressed in the case report. However this epithelium–stroma interaction has been studied in vivo and in vitro. Another point that might corroborate the hypothesis is that the patient was later submitted to an 5-FU injection far from the incisions with no sign of toxicity.

We found only 1 other paper reporting epithelial downgrowth after clear corneal phacoemulsification. One of the 2 patients was treated with cryotherapy, which resulted in corneal decompensation requiring a PKP. The other patient was treated with an en bloc excision and a corneoscleral graft to restore the structure and function of the eye. Our findings in confocal microscopy were similar to those described by dos Santos Forsesto et al., confirming that this noninvasive method is helpful in diagnosing epithelial downgrowth. Two distinct cellular types were present in the endothelial layer (Figure 2). In the superior part of the cornea, the cells were larger with a polygonal shape and with hyperreflective nuclei, suggesting epithelial...
cells. The posterior corneal line presented at slitlamp examination was well documented on confocal microscopy as a transition line between the involved and noninvolved areas (Figure 2).

Imaging methods in our patient showed that the CCI had been performed in 1 plane (Figures 3 and 4). One-plane incisions are usually shorter and steeper and tend to be more unstable, as demonstrated by Calladine and Packard\textsuperscript{15} and Fine et al.\textsuperscript{16} Anterior segment OCT also showed gaping on the endothelial side, which is relatively common on the first postoperative day (41%), as reported by Calladine and Packard.\textsuperscript{15} However, the imaging of our patient was performed 8 to 9 months after the phacoemulsification with no stromal hydration to justify the gaping. There was no misalignment of the floor and roof of the CCI and no loss of coaptation. The imaging techniques such as high-frequency ultrasound (US) and AS-OCT enabled identification of architectural features such as wound gaping and a hyperreflective line through the incision progressing over the endothelial surface, and these led us to suspect that there was a wound fistula permeable to epithelial cells. Suh et al.\textsuperscript{17} and Chen et al.\textsuperscript{18} have reported the use of AS-OCT to diagnose and follow cases of epithelial downgrowth after DSAEK and PKP, respectively. Epithelial downgrowth was described as a hyperreflective layer.

Although the epithelial downgrowth looked stable, the patient’s visual acuity decreased and a PKP was performed. Two years after corneal transplantation, the eye remained quiet, the IOP was stable, and the epithelial layer did not appear to have increased. To our knowledge, this is the first case of epithelial downgrowth after a CCI and corneal melting after intracameral 5-FU injection. It might also be the first attempt to analyze a CCI after epithelial downgrowth using anterior segment imaging methods such as AS-OCT and high-frequency US.

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First author: Lauro A. Oliveira, MD
Department of Ophthalmology and Visual Sciences, Federal University of São Paulo, São Paulo, Brazil