

# Netarsudil-associated reticular epithelial corneal edema after phacoemulsification



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**Introduction:** To the authors' knowledge, this is the first reported case of netarsudil-associated reticular corneal edema noted shortly after phacoemulsification with intraocular lens (IOL) implantation.

**Patient and Clinical Findings:** A 68-year-old woman with a history of chronic angle-closure glaucoma with a long-term history of tolerance to netarsudil presented with "honey-comb" epitheliopathy shortly after phacoemulsification with IOL implantation.

**Diagnosis, Intervention, and Outcomes:** Netarsudil was discontinued, and the patient's reticular corneal edema resolved shortly thereafter.

**Conclusions:** Reticular corneal epitheliopathy can be seen in patients being treated with netarsudil after phacoemulsification with IOL implantation. Fortunately, this condition resolves shortly after the drug is discontinued.

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Approved by the U.S. Food and Drug Administration in 2017, netarsudil ophthalmic solution 0.02% (Rhopressa, Aerie Pharmaceuticals) is a first-in-class medication used in the treatment of primary open-angle glaucoma and ocular hypertension.<sup>1</sup> As a rho kinase (ROCK) inhibitor, netarsudil lowers intraocular pressure (IOP) by decreasing aqueous production, increasing episcleral venous outflow, and increasing the outflow facility of the trabecular meshwork by reducing actin-myosin-mediated meshwork contraction and profibrotic extracellular matrix proteins.<sup>2-4</sup>

Although well tolerated, phase 3 clinical trials showed that the most common side effects attributed to netarsudil are conjunctival hyperemia, corneal verticillata, and conjunctival hemorrhage.<sup>3</sup> These side effects were not found to significantly affect patient visual acuity (VA) and resolved spontaneously on cessation or within the poststudy follow-up period. Now that it has become a well-established treatment modality for glaucoma, there have been several recent reports of visually significant reticular epithelial corneal edema associated with netarsudil. In this article, to our knowledge, we describe the first case of reticular corneal edema associated with netarsudil after phacoemulsification with intraocular lens (IOL) implantation.

## Patient Consent

The patient discussed in this report has provided written informed consent for her information to be published in a deidentified manner.

## CASE REPORT

A 68-year-old woman with a medical history of hyperlipidemia presented to the clinic complaining of decreased vision and blurriness in the left eye. Her ocular history was notable for chronic angle-closure glaucoma of both eyes (severe in the right eye and moderate in the left) and amblyopia of the right eye. Two years before her examination, the patient was treated with a combined trabeculectomy with mitomycin-C and cataract extraction of the right eye with good result. She had also been treated with laser peripheral iridotomy and iridoplasty in both eyes many years before her incisional surgery.

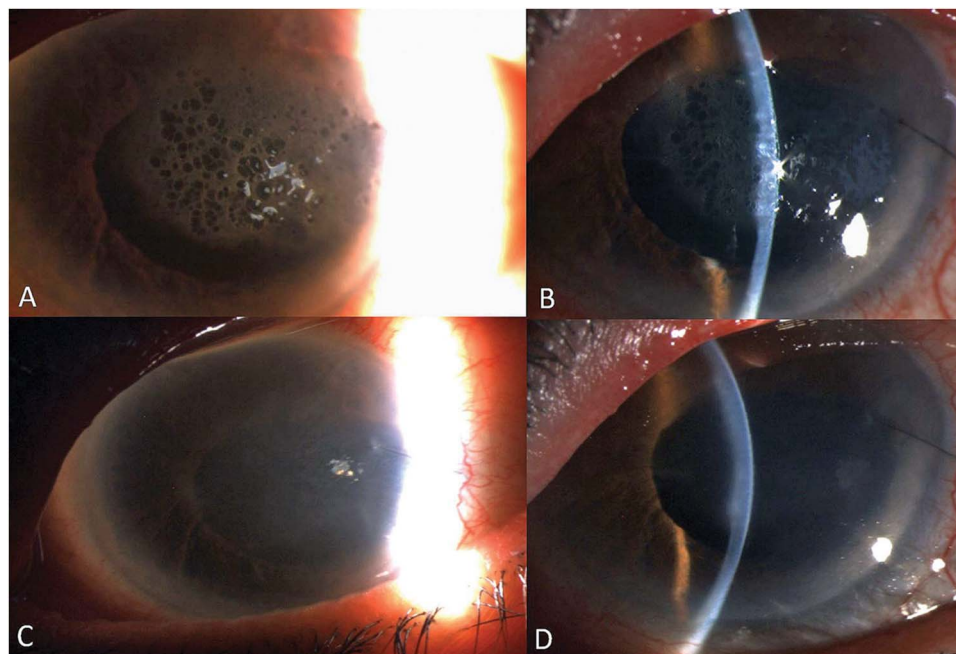
On initial examination, the patient was found to have a VA of 20/70 in the right eye and 20/80 in the left eye. Her IOP was 9 mm Hg in the right eye on zero topical medications and 15 mm Hg in the left on 5 topical medications including netarsudil, latanoprost, pilocarpine, brinzolamide, and brimonidine. IOP-lowering therapy had been unchanged for several months before surgical evaluation, and she had been taking netarsudil in the left eye for a total of 13 months. At baseline, her central corneal thickness was 565  $\mu\text{m}$  in the right eye and 521  $\mu\text{m}$  in the left eye. There was no baseline specular microscopy. Initially, the patient's cornea was found to be clear and without edema or guttae; however, she was noted to have a 3+ brunescent nuclear sclerotic cataract of the left eye. The patient was counseled regarding the risks and benefits of surgical intervention and elected to proceed with cataract extraction and IOL implantation of the left eye.

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**Figure 1.** A and B: Reticular “honeycomb” epitheliopathy seen at postoperative month 1 after phacoemulsification. C and D: Resolution of epitheliopathy 2 weeks after netarsudil discontinuation.

Several weeks later, the patient underwent uneventful phacoemulsification with IOL implantation. She was started on a standard postoperative regimen of topical prednisolone ophthalmic solution 1%, ketorolac, and moxifloxacin eye-drops 4 times daily in addition to her previously prescribed topical antiglaucoma medications. On postoperative day 1, the patient was noted to have a VA of count fingers with an IOP of 11 mm Hg. The patient’s cornea was notable for diffuse microcystic epithelial edema with central Descemet membrane folds. The patient was started on topical sodium chloride hypertonic ointment 5% nightly.

The patient was seen again on postoperative week 1. The patient’s VA in the surgical eye remained at count fingers. On slitlamp examination, her cornea showed a reduction in the amount of microcystic corneal edema and Descemet membrane folds; however, centrally, there was a dense area of reticular epithelial edema with a “honeycomb” appearance (Figure 1, A,B). The patient was taken off netarsudil because of concern for netarsudil-associated reticular epithelial edema.

At postoperative week 3, the patient was seen in the clinic and found to have a VA of 20/80 without correction. Physical examination was notable for complete resolution of her reticular epithelial edema (Figure 1, C,D). A small amount of underlying microcystic corneal edema was still present, but this was significantly improved compared with her prior examination.

The patient was subsequently referred to a cornea specialist for consideration of endothelial keratoplasty. At her 6-month postoperative visit with the cornea specialist, the patient’s corrected distance VA in her left eye was 20/40, her central corneal thickness was found to be 548  $\mu\text{m}$ , and her residual corneal edema had improved. Specular microscopy at this visit revealed an endothelial cell density of less than 500 cells/ $\text{mm}^2$  in both eyes. The corneal

surgeon and the patient have mutually decided to monitor without transplantation at this time.

## DISCUSSION

ROCK inhibitors have demonstrated strong efficacy in controlling IOP. Accompanying the increase in the prevalence of ROCK inhibitor usage has been several new reports of associated “honeycomb” reticular epitheliopathy.<sup>5–11</sup> Here, we present a case of netarsudil-associated reticular epithelial edema in the setting of recent phacoemulsification, a previously unreported phenomenon.

Before cataract extraction, our patient had a 1-year history of tolerance to netarsudil. We believe that the endothelial stress incurred from dispersed phacoemulsification energy predisposed our patient to developing this disease state. This echoes previous reports, which suggest that the development of corneal edema or preexisting pathology may precipitate drug toxicity in these patients; however, there are reports of patients developing this reaction in the absence of edema or significant corneal pathology as well.<sup>8–11</sup> Previously identified risk factors for netarsudil-associated reticular corneal epitheliopathy include corneal transplant, diode cyclophotocoagulation, glaucoma drainage shunt implantation, and Fuchs corneal dystrophy.<sup>12</sup>

Similar to other reported cases, our patient’s VA was significantly affected by her corneal condition. Fortunately, this improved dramatically 2 weeks after netarsudil was discontinued. We suspect that this improvement would be seen sooner if earlier clinical examination had been conducted. Logistical limitations precluded earlier follow-up for our patient. This improvement time period mirrors other studies that show significant improvement or resolution of “honeycomb” epitheliopathy in the order of weeks.

Several different hypotheses have been proposed to explain netarsudil-associated reticular corneal edema. Some postulate

that netarsudil alters the fundamental cellular physiology of the endothelial cell pumping mechanism. Others suggest that ROCK inhibitors alter the integrity of epithelial tight junctions through actin and myosin interaction.<sup>6,7</sup> As suggested by Wisely et al., netarsudil may increase tight junction permeability and may allow edema from stromal layers to percolate through into the epithelial layers of the cornea.<sup>7</sup>

Of interest, ripasudil, an alternate ROCK inhibitor used for IOP-lowering therapy in Japan, has been used as an adjunctive treatment in patients with Fuchs corneal dystrophy undergoing Descemet stripping only.<sup>13</sup> In this trial, patients with Fuchs who received adjunctive treatment with ripasudil showed quicker recovery of VA and increased postoperative endothelial cell counts compared with control patients. Netarsudil has also been used to treat corneal edema associated with Fuchs endothelial dystrophy with promising results both when used adjunctively with Descemet stripping only and as monotherapy.<sup>14,15</sup> Unlike netarsudil, there have been no reported cases of reticular corneal epitheliopathy associated with ripasudil.

Before cataract extraction, we suggest that surgeons consider obtaining baseline pachymetry and specular microscopy to identify patients at increased risk for corneal decompensation because of reduced endothelial cell density. This is particularly relevant for patients with glaucoma who are prescribed netarsudil. It is unclear whether perioperative discontinuation of netarsudil would provide benefit in reducing the risk of reticular corneal edema; however, this is a point that may be useful to discuss during patient preoperative counseling.

Although previously undescribed, reticular corneal epitheliopathy can be seen in patients being treated with netarsudil after phacoemulsification with IOL implantation. Fortunately, this phenomenon resolves within weeks of medication discontinuation. As netarsudil has become a well-established treatment modality for glaucoma, clinicians and surgeons must be cognizant of the associated reticular epitheliopathy, which can be seen after cataract extraction.

### WHAT WAS KNOWN

- Netarsudil use has been associated with reticular “honeycomb” corneal epitheliopathy in patients, particularly those with preexisting corneal pathology.

### WHAT THIS PAPER ADDS

- This paper describes a new case of netarsudil-associated reticular corneal epitheliopathy seen shortly after cataract extraction with phacoemulsification.
- Although previously undescribed, it is important that clinicians be able to recognize that netarsudil-associated corneal edema can occur after phacoemulsification surgery and that the drug should be promptly discontinued to hasten visual recovery.

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**Disclosures:** None of the authors has any financial or proprietary interest in any material or method mentioned.

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