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Case Report

Reticular epithelial edema after penetrating keratoplasty in a patient taking netarsudil

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Summary

Netarsudil is a relatively new medication for the treatment of primary open-angle glaucoma and ocular hypertension. It has been associated with red eyes and burning after instillation. Reticular epitheliopathy is a relatively rare complication of netarsudil that has been described in patients with preexisting corneal edema. We report the case of a healthy 76-year-old woman who developed reticular epitheliopathy after full-thickness penetrating keratoplasty that completely resolved following discontinuation of the medication. In cases where netarsudil is initiated for treatment of glaucoma or, off-label, endothelial dysfunction, reticular epithelial edema should be considered in patients complaining of a decline in vision and severe pain.

Introduction

Netarsudil 0.02% ophthalmic solution (Rhopressa, Aerie Pharmaceuticals, Durham, NC) is a topical medication approved by the US Food and Drug Administration in 2017 for treatment of primary open-angle glaucoma and ocular hypertension. It is a Rho kinase (ROCK) inhibitor that represents a unique class of medication for management of intraocular pressure (IOP). In addition to decreasing episcleral venous pressure and aqueous production, as do other glaucoma medications, ROCK inhibitors are thought to increase trabecular meshwork outflow as a result of decreased actin-myosin cell contraction and reduction of profibrotic extracellular matrix proteins to create a more pliable trabecular meshwork.[1,2]

Additionally, animal studies and early trials suggest that ROCK inhibitors promote corneal endothelial wound healing and can improve corneal edema after cataract surgery[3] and in Fuchs endothelial dystrophy.[4] ROCK inhibitors are being investigated and used off-label for failed corneal grafts and therapy in descemetorrhexis without endothelial keratoplasty.[5]

In phase 2 and 3 clinical trials investigating netarsudil for IOP control, the most common adverse effects were conjunctival hyperemia, followed by corneal verticillata and conjunctival hemorrhage.[1,2,6] These effects were not visually significant and were reversible with drug cessation. Clinical trials examining neutarsudil/latanoprost combination medication revealed a similar side effect profile.[7] However, after public release of this medication, there have been reports noting a reticular, or honeycomb, epithelial edema with an associated decline in vision.[8–11] Below we describe a case of reticular epitheliopathy in a patient with an otherwise healthy penetrating keratoplasty that resolved completely after discontinuation of the medication.

Case Report

A 76-year-old woman presented to the cornea clinic with blurry vision, dryness, and severe pain in both eyes for 2 weeks. Her general medical history included hypertension and hypercholesterolemia, for which she was taking amlodipine and colestipol, respectively. She had a history of juvenile idiopathic arthritis but currently was not on systemic treatment. There were no recent changes to her health or systemic medications.

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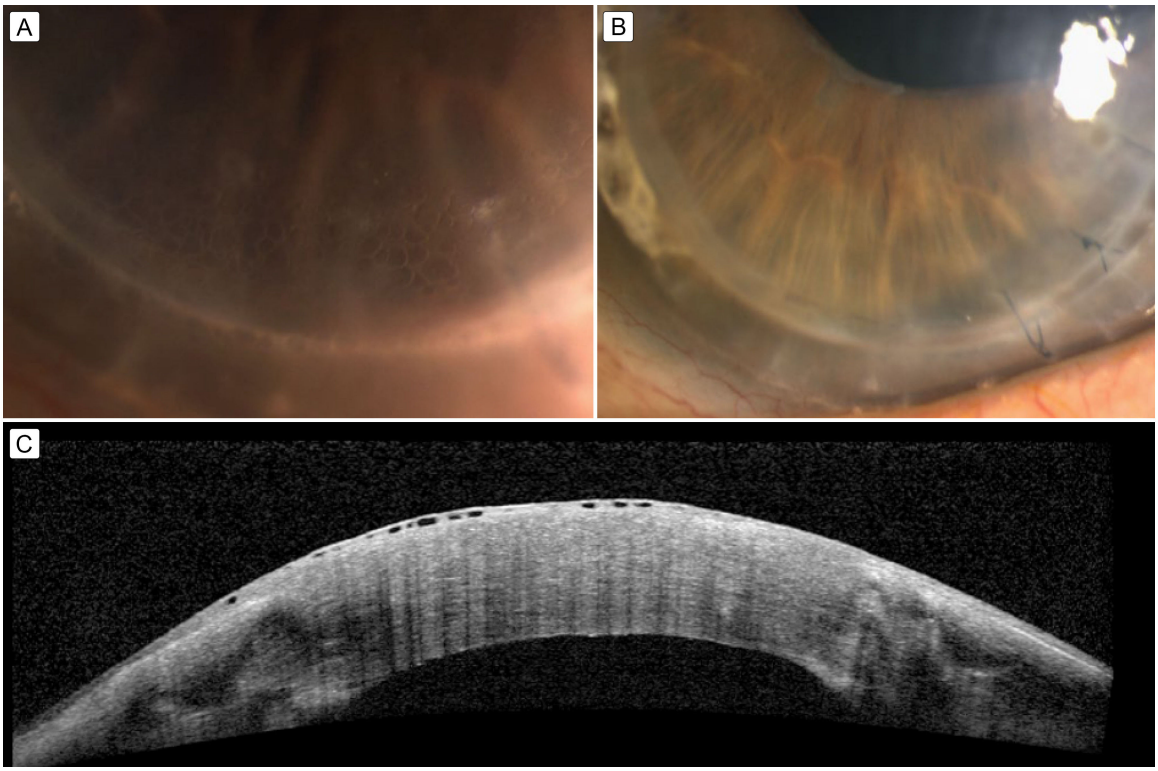

Figure 1. A, Slit lamp photograph of the left eye showing cystic reticular epithelial change over the inferior border of the penetrating keratoplasty after initiation of netarsudil. B, Anterior segment optical coherence tomography shows intraepithelial cystic changes. C, Four months after initial presentation and discontinuation of netarsudil, the reticular epitheliopathy appeared resolved.

The patient's ocular history was extensive and included aphakia, mixed mechanism glaucoma (primary open-angle glaucoma and uveitic glaucoma secondary to juvenile idiopathic arthritis), and band keratopathy in both eyes. She had undergone multiple corneal transplants, most recently a penetrating keratoplasty with pupilloplasty and anterior vitrectomy in the right eye 2 years prior and a penetrating keratoplasty in the left eye 3 years prior. The right corneal transplant was chronically edematous, with a corneal thickness of 928 µm. The left transplant was relatively healthy, with a cell count of 2,793 and corneal thickness of 608 µm. Her baseline corrected visual acuity ranged between counting fingers and hand motion in the right eye, and 20/60 to 20/70 in the left eye. Baseline IOP ranged from 7 to 17 mm Hg in the right eye and 6 to 16 mm Hg in the left eye.

The patient had previously been taking prednisolone acetate 1% twice daily in both eyes, preservative-free brimonidine three times daily in both eyes and timolol twice daily in the right eye. Two weeks prior to this visit the patient had been placed on netarsudil in both eyes for elevated IOP by her outside glaucoma specialist. Due to severe pain starting almost immediately upon starting netarsudil, she returned to the physician 10 days later and was noted to have "ulceration" in the left eye. The medication was discontinued. The patient presented 2 days later to the Cornea Service at the University of Florida for evaluation.

On examination, her corrected visual acuity was count fingers at 3 feet in the right eye and 20/80 in the left eye. On applanation tonometry, IOP was 11 mm Hg in the right eye and 13 mm Hg in the left eye. Anterior slit lamp examination of both eyes was notable for trace conjunctival injection. In the left eye, the penetrating keratoplasty had diffuse thickening inferiorly, with reticular cystic-appearing changes along its inferior border and on the graft host junction (Figure 1A). The inferior portion of the graft also showed greater stromal thickening compared with the central cornea. No epithelial defects were noted. Both eyes had formed anterior chambers, postsurgical iris changes, and aphakia, which was unchanged from previous examinations. Anterior segment optical coherence tomography demonstrated intraepithelial bullae in the area of the reticular changes (Figure 1B). A specular photograph showed no visible hexagonal cells. Pachymetry was 567 µm in the left eye

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centrally. The recommendation was made to remain off netusardil and to increase the frequency of sodium chloride 5% drops and ointment in the left eye. The patient's regimen of timolol daily and prednisolone acetate 1% twice daily were left unchanged.

One month later, the patient returned and complained of subjective worsening of vision in the left eye, which was found to be decreased to 20/200. Her IOP was elevated at 26 mm Hg, and she had diffuse microcystic edema. She was started on oral acetazolamide and returned to her glaucoma specialist for further management. Four months after the initial presentation, the patient returned with subjective improvement in her symptoms and vision. Corrected visual acuity had improved to 20/60, and her IOP was 7 mm Hg on preservative-free timolol-dorzolamide twice daily, latanoprost at bedtime, prednisolone acetate 1% twice daily, sodium chloride 5% drops four times daily, and sodium chloride 5% ointment at bedtime. The patient had mild diffuse graft thickening with Descemet folds superiorly, which was speculated to be caused by starting dorzolamide. The reticular epitheliopathy was completely resolved (Figure 1C).

Discussion

ROCK inhibitors have shown promise in the treatment of elevated IOP and demonstrated a minimal side effect profile in clinical trials. Additionally, its endothelial cell antiapoptotic and proliferative properties have led to its use in treating corneal stromal edema following partial-thickness keratoplasty. However, its widespread use has been accompanied by an increasing number of reports of associated reticular epithelial edema.[8,9,11] This honeycomb-like epitheliopathy tends to appear inferiorly within weeks to months of initiating therapy with a subsequent gradual decline in vision. An inferior predisposition for the corneal edema may be due to the tendency for medications to remain in the inferior fornix after instillation prior to its drainage into the inferior punctum. Several case reports have identified preexisting corneal edema as a risk factor in the development of reticular epithelial edema with netarsudil use.[9,10,12] On the other hand, there are also case reports of patients developing reticular epithelial edema with no reported preexisting corneal findings.[10,13,14] It is noteworthy that our patient had used netarsudil in both eyes but did not develop reticular epithelial edema in the severely edematous penetrating keratoplasty of the right eye. This may be because functional endothelial cells were lacking in the right corneal graft or because of masking by preexisting epithelial edema. Meanwhile, the normal left eye penetrating keratoplasty was affected. Although the majority of cases resolved on discontinuation of the medication, some patients developed persistent corneal clouding.[8,10] Fortunately, prompt discontinuation of netarsudil reversed the epithelial edema in our patient.

Two hypotheses have been advanced regarding the mechanism underlying these clinical findings. One scenario suggests that Rho kinase inhibitors permit greater permeability of basement membrane epithelial tight junctions, allowing fluid to egress from stroma to epithelium but with a corresponding inability of fluid to cross intraepithelial tight junctions. Thus, fluid is able to enter epithelium but unable to percolate to the surface and evaporate.[9] The other hypothesis proposes that Rho kinase inhibition enhances endothelial pump function, which increases clearance of stromal edema anteriorly but is then limited in its ability to push fluid completely to the surface.[9] Both hypotheses suggest innate changes to cell function that alter fluid mechanics.

We propose an additional hypothesis for the formation of intraepithelial fluid based on the action of ROCK inhibitors on epithelial cell motility and adhesion. Studies of epithelial wound healing have shown that ROCK inhibitor Y-27632 increases cell migration, decreases E-cadherin in adherens junctions, and prevents tight junction barrier formation via alterations in actin cytoskeleton.[15] ROCK's effect on actin and myosin IIA is critical for the barrier function and apico-basal polarity of epithelial cells; inhibition of Rho kinase causes a lack of tight junctions in the epithelium, which could lead to solute and fluid influx and formation of intraepithelial cysts.[16] In addition, ROCK inhibitor Y-27632 has been shown to increase epithelial cell spreading, whereby migrating sheets of epithelial cells demonstrate aberrant protrusions and leave more holes between cells.[17] Hole formation may promote spaces for accumulation of fluid. Further studies are required to better understand the specific effects of netarsudil on the corneal epithelium.

Other potential adverse effects of netarsudil that have been described, including corneal hemorrhage in a cornea with neovascularization[18] and mild anterior uveitis with hypopyon and keratic precipitates.[14] Reversible endothelial guttata-like changes after starting neutarsudil/latanoprost combination eye drop has also been reported.[19] Thus far, there have been no reported cases of corneal epithelial edema with use of rispasudil,[12] another ROCK inhibitor that is available in Japan.

In conclusion, we report a rare case of reticular epithelial edema in a penetrating keratoplasty associated with netarsudil therapy. Especially because patients who

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undergo penetrating keratoplasty often develop secondary glaucoma, it is likely that further cases of netarsudil-related epithelial edema in corneal transplants will arise. Therefore, it is important that further studies are conducted to determine the risk factors and the pathophysiology of this phenomenon. Clinicians should be aware that patients with decreased vision or eye pain following use of netarsudil should be promptly evaluated for epitheliopathy. Discontinuation of medication leads to reversal of corneal changes.

Literature Search

PubMed was searched on November 8, 2020, using the terms *netarsudil*, *rho-kinase inhibitors*, and *reticular epithelial edema*.

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