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Case Report

Reticular Bullous Epithelial Corneal Edema after Netarsudil Use for Elevated Intraocular Pressure with Concurrent Fuchs Endothelial Corneal Dystrophy: A Case Report

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Keywords
Netarsudil · Corneal edema · Fuchs dystrophy

Abstract
Introduction: We describe a case of reticular bullous corneal epithelial edema associated with the use of netarsudil ophthalmic solution (0.02%) for elevated intraocular pressure. ***Case Presentation:*** A 74-year-old man with a complex ocular medical history, including Fuchs dystrophy and primary open-angle glaucoma, developed progressively worsening loss of vision 3 weeks following the initiation of topical netarsudil for increased intraocular pressure. Visual acuity in the left eye was counting fingers at 3 feet and intraocular pressure in the left eye was 7 mm Hg. A characteristic "honeycomb" pattern epitheliopathy was seen on ocular examination. ***Conclusion:*** Reticular bullous epithelial corneal edema is an uncommon finding associated with netarsudil use, which can be overlooked in favor of corneal edema associated with Fuchs dystrophy. This is especially relevant given Fuchs dystrophy itself is a predisposing risk factor for netarsudil-induced reticular bullous corneal epithelial edema. Improvement of both the corneal edema and visual acuity should be expected after discontinuing netarsudil and undergoing superficial keratectomy.

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Introduction

Netarsudil is a rho-kinase inhibitor approved by the US Food and Drug Administration in 2017 for the management of elevated intraocular pressure, particularly in patients with ocular hypertension or primary open-angle glaucoma [1]. Studies in human subjects suggested that netarsudil decreases intraocular pressure by increasing aqueous outflow through the trabecular meshwork and dilation of episcleral veins [2]. Known adverse effects include conjunctival hyperemia, corneal verticillata, and subconjunctival hemorrhage, all of which may resolve with discontinuation of the drug [3, 4]. Corneal edema may also arise with netarsudil use, as we present here. Possible predisposing risk factors include a history of corneal endothelial keratoplasty, penetrating keratoplasty, presence of corneal edema, and endothelial decompensation [5, 6]. However, bullous keratopathy and corneal edema are common manifestations of Fuchs endothelial corneal dystrophy. Together, these factors contribute to the challenge in the recognition and management of netarsudil-associated corneal edema in a patient with concurrent Fuchs endothelial corneal dystrophy and netarsudil use. Therefore, it is important for clinicians to be keen of the possible manifestation of this condition when initiating netarsudil.

Case Report

A 74-year-old man with Fuchs dystrophy, primary open-angle glaucoma, and history cystoid macular edema of the left eye initially presented for evaluation of elevated intraocular pressure in the left eye. That patient had undergone a trial of brinzolamide and fixed-combination brimonidine tartrate and timolol maleate. Four weeks prior to current presentation, the patient was treated with intravitreal triamcinolone acetonide in the left eye for cystoid macular edema. At this current time, the visual acuity in the left eye was 20/125 and intraocular pressure in the left eye was found to be 26 mm Hg. He was started on topical netarsudil for increased intraocular pressure, which was likely secondary to a history of intravitreal steroid injections for management of cystoid macular edema.

Three weeks after netarsudil initiation, the patient presented to clinic with worsening vision in the left eye. Visual acuity in the left eye was counting fingers at 3 feet and intraocular pressure in the left eye was 7 mm Hg. On corneal examination, diffuse reticular epithelial bullae involving the visual axis and 3+ microcystic edema were evident in the left eye (Fig. 1a). Although corneal edema secondary to Fuchs dystrophy was considered, netarsudil was discontinued given likelihood of netarsudil-induced reticular bullous corneal epithelial edema.

Seven weeks after cessation of Netarsudil, clinical examination showed moderate improvement of visual acuity to 20/200 on the left eye and improved clinical signs of corneal epithelial edema. Although visual acuity has improved, the patient underwent superficial keratectomy of the left eye to further improve vision, after which the visual acuity of the left eye improved to 20/80, which was consistent with potential acuity meter (PAM) testing. No signs of recurrence were identified at 6 months after discontinuation of netarsudil (Fig. 1b).

Discussion

Netarsudil (Rhopressa; Aerie Pharmaceuticals, Durham, NC) is a ROCK inhibitor, named after its action in inhibiting the Rho family small G-protein kinases [7]. The drug was initially approved by the US Food and Drug Administration in 2017 to treat open-angle glaucoma and

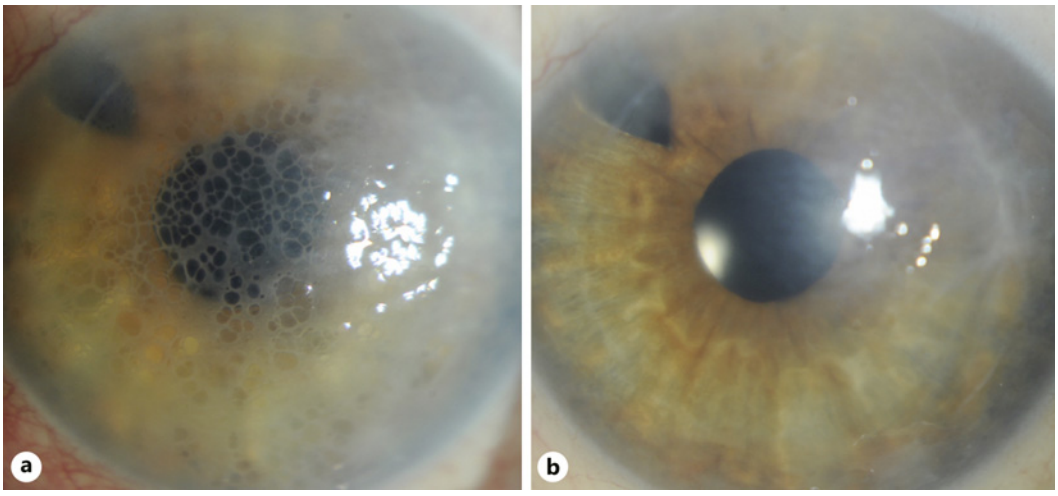

Fig. 1. Slit-lamp photographs of the left eye showing reticular bullous epithelial corneal edema at initial presentation (**a**) and no recurrence 4 months after netarsudil discontinuation and superficial keratectomy (**b**).

ocular hypertension [8]. Phase 3 randomized clinical trials showed 3 months of once daily (QD) netarsudil ophthalmic solution 0.02% lowered intraocular pressure and was noninferior to timolol ophthalmic solution 0.05% twice a day (BID). Mean decreased from baseline intraocular pressures ranged from 3.9 to 4.7 mm Hg for QD netarsudil. The intraocular pressure lowering effects were sustained over 6 months of treatment with no treatment-related serious adverse events observed [9].

Additionally, clinical trials evaluating use of netarsudil for corneal edema due to Fuchs corneal dystrophy demonstrated a reduction in corneal edema and reduction in central corneal thickness [7, 10]. Similarly promising results for Fuchs dystrophy corneal edema were shown with ripasudil, another ROCK inhibitor [11]. An additional clinical trial found netarsudil significantly reduced the time to corneal clearance after descemetorhexis without endothelial keratoplasty from an average of 8 ± 1.9 weeks to 4.6 ± 1.7 weeks [12]. Currently, only surgical approaches offer definitive sight-restoring treatment in patients with Fuchs dystrophy, leaving room for an effective pharmacological treatment [10]. ROCK inhibitors show promise in that regard by promoting adhesion, proliferation, survival of corneal endothelial cells, and may even restore corneal endothelial barrier integrity [10, 11]. Safety of QD or BID netarsudil was tolerated with conjunctival hyperemia serving as the most frequent adverse event [10].

Reticular bullous epithelial corneal edema is a rare finding with topical netarsudil use, more likely to occur in those who have predisposing risk factors for corneal edema [8]. Netarsudil-induced reticular bullous epithelial corneal edema can be mistaken for bullous keratopathy in patients with Fuchs dystrophy, which itself is a risk factor, given the similar presentation. Discontinuation of netarsudil and treatment with superficial keratectomy can result in significant improvement. Although netarsudil-induced reticular corneal edema has been reported in the literature, there have been sparse reports detailing manifestations in patients with concurrent Fuchs dystrophy. To our knowledge, current literature only mentions 2 cases of netarsudil-induced reticular corneal edema was found in a patient with an existing diagnosis of Fuchs dystrophy [6, 13]. However, in both cases, the patients presented with existing corneal edema were prescribed netarsudil for treatment of corneal edema due to Fuchs or Descemet stripping, and then subsequently developed epithelial cysts distributed in a reticular pattern after the initiation of netarsudil. Additionally, neither case involved

elevated intraocular pressure prior to initiation of netarsudil. Future studies should involve a larger cohort of patients and identify differentiating findings favoring edema secondary to netarsudil use versus Fuchs dystrophy.

In conclusion, reticular bullous epithelial corneal edema may be sequelae of netarsudil use. Ophthalmologists should be vigilant of this rare complication of netarsudil, especially in patients with Fuchs dystrophy, in whom corneal edema may concurrently arise or be present. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538119).

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This case report does not contain any personal identifying information. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

Natalie A. Afshari has no relevant financial disclosures. She is a consultant to the following companies not related to this submitted work: Trefoil Therapeutics, GSK, Dompe, Claris Biotherapeutics, Alpine Biotherapeutics, and Aescula Tech. The remaining authors have no financial disclosures.

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Author Contributions

All authors attest that they meet the current ICMJE criteria for authorship. The authors confirm their contribution to the paper as follows: Kathryn S. Park: conceptualization, investigation, and writing – original draft. Alexander C. Lieu: conceptualization, investigation, writing – reviewing, and editing. Michael J. Ang: validation and writing – reviewing and editing. Natalie A. Afshari: conceptualization, validation, writing – reviewing and editing, and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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