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Crystalline keratopathy following long-term netarsudil therapy

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ABSTRACT

Purpose: This case report highlights a possible association between netarsudil use and crystalline keratopathy.
Observations: Presented here is the case of a 72-year-old woman with primary open-angle glaucoma (POAG) who developed corneal crystalline keratopathy after taking netarsudil for 24 months. The patient's medical history was significant for dry eye syndrome, bilateral ptosis with surgical repair, and atopy (including asthma and various ocular and systemic allergies). The patient had previously undergone surgical repair for bilateral ptosis as well. During the interval between two routine visits, this patient experienced worsening vision with associated eye irritation. Further examination revealed crystal deposits on the anterior corneal surface in the left eye, the only eye undergoing netarsudil treatment.
Conclusions and importance: Long-term netarsudil use may be associated with crystalline keratopathy in the anterior stroma, with the potential to cause sight-threatening vision loss if located in the visual axis.

1. Introduction

Netarsudil ophthalmic solution 0.02 % (Rhopressa; Aerie Pharmaceuticals, Durham, NC, USA) was approved by the US Food and Drug Administration in 2017 to lower elevated IOP in ocular hypertension and open-angle glaucoma. It represents a significant addition to the field as the first clinically useful ocular hypotensive since the introduction of latanoprost in 1996.[1,2]

Netarsudil functions via three distinct mechanisms to achieve IOP reduction: increasing outflow through the trabecular meshwork, reducing aqueous humor production, and decreasing episcleral venous pressure.[1,3–5] The combined effect of these mechanisms often yields substantial IOP reduction. Clinical studies have demonstrated IOP lowering ranging from 3.4 to 6.8 mmHg in a randomized controlled trial setting[3] to 2 - >10 mmHg when used as adjunctive therapy in a real-world clinical setting.[4]

Topical antiglaucoma medications may induce or exacerbate ocular surface disease, which often coexists with glaucoma patients.[5] Most reported adverse effects of netarsudil involve the ocular surface and are mild, localized, and resolve after weeks of use or with discontinuation. Conjunctival hyperemia is the most common side effect and approximately 40–60 % of patients experience painless conjunctival hyperemia most commonly in the first weeks of use.[1] The ROCKET-1 and ROCKET-2 trials revealed that approximately 13.5–15 % of patients taking netarsudil nightly develop subconjunctival hemorrhage.[6] Instances of reticular bullous epithelial corneal edema with bullae or honeycombing of the corneal epithelium have also been reported causing blurring of the vision, eye pain, and conjunctival injection.[7–11] Visual acuity can also be affected by netarsudil use. Approximately 8.5 % of patients have a reduction in visual acuity that resolves after drug discontinuation and is likely related to dry eye and the subsequent irregular optical refraction in the setting of an abnormal tear film.[12] Moreover, up to 25 % of patients may develop cornea verticillata, which typically does not affect visual acuity and improves with drug discontinuation.[12]

Topical medication-associated crystalline keratopathy is markedly uncommon in patients on ocular hypotensive drops. After conducting a literature review on August 11, 2023, utilizing PubMed, Web of Science, and Google Scholar using the keywords "netarsudil", "crystal," "crystalline," and "cornea," we did not find any prior reports of corneal crystalline keratopathy associated with topical netarsudil use. In this

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report, we describe a possible case of crystalline keratopathy following long-term netarsudil use.

2. Case report

A 72-year-old woman presented with progressive worsening of her left-sided peripheral vision and associated swelling, redness, and intermittent tearing in her left eye. Her visual acuity decreased gradually over several months, and her family noticed that she had become less attentive to objects and people in her left periphery. Her past medical history included dry eye syndrome in both eyes, remote vitreous hemorrhage in the left eye secondary to a retinal detachment, bilateral upper eyelid ptosis, and POAG with mild-to-moderate stage on the right eye and moderate-to-severe stage on the left eye. She had previously undergone laser retinopexy and bilateral ptosis repair surgery with external levator advancement. A Baerveldt® glaucoma drainage device was implanted in the left eye. At the time of presentation, the patient was using preservative-free dorzolamide/timolol twice daily in both eyes, preservative-free tafluprost each night in both eyes, and netarsudil at night in the left eye. The patient had used dorzolamide/timolol for 3 years, preservative-free tafluprost for 3 years, and netarsudil for almost 2 years. Systemic medications included atenolol 35 mg, gabapentin 400 mg, sumatriptan 100 mg, and several supplements including vitamin D3, coenzyme Q, probiotics, collagen, and elderberry fruit.

The patient was notably atopic. She had a history of asthma, systemic allergies, and drug-related allergic conjunctivitis. She had previously discontinued brimonidine due to a follicular reaction. Interestingly, she had also previously trialed and discontinued netarsudil due to ocular irritation several years before restarting the medication.

The patient's best corrected visual acuity during the visit was 20/20 in the right eye without correction and 20/40 + 1 without correction, 20/25 + 1 with the pinhole test in the left eye. Intraocular pressure was 8 mmHg in the right eye and 7 mmHg in the left. Slit lamp biomicroscopy revealed 2–3 mm of ptosis, superficial punctate epithelial erosions, and two arcuate crystalline deposits with overlying superficial punctate keratopathy inferotemporally and superonasally (Fig. 1A–E). Further evaluation of the corneal opacities revealed two semi-elliptical collections of sharply demarcated, branching, needle-like deposits inferotemporally (Fig. 1C and D) and superonasally (Fig. 1E). These deposits were superficial to a white, hazy corneal opacity (Fig. 1A–E). The fellow eye was unaffected (Fig. 1F). There was no anterior chamber cell, flare, or other signs of an intraocular inflammatory process.

The patient was advised to discontinue netarsudil and to continue using preservative-free artificial tears and her other glaucoma medications as previously mentioned. The patient was seen for glaucoma surgery in her right eye within 45 days of discontinuation of netarsudil. At that time, visual symptoms significantly improved discontinuing netarsudil. The corneal findings had improved but were not resolved at that time and left eye intraocular pressure was 5 mmHg. Five months following the discontinuation of netarsudil, the patient was noted to have persistent crystalline keratopathy superiorly and inferiorly in the affected eye. The patient was unable to return for follow-up anterior segment imaging.

3. Discussion

This case highlights an unusual instance of crystalline keratopathy in a patient undergoing netarsudil therapy. Crystalline keratopathy has a wide differential, including infectious crystalline keratopathy often after penetrating keratoplasty, Schnyder corneal dystrophy, Bietti corneoretinal dystrophy, cystinosis, lymphoproliferative disorders, and medication effects.

Drug-deposition keratopathies have a variety of underlying mechanisms. Certain medications are associated with epithelial deposits. These drugs typically produce cornea verticillata, or vortex keratopathy, which has been previously reported with systemic therapies such as cationic amphiphilic drugs amiodarone and chloroquine.[13] The proposed mechanism for crystal deposition in these circumstances is corneal phospholipidosis, where lysosome dysfunction leads to an accumulation of phospholipids in the corneal layers.[14] A similar mechanism underlies crystal deposition in genetic disorders such as Fabry disease or conditions leading to paraproteinemia, such as multiple myeloma. Topical fluoroquinolones are associated with precorneal epithelial and anterior stromal crystallization, likely related to the interplay between the underlying formulation of the drug, and the tear film.[15–17]

Netarsudil is an α-aryl β-amino-isoquinoline amide that is metabolized by ocular esterases to its active metabolite, netarsudil-M1.[18] As previously mentioned, netarsudil is commonly associated with corneal deposits in the form of cornea verticillata. However, clinical trials typically identified asymptomatic cornea verticillata early in use, usually around the one-month mark, although a case of symptomatic cornea verticillata has been reported.[6,19] In this case, the patient had been using netarsudil without consequence for nearly two years.

The mechanism for netarsudil-associated corneal crystalline deposits is uncertain. It is plausible that this mechanism may be similar to the mechanism described for fluoroquinolone-associated deposits, which is supersaturation of the drug after ocular instillation.[15] Netarsudil is used

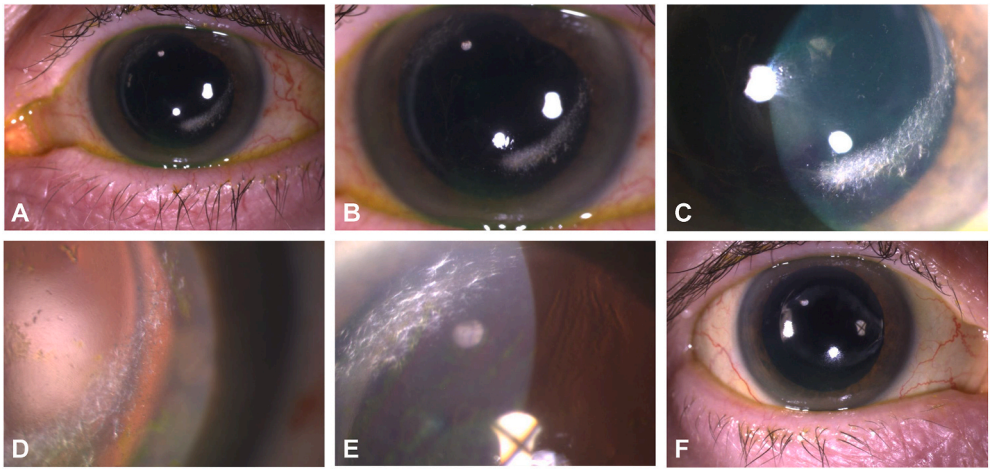

Fig. 1. Demonstration of the patient's corneal findings. Fig. 1A. The external left eye, superonasal and inferotemporal opacities are visualized. Fig. 1B. A closer view of the external left eye, superonasal and inferotemporal opacities are visualized. Fig. 1C. Left eye, inferotemporal opacity. Fig. 1D. Left eye, inferotemporal opacity with retroillumination. Fig. 1E. Left eye, superonasal opacity. Fig. 1F. The patient's unaffected right eye.

in the form of a salt, netarsudil dimesylate, which is a weak acid that is freely soluble in water. The pH of netarsudil 0.02 % ophthalmic solution is approximately 5,[3] less than the tear film's pH of 7.45. Instillation of netarsudil drops naturally shifts the equilibrium toward the solid phase of the drug. Another possible mechanism is related to the effect netarsudil has on the cytoskeleton via modulation of actin dynamics.[20] Notably, fluoroquinolones have also been reported to modulate regulation of the actin cytoskeleton.[21] The patient's underlying abnormal atopy, tear turnover in the setting of dry eye disease, and post-surgical eyelid anatomy may also have contributed to the crystallization.

Long-term use of IOP-lowering eye drops is a known risk factor for glaucoma-related ocular surface diseases.[5] There is no preservative-free netarsudil ophthalmic solution available presently. Therefore, it is challenging to distinguish the specific contribution of netarsudil from that of the preservative, benzalkonium chloride 0.015 %, present in the solution.[22] Boric acid, mannitol, sodium hydroxide, and water are inactive ingredients that are also present in netarsudil solution. However, there are no reported instances of preservative-associated corneal crystallization in the literature despite the widespread use of preservative-containing drops or drops containing the aforementioned inactive ingredients at the time of this publication. Similarly, the patient's symptoms may have been due to crystalline keratopathy from one or more of the glaucoma medications.[23] The corneal deposits observed in the affected eye are unlikely to be associated with the patient's other antiglaucoma medications, namely the preservative-free dorzolamide/timolol and preservative-free tafluprost, which were used in both eyes. Unlike netarsudil, these medications are not known to cause adverse effects to the cornea. It is also important to note that the fellow eye, in which the patient was using all medications except netarsudil, was asymptomatic. Netarsudil was the only drug used uniquely in this patient's affected eye. It is also possible that the deposits were caused by an interaction between different medications, and still in that circumstance it would be likely that netarsudil would be the necessary factor to result in such corneal deposits.

While the patient's keratopathy did not affect the central cornea, the potential risk of progression, worsening visual acuity, peripheral vision decline, and the prospect of devastating sight loss prompted our recommendation to discontinue netarsudil. Subsequently, over the following weeks, there was an improvement in the patient's visual symptoms and keratopathy. However, complete resolution did not occur within the several months of follow-up following discontinuation. This case may be an example of the persistence of some netarsudil-induced changes. Previous studies have observed that adverse effects of netarsudil, such as cornea verticillata, and even active effects like IOP reduction, can persist for months after stopping the medication.[6]

4. Conclusion

This is a case of a 72-year-old woman managed long-term with netarsudil ophthalmic solution for POAG who presented with crystalline keratopathy. This case demonstrates the potential link between long-term netarsudil use and crystalline keratopathy in glaucoma patients receiving topical netarsudil therapy.

Patient consent

Written consent from the patient regarding the publication of this case report and the associated images has been obtained and retained by the study authors.

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CRediT authorship contribution statement

Olivia W. Cummings: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Jesús M. Meléndez-Montañez:** Conceptualization, Investigation, Writing – original draft. **Leah Naraine:** Project administration. **Leyla Yavuz Saricay:** Investigation, Supervision, Writing – review & editing. **Hani El Helwe:** Project administration. **David Solá-Del Valle:** Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

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