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Netarsudil-associated conjunctival pigmentation

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ABSTRACT

Purpose: To present a case of conjunctival pigmentation associated with topical use of netarsudil 0.02 % (Rhopressa, Alcon, Fort Worth, TX).
Observation: Bilateral conjunctival pigmentation and cornea verticillata developed after 21 months of initiating netarsudil treatment. The appearance of the conjunctival pigmentation mimicked primary acquired melanosis. Both the conjunctival and corneal findings resolved 14 months after stopping the medication.
Conclusion: While the correlation between netarsudil use and corneal verticillata is well-established, we could not identify prior reports of such an association with conjunctival pigmentation. Eye care professionals prescribing netarsudil should be aware of this potential sequela of therapy.

1. Introduction

Glaucoma is one of the leading causes of blindness worldwide.[1] Current treatments for glaucoma are focused on lowering intraocular pressure (IOP) through the use of medications, lasers and/or invasive surgical techniques. Netarsudil 0.02 % (Alcon, Fort Worth, TX) is a relatively recent addition to the arsenal of topical medications used to treat glaucoma and ocular hypertension.[2–5] Netarsudil is a rho kinase (ROCK) inhibitor which lowers IOP by increasing aqueous humor outflow through the trabecular meshwork along with other potential mechanisms of action.[3] Its efficacy in regards to IOP lowering has been supported by numerous trials including the pivotal ROCKET trials.[6–8]

The most commonly reported adverse effects include conjunctival hyperemia and edema, corneal verticillata, subconjunctival hemorrhage, decreased or blurred vision, increased lacrimation, eye pain and eyelid erythema or edema.[6] Few systemic adverse effects have been reported.[8] While not observed in initial trials, reticular epithelial corneal edema has also been reported in some eyes exposed to netarsudil.[9,10]

We present the case of a 70-year-old man with primary open angle glaucoma (POAG) who developed bilateral conjunctival pigmentation 21 months after starting netarsudil.

2. Case report

A 70-year-old Caucasian man with POAG (moderate left eye, mild right eye) presented with inadequate IOP control and evidence of glaucomatous progression. Netarsudil qhs was added to his current regimen of latanoprost 0.005 % qhs bilaterally given documented intolerance to all other topical agents and patient desire to avoid laser procedures. At 6 week follow up, IOP decreased, and he was asked to continue therapy without changes. At subsequent follow-up 11 months after initiation of netarsudil, bilateral corneal verticillata was noted without associated visual sequelae. No pertinent corneal findings were noted at any follow-up visits prior to this time. As instructed, he was monitored 3–4 times per year and aside from worsening corneal verticillata, no changes were noted at these visits. At 21 months after netarsudil initiation, new speckled pigment at the temporal limbus in the right eye (Fig. 1), and temporal limbus pigmentation that extended onto the bulbar conjunctiva in the left eye (Fig. 2) was first noted. Pigmentation was also noted along the interpalpebral conjunctiva nasally in the left eye. The patient's current and past medical and surgical history, social and family history and medication list were reviewed at this time and no identifiable etiologies for these findings were found. His medications included only his two ocular medications and lisinopril. Further, he denied any history of amlodipine usage. Given the symmetry bilaterally, and interpalpebral and limbal location of this

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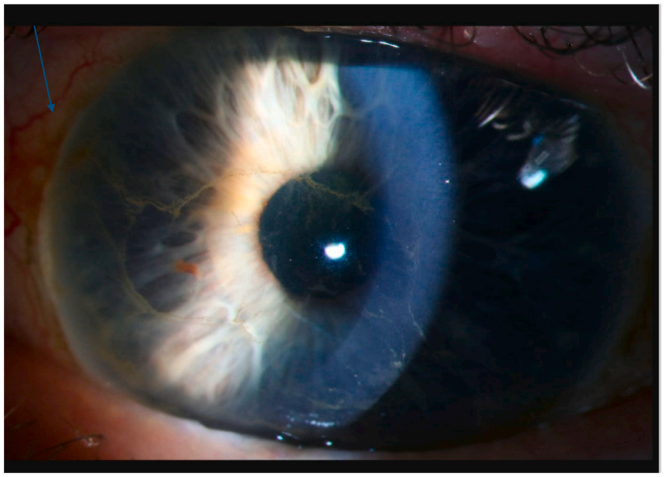

Fig. 1. Slit lamp photo right eye with dense corneal verticillata and limbal conjunctival pigmentation temporally (blue arrow) extending 8 o'clock to 11 o'clock. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

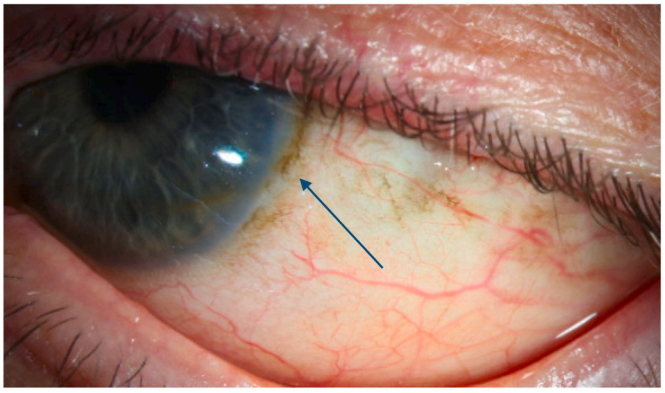

Fig. 2. Slit lamp photo of left eye with conjunctival pigment along temporal limbus (blue arrow) and bulbar conjunctiva. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

pigmentation, we questioned whether this was secondary to netarsudil rather than new onset bilateral primary acquired melanosis (PAM). The patient was offered netarsudil cessation and monitoring versus conjunctival biopsy and chose the former. Selective laser trabeculoplasty was then successfully performed for IOP control.

Six months post-cessation of netarsudil, conjunctival pigmentation and corneal verticillata were less prominent (Figs. 3 and 4). Fourteen months after cessation, both conjunctival pigmentation and corneal verticillata had fully resolved (Figs. 5 and 6). No pigmentary findings have recurred during the subsequent 2-year follow-up off netarsudil.

3. Discussion

Netarsudil 0.02 %, a novel medication to manage glaucoma and ocular hypertension, became available in 2017.[11] This rho kinase/norepinephrine transporter inhibitor is thought to work via multiple mechanisms: increasing outflow facility by means of ROCK inhibition, decreasing aqueous production via norepinephrine transporter inhibition, and decreasing episcleral venous pressure.[8]

Initial data from a small, double blinded randomized study of netarsudil (0.01 % vs. 0.02 %) compared with latanoprost in patients with elevated IOP demonstrated netarsudil's efficacy in reducing IOP in

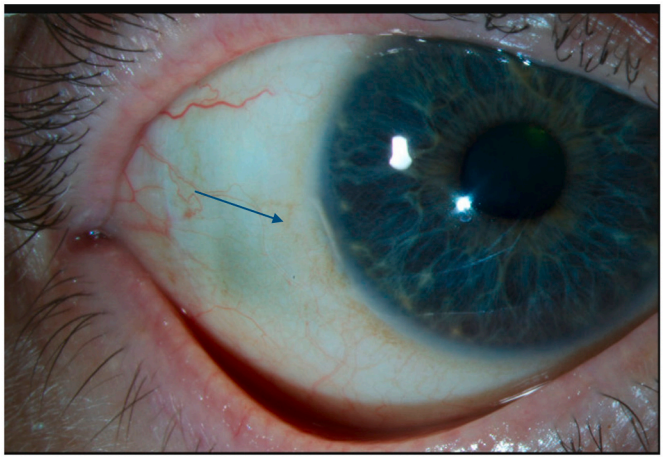

Fig. 3. Slit lamp photo of right eye 6 months after cessation of netarsudil demonstrating conjunctival pigment is less dense (blue arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

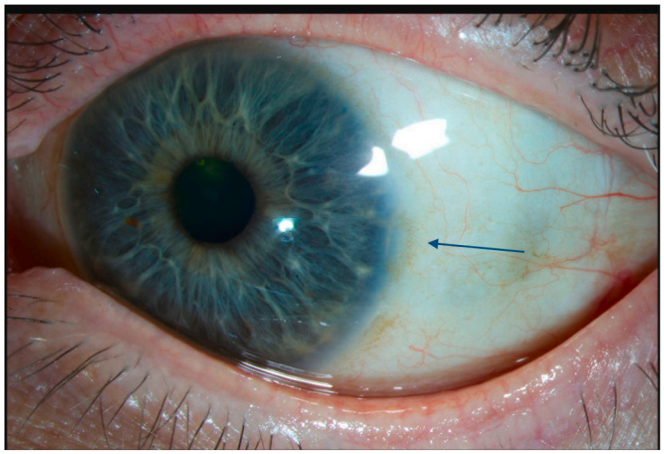

Fig. 4. Slit lamp photo of left eye 6 months after cessation of netarsudil demonstrating conjunctival pigment is less dense on the temporal limbus and conjunctiva (blue arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

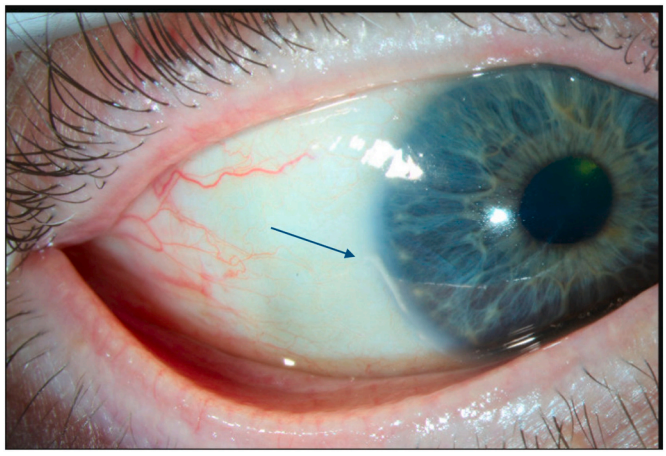

Fig. 5. Slit lamp photo of right eye 14 months after cessation of netarsudil drops demonstrating resolution of corneal verticillata and conjunctival pigmentation (blue arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

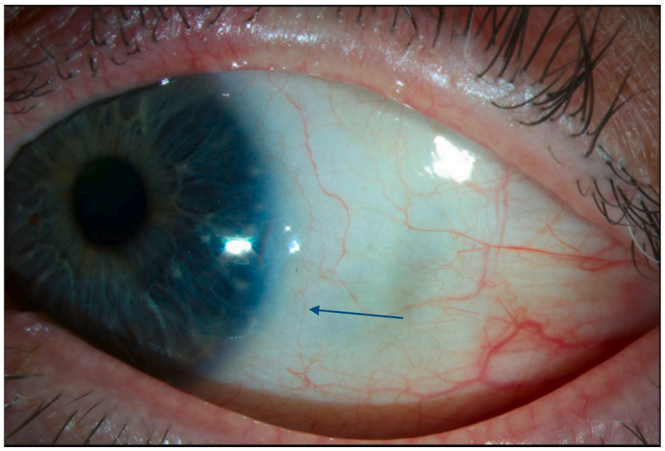

Fig. 6. Slit lamp photo of left eye 14 months after cessation of Netarsudil drops demonstrating resolution of corneal verticillata and conjunctival pigmentation (blue arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

patients with POAG and ocular hypertension (OHT).[8] The most common adverse effect noted in that study was ocular hyperemia, seen more commonly at both dosages of netarsudil when compared to latanoprost.[12] The subsequent landmark ROCKET1 and ROCKET2 trials demonstrated netarsudil 0.02 % ophthalmic solution was non-inferior to timolol in patients with POAG and OHT with a baseline IOP <25 mmHg.[13]

Though generally well-tolerated, the most common associated adverse effects are conjunctival hyperemia (50–53 %), conjunctival hemorrhage (13–15 %), corneal verticillata (5–9 %), corneal staining (4 %), decreased visual acuity (4 %), and increased lacrimation (4–5 %).[13,14] Since the initial clinical trials, case reports have also documented netarsudil induced corneal epithelial edema.[15–18] Recently, crystalline keratopathy in a patient on long-term netarsudil has also been reported.[19]

While our patient did not experience corneal edema, conjunctival hyperemia, or hemorrhages, he did develop corneal verticillata as well as conjunctival pigmentation bilaterally. A conjunctival pigmentation reaction has not previously been documented in the literature. Further, this patient was Caucasian therefore the pigmentation changes were relatively easily identifiable. However in more darkly pigmented individuals, those more likely to have complexion-associated melanosis (CAM), it is possible this netarsudil induced pigmentation is occurring but is masked by CAM which similarly usually presents near the limbus.[20] Compared to PAM which is typically unilateral (87 %) or asymmetric when bilateral, this patient had symmetric pigmentation bilaterally following bilateral use of netarsudil.[20] Further, the coloration of the conjunctival pigment matched that of the corneal verticillata (Fig. 7). PAM or melanotic pigment would commonly be tan or brown, flat and less speckled in appearance when compared to our findings.[19,20] Additionally, his pigmentation was focused primarily at the limbus, with some extension onto the bulbar conjunctiva with sparing of the palpebral conjunctiva. While PAM can occur at the limbus or on the cornea, its primary location is the bulbar conjunctiva (91 %).[21] Because this patient is Caucasian, the pigment may have been more obvious to the provider. It is interesting to note that the conjunctival pigment had an almost one-year delayed presentation compared to the corneal findings. The underlying etiology of netarsudil induced conjunctival pigmentation is unknown. Netarsudil induced corneal verticillata is proposed secondary to netarsudil induced phospholipidosis within the corneal epithelial cells.[22] In contrast, prostaglandin analogs, which are well documented to induce iris darkening in some patients, are thought to induce an increase in melanin content or melanin granule size within a melanocyte.[23] As with previous reports of verticillata resolution with drug

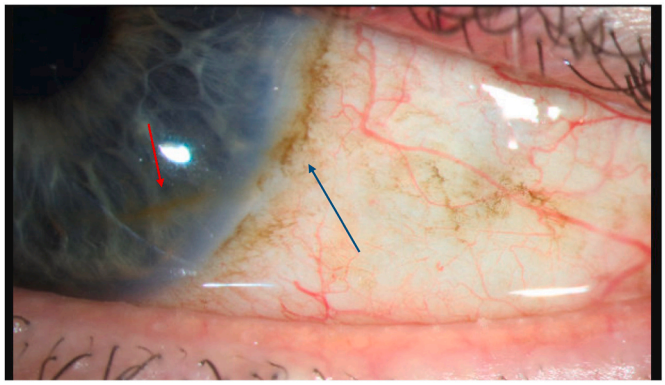

Fig. 7. Slit lamp photo from initial evaluation demonstrating conjunctival pigment (blue arrow) is consistent in color with corneal verticillate (red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cessation, both the conjunctival pigment and verticillata resolved with medication cessation.

4. Conclusions and importance

This case describes a patient who developed bilateral conjunctival pigmentation in addition to corneal verticillata after almost two years of netarsudil use for POAG. The conjunctival pigmentation was somewhat concerning in appearance for PAM, but fully resolved within 14 months of drug cessation and therefore was consistent with a drug related effect instead. There were some subtle differences between the conjunctival pigmentation of this patient compared with other pigmented conjunctival lesions, one of which is the symmetry of pigment in each eye. However, for patients using rho-kinase inhibitors unilaterally, this will not be a reliable indicator. In patients using a Rho-kinase inhibitor who subsequently develop conjunctival pigmentation, thought should be given to medication cessation and close monitoring in low-risk cases prior to conjunctival biopsy or excision.

Claims of priority

After conducting a literature review on (12/08/2024) utilizing PubMed using the key words “netarsudil,” “Rhopressa,” in combination with “conjunctival pigment,” “conjunctival pigmentation,” and “primary acquired melanosis”, we did not find any prior reports of conjunctival pigmentation associated with Netarsudil.

CRediT authorship contribution statement

Soufiane Azargui: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Joana Karanxha:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Scott CN. Oliver:** Writing – review & editing, Formal analysis. **Malik Y. Kahook:** Writing – review & editing. **Cara E. Capitena Young:** Writing – review & editing, Formal analysis, Conceptualization.

Patient consent

Written and verbal 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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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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