



Corneal thinning following bevacizumab intrastromal injection for the treatment of idiopathic lipid keratopathy

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ARTICLE INFO

Keywords:

Corneal thinning
Bevacizumab injection

ABSTRACT

Purpose: To describe the occurrence of corneal thinning in a patient following intrastromal injection of bevacizumab to treat lipid keratopathy.

Observations: A 36-year-old female presented with decreased vision in her right eye with central posterior corneal haze and underwent a treatment regimen including artificial tears, cyclosporine 0.05% drops, prednisolone 1% and oral Valacyclovir 1g with no improvement. Neovascularization was noted at 18 months follow up and treated with intrastromal bevacizumab injections at 24 months. The feeder vessel was attenuated at 3- and 6-months post-injection, but tomography indicated sustained thinning and flattening of the cornea at the injection site contributing to the development of irregular astigmatism.

Conclusions and Importance: Corneal thinning is an uncommon potential side effect of intrastromal bevacizumab injection that may affect postoperative visual acuity.

1. Introduction

The cornea is characterized by a lack of blood vessels and lymphatics, ensuring its transparency and immune privilege. Its avascular properties are maintained through a fine balance of angiogenic and antiangiogenic cellular mechanisms.¹ In disease conditions, such as inflammation, trauma, or hypoxia, this homeostasis can be disturbed leading to corneal neovascularization (CNV) with secondary hemorrhage, lipid deposition, and scarring.² Multiple treatment modalities have been studied including topical steroids, argon laser vessel ablation, and fine needle diathermy.^{3,4} Vascular endothelial growth factor (VEGF) has been found to be a key factor in the development of CNV, and has been a popular target for CNV treatment modalities.^{5,6} Bevacizumab (Avastin; Roche, Weyln Garden City, UK) is a recombinant humanized monoclonal antibody that binds the VEGF-A isomer, and is widely regarded as a safe and effective treatment for choroidal neovascularization. Since then, limited publications have described outcomes of treatment of CNV with topical, subconjunctival, and intrastromal bevacizumab with variable outcomes.⁶⁻¹¹ While generally regarded as a safe treatment, the literature lacks good description of complications of bevacizumab administration in the cornea. In this report, we describe the occurrence of corneal thinning, a newly

described complication, following intrastromal injection of bevacizumab for lipid keratopathy.

2. Case report

A 36-year-old female was referred for evaluation of progressively decreased vision in her right eye. On presentation, the patient complained of onset of symptoms one year prior. She had a history of migraines that are controlled with topiramate. Aside from being a daily contact lens wearer for the past 20 years, she had no other past ocular history of eye infection or previous eye surgeries. She had no known family history of corneal diseases or dystrophies.

At presentation, her corrected distance visual acuity (CDVA) was 20/30 in the right eye (OD) and 20/20 in the left eye (OS). Her intraocular pressures were normal. On slit lamp examination of the right eye, the eye was noted to be quiet with no signs of inflammation. The corneal epithelium and anterior 2/3 of the stroma were clear. A diffuse posterior haze spanning the central cornea and sparing the periphery was noted (Figs. 1 and 2). The anterior chamber was quiet. The iris did not exhibit synechiae or *trans*-illumination defects on retroillumination. The left eye examination was unremarkable. The patient was started on a trial of artificial tears, cyclosporine 0.05% drops twice a day, prednisolone 1%

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<https://doi.org/10.1016/j.ajoc.2022.101618>

Received 13 December 2021; Received in revised form 9 June 2022; Accepted 12 June 2022

Available online 24 June 2022

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Fig. 1. 2017 Right Eye (OD) Slit Lamp (SL) Photography demonstrating diffuse posterior stromal haze.

drops three times a day and oral Valacyclovir 1g twice a day with little improvement over the following 6 months. At the 18 months follow-up visit, a fine, deep, neovessel was noted at 8 o'clock, which was believed

to be contributing to the posterior haze. The patient was asked to limit contact lens wear to 8 hours a day, but the haze continued to worsen. At her 2-year follow-up, CDVA decreased to 20/100 in the right eye.

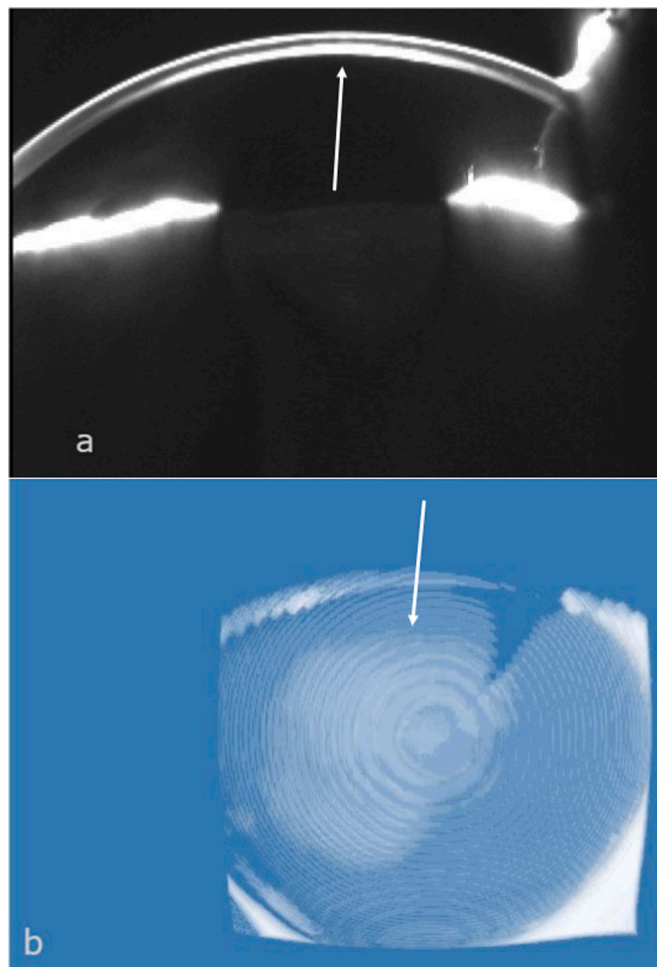


Fig. 2. (a) Scheimpflug image with arrow pointing to posterior high reflectivity opacity and (b) Tomography of source Scheimpflug cross-sectional images resulting in en face view of the opacity in the central and temporal midperipheral cornea.

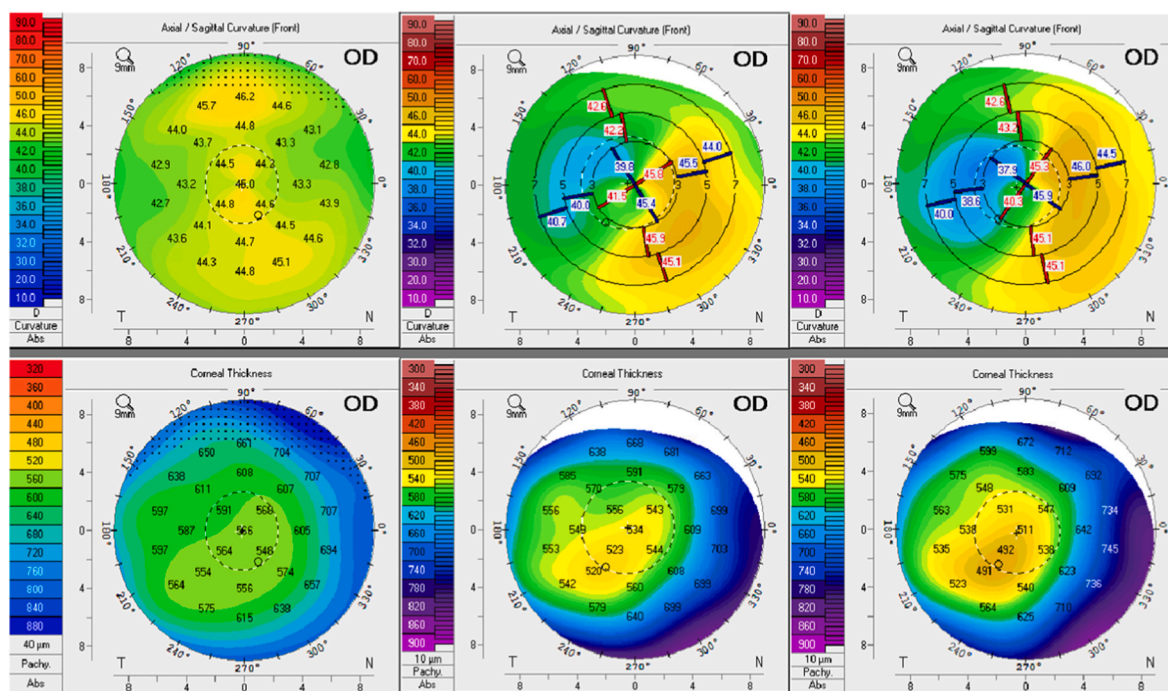


Fig. 3. 2017, 2019 and 2021 (Right to Left) OD tomographic (Pentacam) maps demonstrating progressive flattening and thinning over the area of posterior haze.

Given the persistence of the deep feeder vessel and worsening premed lipid keratopathy, it was decided to proceed with intrastromal bevacizumab injections to obliterate the vessel. After patient consent was obtained, the patient was anesthetized with proparacaine hydrochloride and the ocular surface was disinfected with 5% povidone iodine solution. With a 30G needle, 0.1 cc of bevacizumab 25mg/ml was injected at the corneal limbus close to the feeder vessel. During the procedure, a blanching of the vessel was noted. The patient tolerated the procedure well. She was placed on a post-operative regimen of ofloxacin 0.3% four times per day for four days, and instructed to continue prednisolone 1% drops two times a day.

Three months following the injection, the patient’s vision deteriorated further to 20/200. Slit lamp exam revealed attenuation of the feeder vessel but no improvement in the posterior haze. Tomography revealed irregular astigmatism over the intrastromal injection site causing a 60 μm decrease in corneal thickness (Fig. 3). Pentacam Scheimpflug imaging revealed a diffuse hyperreflectivity in the posterior cornea, representing the area of haze (Fig. 4). At 6 months post-operatively, the patient’s vision improved to the pre-injection baseline of 20/100 and the haze was found to be less dense. However, tomography still showed irregular astigmatism contributing to decreased vision. She was referred for RGP lens fitting but experienced minimal improvement in vision presumably due to the remaining stromal haze. At her last visit, the patient was engaged in a discussion about possible full thickness or deep anterior lamellar corneal graft to improve her vision.

3. Discussion

Lipid keratopathy is a condition classified by lipid deposits in the cornea that result in corneal opacification.^{3,12} There are two recognized etiologies of lipid keratopathy: idiopathic, which is spontaneous, and secondary, due to neovascularization, inflammation, trauma or other systemic disease of the eye (e.g., herpes, interstitial keratitis).^{3,13,14}

Bevacizumab is known to bind VEGF, preventing VEGF from binding to its endothelial cell surface receptors. This inhibits angiogenesis, as well as potentially reducing existing abnormal vasculature.¹⁴ Due to bevacizumab’s ablative properties, we propose a potential mechanism to explain the corneal thinning: after vessel regression, edema may be resorbed. The expected result is a return to baseline corneal thickness, but if accompanied by subsequent resorption of collagen or other corneal structural tissue, ablation resulting from intrastromal bevacizumab injection may result in secondary local thinning and the development of astigmatism. An inflammatory process or ulceration is less likely, since no epithelial defect was noted after injection. However, this conclusion is limited by the solitary nature of this case report. We recommend caution when considering use of intrastromal bevacizumab injection due to the possibility of corneal thinning. Alternative modalities to treat neovascularization, such as laser ablation and topical steroids, may be more appropriate initial considerations.

To conclude, intrastromal and subconjunctival bevacizumab injection has been recommended in the literature as a safe and generally effective way to address corneal neovascularization. Occasionally temporary side effects have been noted, but thus far no long term or systemic side effects have been described. There have been no documented associations between bevacizumab injection and corneal thinning or flattening. Potential underreporting of this phenomenon may be related to eyes with lipid keratopathy often having poor visual potential due to other comorbidities (multiple prior surgeries, retina or glaucoma issues, etc.), thus making visual changes due to corneal thinning and irregular astigmatism less noticeable. In our case, the patient had normal visual potential. This case presents the first known documentation of an intrastromal bevacizumab injection resulting in corneal thinning and flattening. The mechanisms underlying the observed effects are still unclear, and require further examination. In the meantime, caution should be applied when considering treatment modalities to address corneal neovascularization and lipid keratopathy, particularly for eyes with otherwise normal visual potential.

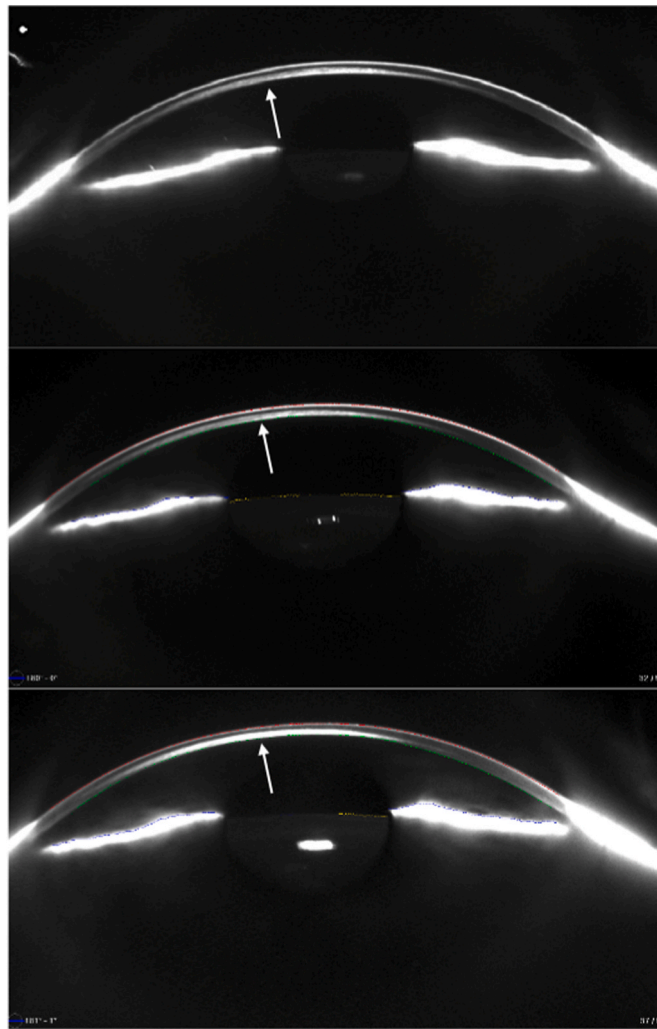


Fig. 4. 2017, 2019 and 2021 (Top to Bottom) Pentacam scheimpflug demonstrating the area of haze.

Patient consent

This report does not contain any personal information that could lead to the identification of the patient.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: KS, AJ, KB, DD, SJ.

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