American Journal of Ophthalmology Case Reports 20 (2020) 100856

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

A corneal ring ulcer

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ARTICLE INFO

Keywords:
Cornea
Neurotrophic ulcer
Acanthamoeba keratitis
Ring ulcer
Cenegermin

ABSTRACT

Purpose: The aim of this report is to present the case of a corneal ring ulcer that presented with diagnostic and therapeutic challenges.
Observations: A 52-year-old woman was referred by her retina doctors for ulceration of the left cornea and pain 8 days after intravitreal ranibizumab injection for diabetic macular edema. She had been treated with erythromycin ointment, topical moxifloxacin, and therapeutic soft contact lens, which she tolerated for less than 24 hours prior to referral. Visual acuity of the left eye was counting fingers. Slit lamp examination revealed a ring-shaped corneal ulcer.
Conclusions: Neurotrophic corneal ulceration can mimic acanthamoeba keratitis. Neurotrophic disease should be considered in patients with underlying risk factors in whom infectious etiology cannot be confirmed and/or who don't respond to anti-microbial therapy.

1. Introduction

Neurotrophic Keratopathy is a degenerative corneal condition caused by impaired sensory innervation. This condition can result in impaired protective lacrimal and blink reflexes, epithelial breakdown, delayed epithelial healing and corneal ulceration. Common etiological factors include: a history of HSV or VZV infection, diabetic neuropathy, extensive pan-retinal photocoagulation and topical anesthetic abuse.[1] Symptoms and signs are mild and nonspecific initially, but can progress into non-healing epithelial defects with rolled epithelial edges, corneal edema, and Descemet's membrane folds. If not treated appropriately, infection or sterile stromolysis may develop, leading to ulceration, descemetocele, perforation, loss of vision and loss of the eye.[2] This report presents a case of neurotrophic keratopathy that presented as a ring-shaped corneal ulcer. We discuss the diagnostic challenges and therapeutic options, and review the treatment chosen and outcome.

2. Case report

A 52-year-old woman was referred by her retina doctors for cornea ulceration and pain 8 days after intravitreal ranibizumab injection for diabetic macular edema. She had been treated with erythromycin ointment, topical moxifloxacin, and therapeutic soft contact lens, which she tolerated for less than 24 hours prior to referral.

On initial presentation to our clinic, the left eye visual acuity was count fingers. Slit lamp examination is depicted in (Fig. 1A and B). Corneal smears and cultures, including those to identify atypical pathogens, were obtained. Confocal microscopy showed only possible double-walled cysts in two images from one sequence.

The patient was started on fortified vancomycin and tobramycin, topical chlorhexidine and oral valacyclovir. Cultures and smears were all negative. Fortified antibiotics were discontinued after 2 weeks, and ofloxacin 0.3% 4x/day and polymyxin/bacitracin ointment nightly were substituted. Slit lamp examination three weeks after the treatment initiation is depicted in (Fig. 1C). Repeat smears and cultures at 3 and 5 weeks were negative, as was confocal microscopy.

At 6 weeks, acanthamoeba keratitis was excluded and chlorhexidine was discontinued. The ring infiltrate had not changed in size and appearance. At this point, a presumptive diagnosis of neurotrophic ulcer was made. Ofloxacin, polymyxin/bacitracin ointment and lid taping were continued and topical loteprednol 0.5% twice daily was added. An in-office trial of a therapeutic soft contact lens with brand and parameters different from what was previously tried was again intolerable to the patient.

Ten days later, the epithelial defect healed with modest symptomatic relief, but a 3 × 4mm recurrence was noted at examination 9 days later (Fig. 1D).

The patient was then treated with topical cenegermin, 6x daily,

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https://doi.org/10.1016/j.ajoc.2020.100856
Received 8 October 2019; Received in revised form 14 July 2020; Accepted 17 July 2020
Available online 5 August 2020

which was well tolerated and led to symptom reduction, decreased central ring density/opacity and closing of the epithelial defect. One week after an 8-week course of cenegermin, vision was 20/400, the epithelium remained intact, and ring and stromal opacities were reduced (Fig. 2). The epithelium remained intact at subsequent examinations, the most recent occurring 16 weeks after cessation of cenegermin therapy.

3. Discussion

The initial presentation of a ring-shaped corneal stromal infiltrate with overlying epithelial defect and pain, along with prior use of a therapeutic contact lens and suspicious confocal microscopy, suggested acanthamoeba keratitis as a plausible diagnosis, particularly to the less experienced clinicians evaluating her on an urgent basis. Pseudomonas infection, which can also present as a ring ulcer, was also in the differential for this presentation, but there was the lack of suppurative discharge and lack of early growth on cultures. Given the failure of response to treatment, appreciation that ring-shaped corneal stromal infiltration is only a late manifestation of acanthamoeba keratitis,[3] and negative subsequent smears, cultures, and confocal microscopy, anti-amoebic therapy was stopped.

At that point, a diagnosis of neurotrophic keratitis was made. This was based on a history of diabetes, a history of PRP and a history of anti-VEGF injections, shown recently to reduce corneal nerve parameters identified by *in vivo* confocal microscopy.[4] The following treatment options were considered:

1. Hospital admission for anesthetic abuse
2. PROSE scleral lens or self-retaining amniotic membrane graft
3. Lateral tarsorrhaphy
4. Topical cenegermin (rhNGF)

A diagnosis of anesthetic abuse can be difficult to establish. Topical anesthetic has toxic effects on corneal epithelium and can predispose to neurotrophic keratitis.[5] Hospital admission for observation with monitoring of occlusive dressing could help to exclude a possibility of anesthetic abuse. The patient refused admission.

PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) treatment has shown efficacy in healing persistent epithelial defects by maintaining an improved environment at the ocular surface.[6] Sutureless amniotic membrane grafting, such as Prokera®, can accelerate corneal epithelial defect healing by promoting epithelial cell migration and differentiation, suppressing inflammatory mediators and preventing angiogenesis.[7] The patient refused these options after failing to tolerate trial of two different brands and parameters of bandage contact lens by the retina specialists and trial of yet a third type of bandage contact lens in the office of the cornea consultant.

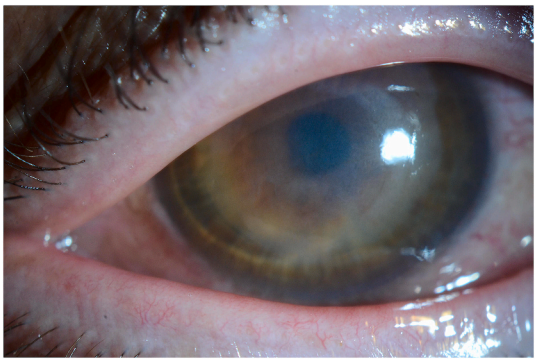

Fig. 2. Slit lamp photograph of the left eye after completing the course of Cenegermin (rhNGF). This image was taken 8 weeks after treatment with cenegermin, and depicts intact epithelium and markedly reduced ring and stromal opacities.

Lateral tarsorrhaphy is an effective surgical approach for neurotrophic ulcers refractory to medical treatment. One study has shown that tarsorrhaphy may achieve healing of 90.9% of epithelial defects within 18 days.[8] This patient was resistant to the concept of lateral tarsorrhaphy. Furthermore, lateral tarsorrhaphy may limit retinal examination in a patient recently treated for proliferative diabetic retinopathy. The patient agreed to and adhered to lid taping, but this was insufficient for healing.

Autologous serum tears have long been utilized for both persistent epithelial defects and for neurotrophic keratopathy, but were not considered for this patient who was thought to be at high risk of superinfection. It is believed that various epithelial growth factors

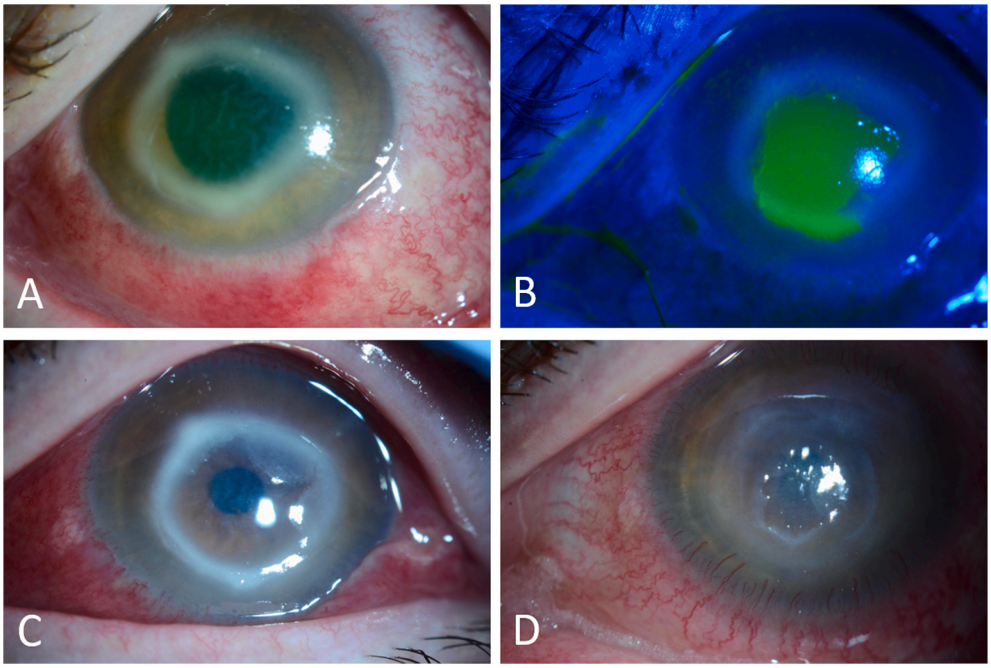

Fig. 1. Slit lamp photographs of the left eye demonstrating the clinical course of the case. (A,B) are the digital images taken during the initial presentation, which show a corneal ring ulcer of 5 × 5 mm, central epithelial defect of 3 × 3 mm stained with fluorescein, and surrounding chemosis and corneal edema. (C) Image was taken 3 weeks after the initiation of anti-amoebic therapy, without noticeable improvement. (D) Image demonstrates the recurrence of the epithelial defect with a size of 3 × 4 mm, at 10 weeks after presentation and 9 days after the epithelial defect had healed.

contained in serum including epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-B (TGF-b), fibroblast growth factor (FGF), fibronectin, substance P, insulin-like growth factor (IGF), and nerve growth factor (NGF) play a role in neural and ocular surface healing.[9,10]

Nerve growth factors (NGF) were first discovered in 1950s.[11] Cenegermin is a recombinant human NGF, which acts on TrkA (high affinity) and p75NTR (low affinity) NGF receptors and is approved for the treatment of neurotrophic keratitis.[12] When used topically 6 times daily for 8 weeks duration, cenegermin was shown to promote complete corneal epithelial healing in up to 74% of neurotrophic keratitis ulcers, with 96% remaining healed after a duration of one year.[12] Giving its effectiveness and safety profile, and having excluded the remaining 3 treatment options, we decided to initiate a course of cenegermin. It may be relevant that this patient suffered from peripheral neuropathy of lower extremities related to her diabetes, suggesting susceptibility elsewhere.

In this case of neurotrophic ulcer, the pain that the patient experienced on presentation is somewhat paradoxical. As noted in the TFOS DEWS II Pain and Sensation Report: the "Perpetuation of molecular, structural and functional disturbances in ocular sensory pathways ultimately leads to dysesthesias and neuropathic pain referred to the eye surface."[13] Indeed, some diabetics have neuropathic pain in the same leg that they develop diabetic neuropathy and foot ulcers. Overall, the mechanism of neuropathic keratopathy and pain is poorly understood.

We suggest that the rapid appearance of the ring ulcer might be related to altered vascular permeability and wound healing from the combination of diabetes and the VEGF inhibitor.

4. Conclusions

We report a case of neurotrophic keratitis mimicking acanthamoeba keratitis. Neurotrophic disease should be considered high in the differential diagnosis in ulcer patients with underlying risk factors in whom infectious etiology cannot be confirmed and/or who don't respond to anti-microbial therapy, and in any patient with longstanding diabetes with corneal surface issues. Cenegermin is a new and useful therapeutic option for neurotrophic keratitis, resulting in durable healing response in this diabetic patient who developed corneal ulceration after intravitreal anti-VEGF injection.

Patient consent

Informed patient consent was obtained in writing for publication. This case report does not contain any personal identifying information.

Funding

No finding or grant support.

Authorship

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

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Declaration of competing interest

No conflicting relationship exists for any author.

Acknowledgements

None.

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