## Late-onset diffuse lamellar keratitis after treatment with cenegermin

Cenegermin 0.002% ophthalmic solution (Oxervate, Dompe, Boston, Mass.) is a recombinant human nerve growth factor (NGF) that has been a promising novel topical treatment dosed 6 times daily for 2 months to treat neurotrophic keratitis (NK).[1,2] NK is a degenerative ocular disease characterized by reduced or absent corneal sensation. One iatrogenic etiology of NK, for which cenegermin has garnered interest, is after laser in situ keratomileusis (LASIK).[3]

Diffuse lamellar keratitis (DLK) is a well-documented noninfectious inflammatory reaction that presents as a white, granular cellular infiltrate in the flap interface usually within 1−5 days after LASIK.[4] Late-onset DLK also has been reported months to years after LASIK typically induced by anterior-segment inflammation, such as epithelial defects, trauma, and uveitis.[5] Herein we present a unique case of late-onset DLK after cenegermin initiation.

A 77-year-old female with a history significant for Sjögren's syndrome dry eye OU, LASIK OD 19 years prior, conductive keratoplasty OS, pseudoexfoliation syndrome OU, and herpes simplex virus (HSV) keratitis OU developed a persistent epithelial defect (PED) OD related to NK (0% corneal sensation in all quadrants and centrally by Q-tip wisp). Of note, the patient had had recent complex cataract surgery OD (3 months prior) requiring 5 iris hooks for pupil expansion and developed both ocular surface decompensation and HSV keratitis postoperatively.

The PED failed to resolve with generous lubrication, chronic bandage contact lens placement, tape tarsorrhaphy, amniotic membrane extract eye drops bid (Regener-Eyes Ophthalmic Solution, Regener-Eyes, Palm Harbor, Fla.), and dehydrated amniotic membrane (AmbioDisk, IOP Ophthalmics Inc, Costa Mesa, Calif.). After 2 months of a nonhealing 5 × 6 mm PED, the patient was started on topical cenegermin 6 times daily (in the off-label setting with a bandage contact lens). The patient remained on valacyclovir and topical trifluridine at the time. She was also on aggressive preservative-free tears, prednisolone twice daily (tapering from previous HSV episode), tobramycin tid, and cyclosporine tid.

Five days after starting cenegermin, the patient presented with increasing ocular pain, photophobia, tearing, and periocular erythema. Examination revealed +1−2 conjunctival injection, an 8 × 8 mm epithelial defect, and grade 2 DLK, worse inferiorly and superiorly (Figs. 1 and 2). Cenegermin was decreased to tid as tolerated, and topical prednisolone was held due to the worsened epithelial defect (Fig. 2A). To treat the DLK, a subconjunctival dexamethasone injection was administered, and 40 mg of oral prednisone was started. Over the next 2 weeks, the epithelial defect healed and the DLK regressed. The cenegermin was slowly increased to the usual recommended 6 times daily dose. Treatment was extended past 8 weeks because of the decreased frequency initially. Cenegermin was discontinued when the patient developed an ocular ache after 3 additional weeks, but this resolved over time after her cenegermin course was completed (Supplementary Fig. 3, available online). The patient has maintained an epithelized surface with more than 9 months of follow-up. Corneal sensation improved, with intact sensation in 3 quadrants and centrally. Epithelialization, albeit with dryness, was maintained during a trial of bandage lens removal; however, the patient has requested the bandage lens for now because it provides improved comfort.

We present a case of late-onset DLK following cenegermin initiation for multifactorial NK (HSV, LASIK, iatrogenic—multiple cataract surgery incisions). While disruption of the corneal epithelium most commonly leads to late-onset DLK, any anterior-segment inflammation can incite DLK, enabling leukocyte spread via the path of least resistance, the flap interface.[5] Because DLK often presents within 1−5 days of the inciting factor,[3] the original epithelial defect of greater than 2 months' duration is unlikely to have been the inciting factor of DLK in our patient's case. Similarly, it is unlikely that the DLK was triggered by HSV reactivation because the patient's HSV had fully resolved, she was still on oral and topical antiviral treatment, and NGF has potent antiviral properties.[6] The clinical change in our patient was more consistent with DLK, a sterile inflammatory infiltrate, rather than an acute infectious process.

Treatment for late-onset DLK is less well defined than that for acute-onset DLK given the relative infrequency of presentation.[5] In general, aggressive treatment with oral and topical corticosteroids is considered before lifting the LASIK flap, especially for stages I−III, as long as infection is not suspected and inciting debris or focal aggregates are not seen in the interface. Although our patient presented with stage II DLK, for which topical corticosteroids are typically the initial treatment, we proceeded with systemic and periocular corticosteroid treatment to avoid frequent topical corticosteroids and potential HSV reactivation. The dose of cenegermin was also reduced to help the patient tolerate administration. It is unclear if this helped with resolution of the DLK, but the dosing was eventually escalated to the recommended 6 times daily.

While cenegermin is often perceived as "epitrophic," NGF itself has both anti-inflammatory and proinflammatory effects.[6,7] Nerve regeneration may be partially attributable to neurogenic inflammation.[6] NGF has been shown to both enable the budding of additional nerve terminals and initiate immunologic and inflammatory cascades. In patients

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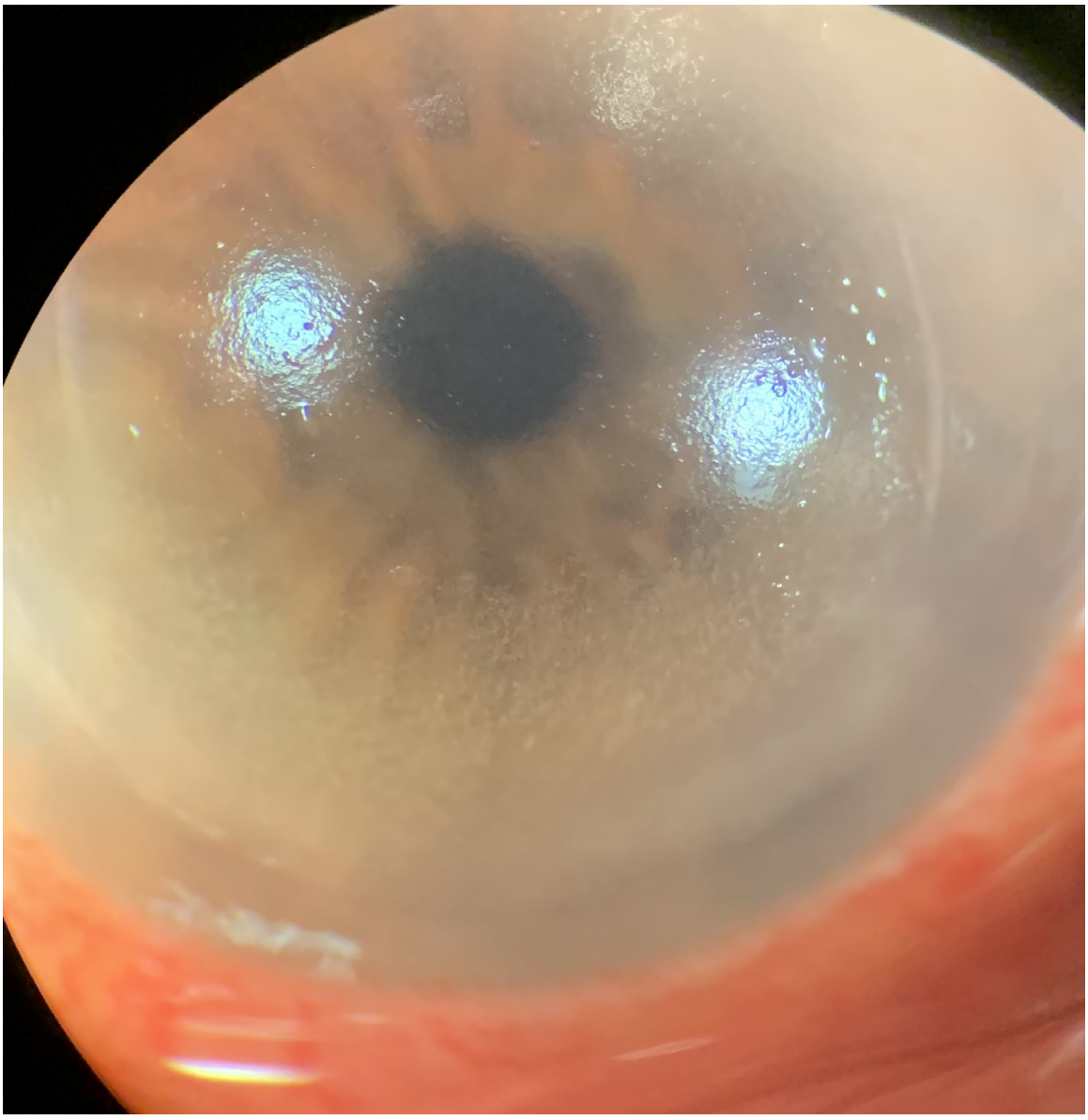

**Fig. 1—Slit-lamp photograph demonstrating stage II diffuse lamellar keratitis with a white, granular cellular infiltrate affecting the lower third of the cornea.**

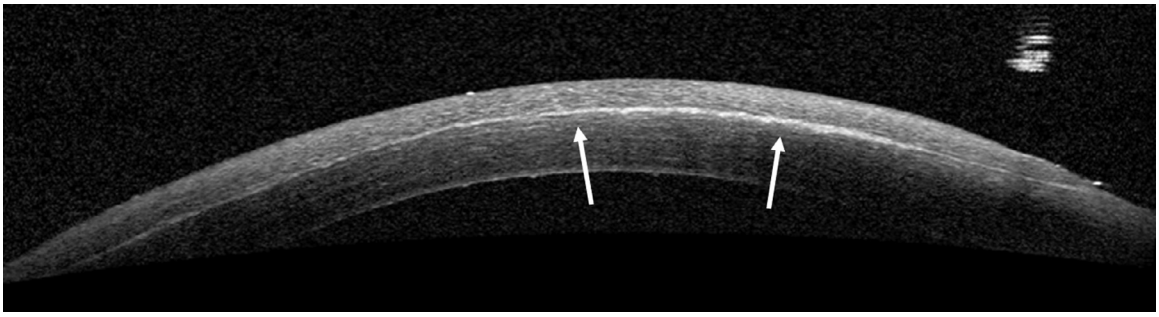

**Fig. 2—Anterior-segment optical coherence tomography image highlights the inflammatory cells located in the flap interface (arrows).**

with inflammatory conditions, the levels of these mediators, including NGF, are often abnormal at baseline.[6]

From the original REPARO and NGF0214 trials, inflammatory adverse events (i.e., anterior-chamber inflammation, eye inflammation, and keratitis) were uncommon with cenegermin, with only 1 affected eye in the REPARO studies and 3 in the NGF0214 study.[1,2] Formation of a corneal epithelial defect was rarely reported.[2] A review of the literature did not reveal other reported inflammatory adverse events.

Here we report a case of late-onset DLK following cenegermin administration that resolved with both systemic and periocular corticosteroids and reduced frequency of cenegermin. Presumably in our case, baseline immunologic dysregulation resulted in acute inflammation in the form of DLK after the increase in NGF levels. Our patient's neurotrophic keratitis and corneal sensation improved with careful titration of cenegermin. Close monitoring is warranted in patients with a history of LASIK while initiating cenegermin therapy to screen for this potential adverse event.

## Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2022.02.011.

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## Footnotes and Disclosure

Albert Y. Cheung has consulted for LayerBio. Rachel A. Dandar and Jessica Schiffbauer do not have any disclosures to report. The authors did not receive funding for any of this work.