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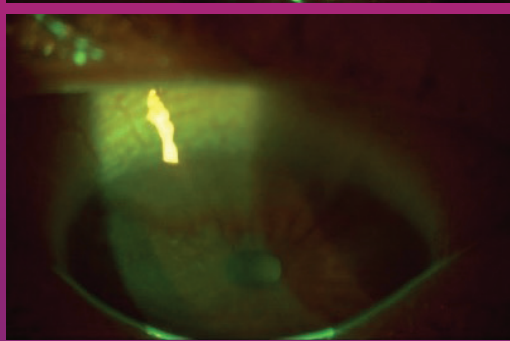
Patient Saves in OSD & NK: A Case Series





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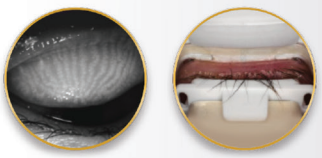

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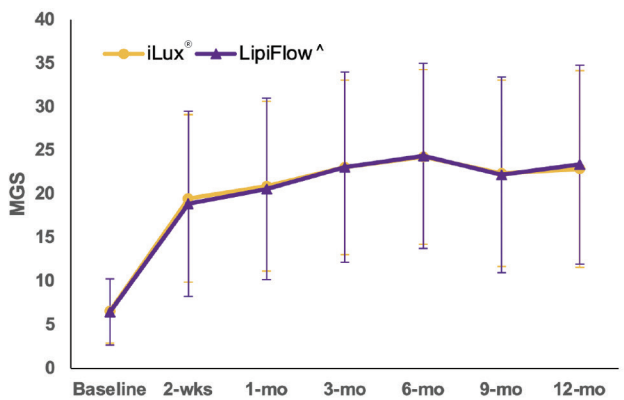
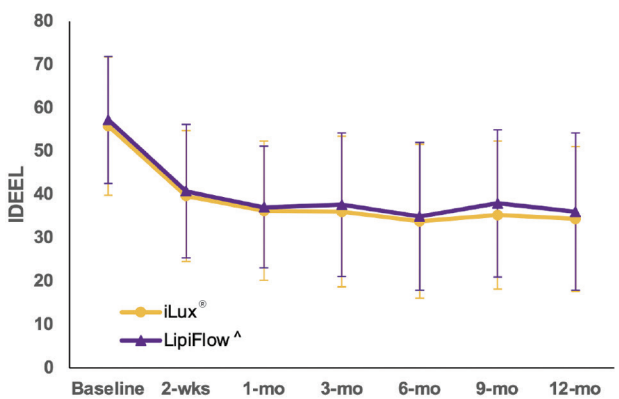


IDEEL-SB Score**



Key Results

Non-inferiority of iLux® to LipiFlow^ was demonstrated in change from Baseline MGD scores (95% LCL of the LSM difference >-0.5), and change in Baseline IDEEL-SB module score (95% UCL of the LSM difference <12)

*Meibomian gland scores (0-45) measured using meibomian Gland Evaluator to assess the 15 glands of the lower lid of each eye with a grade from 0-3.
**Impact of dry eye on every day life (IDEEL - SB) symptom bother score (with 20 questions).
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Alcon

References: 1. Tauber J, Owen J, Bloomenstein M, Hovanesian J, Bullimore MA. Comparison of the iLUX and the LipiFlow for the Treatment of Meibomian Gland Dysfunction and Symptoms: A Randomized Clinical Trial. *Clin Ophthalmol.* 2020;14:405-418. **2.** Alcon data on file, 2019. **3.** Alcon data on file, 2021.

IMPORTANT PRODUCT INFORMATION

Indication:

The *Systane*® *iLux2*® is indicated for the application of localized heat and pressure therapy in adult patients with meibomian gland dysfunction (MGD), which is associated with evaporative dry eye, and to capture/store digital images and video of the meibomian glands.

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Do NOT use the *Systane*® *iLux2*® in patients with the following conditions: Patients whose pupils have been pharmaceutically dilated; patients with ocular injury or trauma, chemical burns, or limbal stem cell deficiency (within prior 3 months); patients with active ocular herpes zoster or simplex of eye or eyelid or a history of these within prior 3 months; patients with cicatricial lid margin disease; patients with active ocular infection, active ocular inflammation or history of chronic, recurrent ocular inflammation within prior 3 months; patients with an ocular surface abnormality that may compromise corneal integrity; patients with lid surface abnormalities that affect lid function in either eye; patients with aphakia; or patients with permanent makeup or tattoos on their eyelids.

Warnings/Precautions:

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Potential Adverse Reactions:

Potential adverse effects may occur because of the procedure. These effects include but are not limited to, the onset or increase in: eyelid/eye pain requiring discontinuation of the treatment procedure, eyelid irritation or inflammation, temporary reddening of the skin, ocular surface irritation or inflammation (e.g., corneal abrasion, conjunctival edema or conjunctival injection (hyperemia)), and ocular symptoms (e.g., burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light).

Attention: Please refer to the User Manual for a complete list of contraindications, instructions for use, warnings and precautions for the *Systane*® *iLux2*®.

Patient Saves in OSD & NK: A Case Series

INTRODUCTION BY JENNIFER LOH, MD, AND JUSTIN SCHWEITZER, OD, FAAO


We clinicians tend to think of a good clinical "save" as a case in which the doctor recognizes an atypical condition based on limited evidence, potentially early in the natural history, so that treatment can be initiated before complications lead to irreversible damage. Although our medical training teaches us to think about horses before zebras, the cases in which we find a rare disease tend to stick longer in our memories.

As the cases in this article highlight, however, a good clinical "save" does not need to be associated with a rare clinical entity. While the routine nature of recognizing ocular surface disease (OSD) based on a hunch, or incidentally identifying neurotrophic keratitis (NK) because of corneal anesthesia, may make it seem like these diagnoses are not special cases, they are, indeed, very meaningful for patients. The expanding array of dry eye and ocular surface disease treatments, as well as broadening options for NK (e.g., cenegermin-bkbj ophthalmic solution 0.002% [20 mcg/mL]; Oxervate; Dompé), means that early diagnosis and prompt initiation of treatment does not just resolve the disease, and it does not just stop progression or aid in disease control, it also impacts positively on patients' quality of life and potentially saves vision. The market availability of OSD and NK treatments has the effect of sharpening our focus in the clinic: they get us thinking about when to use them, over time we hone criteria for patient selection, and in the end, we become more proficient at recognizing subtle disease features.

In this article, we are pleased to present a series of cases from ophthalmologists and optometrists in the categories of OSD and NK. They are remarkable cases not because of their rarity, but rather because of how relatable the findings are to everyday clinical practice. Each case demonstrates a good "save," not only in the sense of saving vision, but in some cases aiding in the diagnosis of underlying systemic issues that required specialty care.

Eye care providers don't typically think about "saves" when they diagnose common clinical entities. Perhaps they should recognize the lifetime of suffering they are saving the patient from when they do recognize and treat OSD or NK before the disease results in permanent vision loss. ■

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Ocular Surface Disease Secondary to Nutritional Deficiency in a 12-Year-Old Girl

Although the prevalence of nutritional deficiency is higher in developing nations, vulnerable populations everywhere are at high risk.

BY NIKITA ARORA, MS

Ocular surface disease is a wide category of clinical entities. In the majority of cases, the manifestations at the surface of the eye are caused by a local inflammatory reaction. Thus, the exact etiology may not always be consequential for how the patient is treated. However, a wide assortment of systemic conditions can contribute to dry eye and other ocular surface diseases, which in turn requires a more holistic approach to both gain control at the ocular surface and to address the underlying cause of the imbalance.

BACKGROUND AND TREATMENT

A 12-year-old girl was referred to our clinic with a history of night blindness for about a month. On examination, her conjunctiva looked extremely dry, and the cornea was hazy with a normal fundus (Figure 1). Schirmer testing demonstrated 1 mm OD and zero mm OS. She had a history of recurrent diarrhea. The young age coupled with night blindness and gastrointestinal symptoms raised our suspicion for nutritional deficiency. Another important thing to be noted in the history was that the patient had lost her mother a few months earlier and was being taken care of by a single parent. Based on the history, the patient was referred to a pediatrician, was subsequently diagnosed with low weight for her age and other nutritional deficiencies (including Vitamin A deficiency), and was started on treatment. One month after starting treatment, the patient's cornea was clear (Figure 2), the conjunctiva looked relatively healthy, Schirmer testing demonstrated 7 mm OD

and 5 mm OS, and she did not have any night blindness.

DISCUSSION

Ocular surface disease often requires active treatment by the ophthalmologist to reverse signs and to provide the patient relief from symptoms, which can be severe and sight-threatening. In other instances, though, corneal findings are limited, resolving after treatment for the underlying systemic cause.

The link between vitamin A deficiency and ocular morbidity is well known, and it is a major cause of childhood blindness in developing countries. Vitamin A deficiency occurs when body stores are exhausted and supply fails to meet the body's requirements, either because there is a dietary insufficiency, requirements are increased, or because intestinal absorption, transport, and metabolism are impaired.[1] Early ocular changes associated with vitamin A deficiency include keratinization of the conjunctiva and development of superficial punctate keratopathy, and later characteristics include corneal keratinization, ulceration, and necrosis.[2] The younger the child, the more severe the disease and the higher the risk that corneal destruction will be followed by death.[1] Additional evidence for the role of micronutrient deficiency in ocular surface disease etiology and pathophysiology may be extrapolated from the positive therapeutic effects associated with nutritional supplementation (ie, omega-3 essential fatty acids) in resolving signs and symptoms.[3]

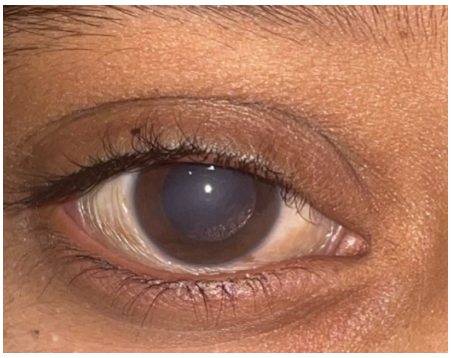

Figure 1. Ocular surface disease, coupled with gastrointestinal symptoms and a history of night blindness, raised our suspicion for nutritional deficiency.

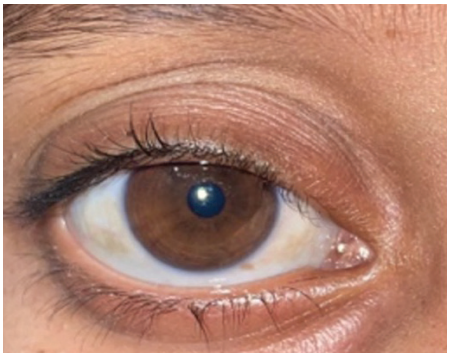

Figure 2. Treatment of the underlying nutritional deficiency led to resolution of signs of ocular surface disease.

The current case highlights the correlation of nutritional deficiency with ocular surface disease. The fact that the keratinization resolved without direct treatment—that it resolved after addressing the nutritional deficiency—provides strong evidence that the patient's poor tear film was something more insidious than standard dry eye. Of note, while the prevalence of ocular surface disease secondary to vitamin A deficiency is classically higher in developing nations and resource-poor areas, it is being increasingly recognized in vulnerable populations in the developed world, as well.[4] Any report of unresolving gastrointestinal illness in a patient with hazy cornea on examination, especially in very young children who look small for their age, warrants special consideration for possible nutrient deficiency.

DECLARATION OF PATIENT CONSENT

The author certifies that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be used. Participating patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. ■

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Sjögren Syndrome: Ocular Manifestations of an Underlying Systemic Disease

The importance of prompt recognition and treatment before vision-threatening complications occur.

BY EMILIE SEITZ, OD

Sjögren syndrome (SS) is a chronic inflammatory disorder that may occur alone (primary) or in association with another autoimmune disease (secondary). The precise etiology is unknown, although a genetic predisposition has been suggested to increase relative risk in some cases.[1] SS affects about 4 million Americans, and it is estimated that 1 in 10 cases of clinically significant aqueous-deficient dry eye (ADDE) is associated with underlying SS.[2] Serious ocular manifestations, including

conjunctival and corneal inflammation, uveitis, scleritis, optic neuritis, and retinal vasculitis, can result in decreased vision or permanent vision loss.[3] Although associated with more severe ocular signs, such as advanced corneal staining, patients with SS-related ADDE commonly present with symptoms that are less severe than other forms of dry eye and disproportionate to their ocular surface findings.[4,5] This suggests that proinflammatory factors from the disease may consequentially reduce corneal sensation.[6]

BACKGROUND

A 57-year-old white woman presented as a referral for dry eye disease. She reported an exacerbation of symptoms in the last few months, rendering her unable to drive. She reported her pain level to be 6/10. Her medical history was significant for pemphigus, for which she occasionally took prednisone for skin flares, and hypothyroidism, controlled with levothyroxine. Her surgical history included LASIK OU (2002) and bariatric surgery. Previous treatments for her dry eye disease included warm compresses, Lotemax QID OU for 2 weeks, omega-3 fatty acids, lid scrubs, Retaine artificial tears (OcuSoft) up to 6 times per day, and lubrication ointment, all of which provided minimal improvement.

On ocular examination, visual acuity was 20/50+2 OD and 20/25 OS. The right eye revealed 4+ corneal staining with approximately 14 corneal filaments along the superior aspect of the cornea (Figure 1). OSDI scoring was 77, indicating severe dry eye disease. Meibography showed severely truncated glands with dropout to both upper and lower eyelids. InflammaDry (Quidel) was strong positive OD, weak positive OS. I classified the patient as a Type II skin type by the Fitzpatrick grading scale. Schirmer testing with anesthetic revealed <5 mm wetting OU. The patient was diagnosed with filamentary keratitis OD, meibomian gland dysfunction OU, and keratoconjunctivitis sicca OU (pending additional Sjögren's testing).

TREATMENT AND FOLLOW-UP

I treated the patient's filamentary keratitis with a dry amniotic membrane with overlying bandage contact lens, which I removed after 6 days (Figure 2). I encouraged the patient to apply copious lubrication with Retaine MGD artificial tears. After the amniotic membrane, I started the patient on acetylcysteine TID OD and Regener-Eyes LITE Ophthalmic Solution (Regener-Eyes) TID OU. I am treating her underlying meibomian gland dysfunction by IntensePulsed Light (IPL) therapy. A laboratory panel was ordered to evaluate for SS.

The following bloodwork was ordered: Early Sjögren Syndrome Profile (PSP, CA6, SP-1) IgG/M/A for each; Sjögren Ab Anti-SS-A and Anti-SS-B; Anti-Nuclear Antibody (with Hep-2 cell pattern analysis); and Rheumatoid Factor IgM. Results showed elevated salivary protein 1 (SP-1) IgG and IgM Abs, elevated carbonic anhydrase 6 IgG and IgM Abs, and elevated parotid secretory protein IgM Abs. Sjögren Ab Anti-SS-A and Anti-SS-B, Anti-Nuclear Antibody (Hep-2), and Rheumatoid Factor IgM were all within normal limits. Antibodies SP-1, CA6, and PSP are known to occur earlier in the disease process than antibodies Ro or La, indicating early SS in this patient. These findings were communicated with the patient's rheumatologist, dermatologist, and primary eye doctor for continued comanagement.

Since initiating treatment, the patient's symptoms have subjectively improved, resulting in her feeling comfortable enough to return to driving.

DISCUSSION

SS is considered a relatively common disease in the realm of autoimmune disorders, with an incidence between 3.9 and 5.3 per 100,000 population.[7] Prevalence rates are variable throughout the literature and depend on the population and criteria used for case definition; no associated race or geographic predilection has been identified. SS has been described as occurring alone (primary) or secondary to other systemic autoimmune disorders.[1] Primary SS is believed to disproportionately affect women compared to men, with mean age of onset in the fourth and fifth decades.[7] Notably, more advanced age is associated with greater prevalence of SS.[7] SS-related ADDE remains somewhat of a diagnostic challenge. Limitations exist with regards to repeatable, evidence-based, clinically available instruments and algorithms that are specific for SS-related dry eye.[2] Furthermore, primary SS is indistinguishable in clinical presentation from its secondary occurrence. Regardless, prompt diagnosis and systemic treatment are of the utmost importance to avoid severe ocular and life-threatening complications.[2]

There are clues that should prompt the eye care specialist to investigate for SS. For example, when confronted with

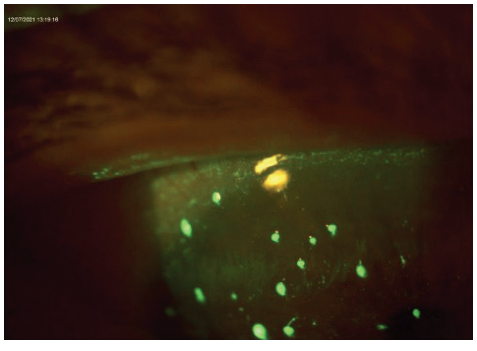

Figure 1. Anterior segment findings in the right eye revealed 4+ corneal staining with approximately 14 corneal filaments along the superior aspect of the cornea.

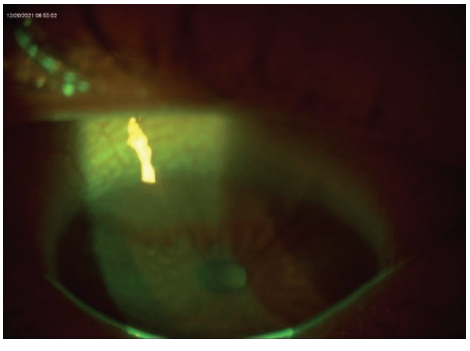

Figure 2. The patient's filamentary keratitis was treated with a dry amniotic membrane with overlying bandage contact lens, which was removed after 6 days.

severe dry eye, inquire about additional symptoms related to glandular secretion, such as dry mouth or gynecological changes. Women of post-menopausal age or status, and patients with connective tissue autoimmune disease, are at higher risk. In this case, the previous diagnosis of pemphigus was a sign of a potential comorbid autoimmune disease that prompted a more extensive laboratory work-up, including testing for SS.

There are three main clinical lessons that I have learned while co-managing this patient's case:

- **Lesson One: Choose your tools wisely.** I initially used a cotton tip applicator to remove the corneal filaments, but I believe this method only depressed the epithelium and resulted in recurrence. In the future, I will reach for jewelers forceps or my trusty Tweezerman tweezers to excise the filaments with cleaner margins.
- **Lesson Two: It's a matter of trust.** When prescribing acetylcysteine to treat the filamentary keratitis, it took 3 weeks for the pharmacy to fill the script, ultimately delaying our intended treatment. In future practice, I'll remember the importance of establishing a relationship with a trustworthy compounding pharmacy.
- **Lesson Three: Implement what's known and novel.** It's been 10 years since novel autoantibodies PSP, CA6, and SP-1 were first proposed as early biomarkers for SS.[8] The benefit of performing laboratory testing for these markers is two-fold. First, PSP, CA6 and SP-1 are thought to occur earlier in the disease process.[9] Second, novel autoantibodies can be detected in patients who traditionally test negative for anti-Ro or La, as seen in this case. In communication with rheumatology, the combined effect could result in a more prompt diagnosis of SS and thereby treatment of the underlying systemic disease. ■

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NK Secondary to Complex Regional Pain Syndrome

Treatment and management of ocular manifestations of a complicated systemic nerve condition.

BY BRENT KRAMER, MD

Neurotrophic keratitis (NK) is a degenerative corneal disease resulting from the partial or total impairment of trigeminal innervation.[1] A wide array of systemic and ocular causes have been implicated in the pathogenesis of NK. On physical examination, later-stage NK appears as epithelial defects that may be confused with other eye diseases, including dry eye, exposure keratitis, topical drug toxicity, contact lens abuse, and corneal limbal deficiency; however, symptoms are often absent, as a loss of corneal sensation is a hallmark characteristic.[2] Thus, identifying NK early can be challenging yet important, as the progression to later stages of NK is associated with stromal involvement, with an increased risk for developing corneal ulcer, melting, and perforation.[3]

BACKGROUND

An 18-year-old woman presented to Duke's Foster Center for Ocular Immunology for evaluation of decreased vision (fluctuating from 20/200 to hand motion), eye pain, and recurrent corneal erosions. Her past medical history included a diagnosis of complex regional pain syndrome initially affecting the right lower extremity with progressive spread to bilateral upper extremities and the right side of the face. At the time of the visit, she was using three medications: gabapentin, amitriptyline, and oxcarbazepine. Ophthalmic examination revealed whirl-like epitheliopathy and corneal haze (Figure 1A). Because we suspected NK, Cochet-Bonnet esthesiometry was performed, which showed severely compromised corneal sensitivity. Based on the findings, the patient was diagnosed with very late Stage 1 NK, presumably secondary to her complex regional pain syndrome. She had not yet developed a non-healing epithelial defect or thinning. A confocal microscopy image displaying rarefaction of the corneal nerves at the epithelial subbasal plexus level helped confirm the diagnosis (Figure 1B).

TREATMENT AND FOLLOW-UP

The patient was treated with superficial keratectomy, amniotic membrane graft, bandage contact lens, and plasma rich growth factor tears, and was started on an

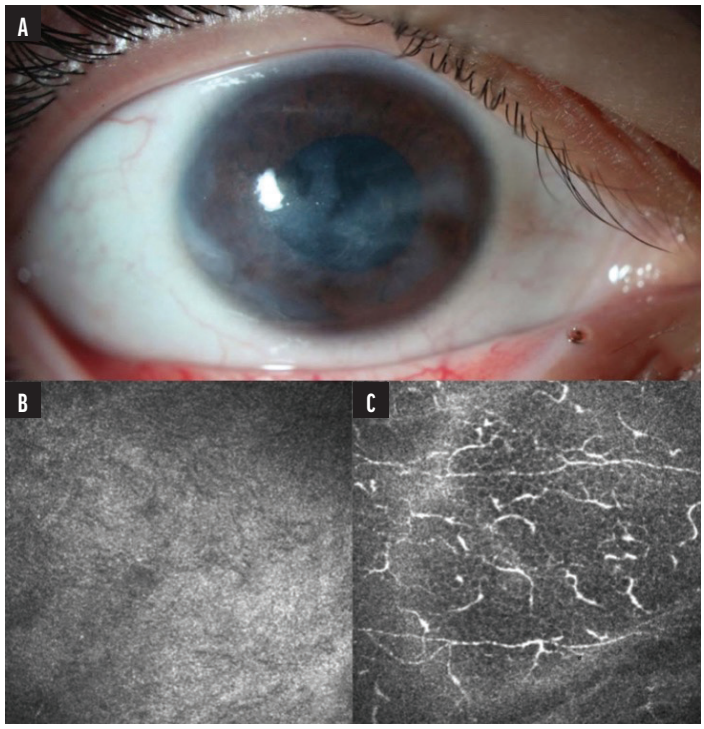

Figure 1. A slit-lamp photo showed diffuse epithelial irregularity and subepithelial haze (A) and rarefaction of corneal nerves at the epithelial subbasal plexus level on confocal microscopy (B). For comparison, a normal density of nerves at the subbasal plexus level in the contralateral eye is also shown (C).

8-week course of (cenegermin-bkbj) ophthalmic solution 0.002% (Oxervate; Dompé Farmaceutici SpA, Milan, Italy). Eleven months after treatment, the patient had improved visual acuity (20/25), resolution of ocular symptoms, increased corneal sensation to 30 mm, and showed no recurrence of neurotrophic manifestations or neuropathic facial symptoms (Figure 2).

DISCUSSION

NK is a disease that receives little attention. With effective treatments now available, and more around the corner, earlier diagnosis and prompt initiation of treatment offers the potential to save these patients from vision-threatening complications. In a busy clinical practice, it is easy to get caught up in examining the eye and skipping over the patient's history. Especially in instances where epithelial defects are present and impairment of corneal nerves is suspected, it is important to go back and ask questions that might unearth NK, such as:

- "Is there any known history of herpes simplex virus in the eye, or fever blisters, cold sores, or shingles?"
- "Have you been using eye drops for glaucoma or other eye issues for a long time?"
- "How long have you had dry eyes?"
- "Do you have any history of eye surgery, eye trauma, or chemical injury?"

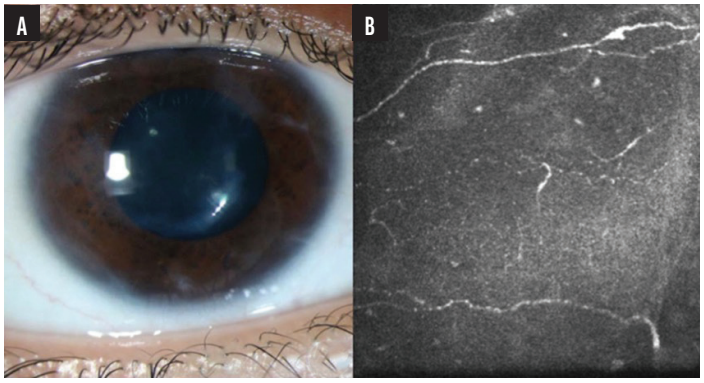

Figure 2. Eleven months after treatment, photos showed an improved corneal surface with only peripheral scarring (A) and significant regrowth of corneal nerves at the subbasal plexus level on confocal microscopy (B).

In this case, NK was not a known complication of complex regional pain syndrome; however, a literature search revealed this disease is a poorly understood condition thought to affect the nerves. Our corneal findings, in addition to the known diagnosis, raised our index of suspicion for NK.

Testing for corneal sensation prior to administering anesthetic drops is key in diagnosing NK, which can be done with a Cochet-Bonnet esthesiometer or even the loosened tip of a cotton swab. Other features may include fluorescein staining (especially significant stain without pain), whirled epithelium (which can be accompanied by subepithelial haze), non-healing defects, and corneal thinning in more severe disease. Confocal microscopy is not a widely available tool in ophthalmology, and its use is not essential in diagnosing NK. Nevertheless, my colleagues and I have found that imaging from confocal microscopy is supportive in confirming a diagnosis.

Treatment options for NK have expanded with the availability of growth factor agents. The fundamental goal of NK management is to promote corneal healing and avoid complications. In our clinic, we are quick to prescribe cenegermin 0.002%, which contains recombinant human nerve growth factor. In clinical trials, topical cenegermin treatment resulted in increased healing compared to vehicle in eyes with Stage 2 or later NK.[4,5] A more recent clinical trial is seeking to understand if there is a role for cenegermin treatment for Stage 1 NK (NCT04485546).

Newer treatment options are improving the visual prognosis for eyes with NK. However, concomitant medical conditions, especially those that may contribute to the impairment of corneal innervation, must be closely monitored. This patient's complex regional pain syndrome has followed a progressive course. NK surfaces can decompensate quickly with minimal or no pain sensation. And so, I have recommended the patient return for follow-up every 6 months for reevaluation. In the interim, the patient is willing and able to use a scleral contact lens, which is key in this specific situation, and she continues to use plasma-rich growth factor tears. Based on the status of the

cornea, treatment with the recombinant human nerve growth factor-containing agent may be repeated. ■

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Neurotrophic Keratitis Secondary to Long-Duration Contact Lens Wearing

Taking a thorough patient history is additive to clinical findings in unmasking signs and symptoms of NK.

BY LAUREN MCLOUGHLIN, OD

Neurotrophic keratitis (NK) is a degenerative corneal disease typified by reduction or loss of corneal sensitivity.[1] Several potential causes have been identified, including infections, corneal pathologies, topical medications, 5th cranial nerve palsy, systemic diseases, and iatrogenic etiology. Of note, contact lens abuse is frequently cited as a cause of NK, which may refer to not following correct wearing and cleaning procedures, or very long duration of use.[2] In some instances, testing corneal sensitivity to rule in/out NK is justified by the results of the clinical examination: any recalcitrant punctate keratitis or unresolved severe dry eye should be carefully investigated. However, the patient interview is just as important for unmasking suspicious findings that lead to additional work-up.

CASE INFORMATION

A 70-year-old patient presented to our practice for cataract evaluation due to decreased vision OS>OD. During the consultation, superficial punctate keratitis (SPK) OS was observed, and the cataract surgeon referred him internally to my dry eye clinic for further evaluation. Corneal staining showed 3+ SPK OS and punctate erosions, and clinical examination revealed MGD 2+ OU (Figure 1). The patient was using Lotemax and artificial tears. His VA was 20/25 OD and 20/70 OS. During the interview, the patient said he had been wearing monovision contact lenses for more than 35 years. He subsequently revealed that he had been prescribed various treatments for dry eye by another optometrist, including multiple doses of steroids and different dry eye drops, all with no discernible effect. Corneal sensitivity was tested with a cotton swab, revealing decreased corneal sensitivity in all but the superior quadrant.

Based on the totality of the clinical evidence, the patient was diagnosed with NK, likely secondary to his long duration of contact lens wearing. The patient was started on Oxervate (Dompé) 6 times per day for 8 weeks. VA was 20/20 OS after the treatment and repeat corneal staining suggested a healthy cornea (Figure 2).

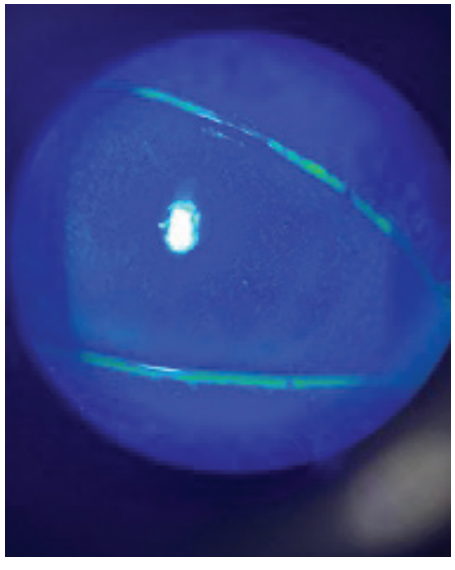

Figure 1. Corneal staining showed 3+ SPK OS and punctate erosions.

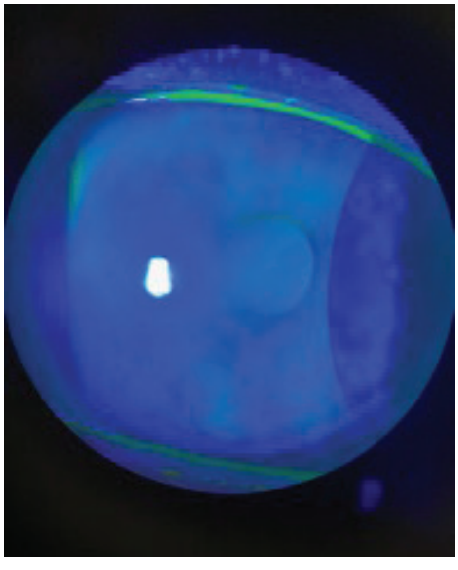

Figure 2. The cornea is clear after 8 weeks of treatment.

DISCUSSION

Sometimes a good diagnosis is the result of asking the right question. In this case, one question unearthed a wealth of useful information. When I asked who had referred him for cataract surgery, the patient responded that he had been visiting his regular eye doctor around every 4 weeks and had tried numerous treatments for painful and irritating dry eye. His unexplained vision loss prompted a surgical

consultation, but it is what he said in my examination chair that caused me to retrieve a cotton swab and test for corneal sensitivity. That information, combined with an impression that the vision changes didn't match his cataract, led me to suspect NK.

There is some selection bias in the case presented here. As a specialist in dry eye disease, I may see more patients in my clinic with undiagnosed NK than a community optometrist. That said, NK is an undertreated and likely underdiagnosed clinical entity, despite its potential for severe visual complications. I have personally become more attuned to thinking about NK since Oxervate was released. In my experience, when I have a patient with recalcitrant SPK, unresolving dry eye despite treatment, and progressing signs, it takes very little effort to quickly test corneal sensitivity. A neurotrophic cornea is a hallmark finding in NK.[3]

Contact lens suspension is not mandatory while patients are being treated for NK. The clinician needs to make a judgement call on whether continued contact lens use while on treatment could prolong healing. However, contact lens wearing is not contraindicated with the use of Oxervate. This patient decided he would wear glasses during the 8 weeks of treatment, which was encouraging, and then he resumed wearing contact lenses. I will continue to follow this patient to monitor for corneal changes. Any recurrence might suggest that the contact lens was the insult and therefore needs to be stopped permanently. ■

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2. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579.
3. Feroze KB, Patel BC. Neurotrophic keratitis. 2021 Nov 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 28613758

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oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

Dompé

Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

OXERVATE is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis (NK)[2]

Cenegermin-bkbj, the active ingredient in FDA-approved OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.[3]

Endogenous NGF is a protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms (in preclinical models): corneal innervation, tear secretion, and epithelial cell growth.[3-5]

In clinical studies, with a single 8-week course of therapy:

- Up to **72%** of patients with NK achieved complete corneal healing*†[2]
- **80%** of patients who achieved complete corneal healing remained completely healed at 1 year (REPARO trial)[6]

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

Please see additional Important Safety Information on accompanying page and full Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

TREAT NK TODAY
OXERVATE.com/HCP

*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%[2,7]

†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

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