Primary *Neisseria meningitidis* Keratitis

To the Editor:

Neisseria meningitidis is a gram-negative coccobacillus known for its primary infection of the meninges. A MEDLINE search for primary meningococcal keratitis produces only 1 case series consisting of 2 cases.[1] Here, we present a case of meningococcal keratitis treated with levofloxacin 1.5% ophthalmic solution and managed with systemic therapy for potential associated complications.

CASE DESCRIPTION

A 38-year-old male construction worker with an ocular history of pseudophakic bullous keratopathy secondary to traumatic aphakia in his left eye presented with a 1-week history of mild discomfort in the same eye, progressing to more severe pain, decreased vision, conjunctival injection, and discharge over the prior 24 hours. The patient reported a dry cough for the few days before presentation but denied any recent sick contacts. His most recent ocular exam was 9 months before presentation and revealed stable bullous keratopathy treated with sodium chloride 5% ophthalmic solution (Muro 128, Bausch & Lomb) as needed.

Upon presentation, visual acuity was hand motions at 1 foot (baseline acuity was hand motions at 3 feet). Slit-lamp exam revealed a 3.2 × 2.3-mm, central, purulent, corneal infiltrate involving greater than 50% of the stromal depth with an overlying epithelial defect (Fig. 1). There was deep corneal stromal vascularization and a 1-mm hypopyon. Corneal scrapings were sent for bacterial and fungal cultures, after which empiric treatment with levofloxacin 1.5% ophthalmic solution (Iquix) was started every 15 minutes for 1 hour, then every hour while awake, and every 2 hours at night.

Two days later, the cultures revealed *N. meningitidis* (gram-negative coccobacilli, beta-lactamase negative) for which sensitivities are not normally performed in our lab. Because the bacterium is known to be sensitive to fluoroquinolones and because the patient was showing improvement, his therapy was continued. He was also started on oral levofloxacin (Levaquin) 750 mg daily for 5 days, and an infectious diseases consult was obtained. His physical exam and labwork, including blood cultures, did not indicate systemic infection. He was, however, prophylactically treated with 2-g intravenous ceftriaxone every day for 7 days and given one 600-mg oral dose of rifampin. His wife was treated with a single prophylactic dose of ciprofloxacin, but his asymptomatic children were not treated. The patient's corneal ulcer improved, and on day 17, the levofloxacin 1.5% was reduced to 4 times a day and topical prednisolone acetate 1% 4 times a day was added, ultimately leaving him with a sterile corneal stromal scar as the drops were tapered off (Fig. 2).

COMMENT

Neisseria meningitidis is found only in humans and is present in the normal oropharyngeal flora of 5%–15% of healthy adults and children.[2] It is transmitted person to person via the respiratory route.[2] Primary ocular meningococcal infection is uncommon, and primary meningococcal keratitis is extremely rare. Tan et al[1] published the only documented cases of primary meningococcal keratitis—a series of 2 young healthy adults. One of these patients was treated with hourly topical levofloxacin 0.5% and cefazolin 50 mg/mL, whereas the other was treated with hourly cefazolin 50 mg/mL and gentamicin 14 mg/mL. An additional 9 cases of corneal ulceration secondary to primary meningococcal conjunctivitis have also been reported.[3]

Our patient was successfully treated with a single topical agent, levofloxacin 1.5% (Iquix). Levofloxacin has been formulated at a higher concentration than other fluoroquinolones because of its higher water solubility at neutral pH.[4] Topical levofloxacin has demonstrated excellent corneal penetration at both 0.5% and 1.5% concentrations.[4–6] Because of the greater penetration and residence time in the cornea (area-under-the-curve concentration of antibiotic) of the 1.5% concentration, it is feasible that we could have used a less frequent dosing regimen and maintained success in treatment.

Barquet et al[3] emphasized adjunctive systemic therapy in their review of 84 cases of primary meningococcal conjunctivitis dating from 1899. In this review, septicemia and meningitis developed in 17.8% of patients. Those patients initially treated only with topical therapy had a 19-fold higher risk of developing systemic meningococcal disease. In the 2 cases of primary meningococcal keratitis reported by Tan et al,[1] both patients were prophylactically isolated and treated with intravenous therapy. Because of the potential for severe systemic complications in our patient, we

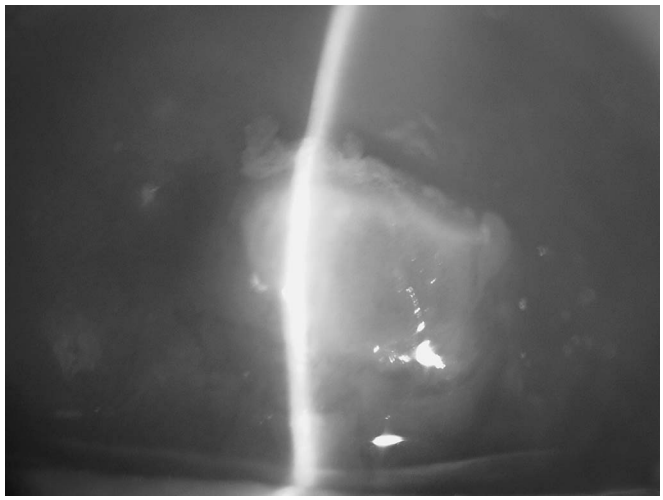

FIGURE 1. Purulent central corneal ulcer because of *N. meningitidis* infection.

Dr. Pandit has received speaking honoraria from Vistakon Pharmaceuticals.

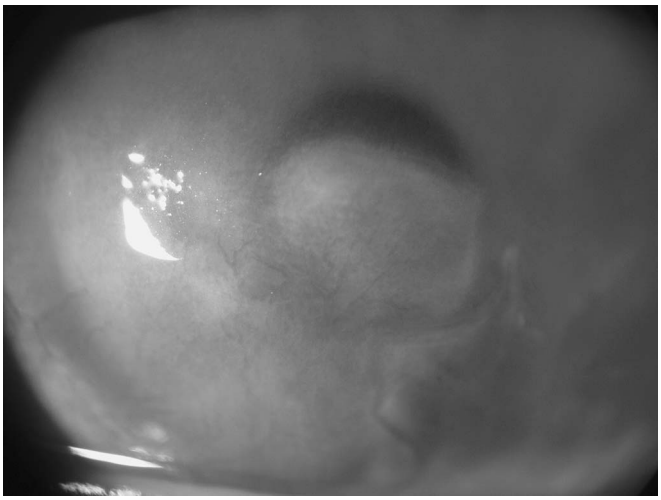

FIGURE 2. Residual central stromal scar after treatment for *N. meningitidis* keratitis with levofloxacin 1.5%.

felt that concomitant systemic therapy was warranted.

Only 1 of the 2 cases reported by Tan et al[1] suffered antecedent trauma, whereas the other had no known risk factor for meningococcal infection. In the review of meningococcal conjunctivitis by Barquet et al,[3] ocular trauma occurred in 14% of cases and close contact with a patient with systemic meningococcal disease was present in 4.7% of cases. Our patient had no sick contacts but was at risk for primary keratitis because of his pseudophakic bullous keratopathy. It is likely that our patient's keratopathy led to a frank epithelial defect, predisposing him to corneal infection.

In summary, this report describes the rare case of primary *N. meningitidis* keratitis treated successfully with topical levofloxacin 1.5% and systemic antibiotic therapy. Prophylactic systemic treatment of primary ocular meningococcal infection is discussed.

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Long Term Use of Topical Tacrolimus (FK506) in High-Risk Penetrating Keratoplasty

To the Editor:

We read with interest the work of Dhaliwal et al dealing with topical FK506 after high-risk keratoplasty.[1] Alternatives to topical steroids are desirable in the treatment of normal and high-risk keratoplasties as a result of the side effect profile of topical steroids. Our study group has performed 3 pilot studies with topical FK506 0.06% eyedrops and with FK506 ointment, respectively.

In a pilot study with the commercially available FK506 ointment Protopic, we observed good efficacy and tolerability in the treatment of severe atopic blepharokeratokonjunktivitis.[2]

In a further pilot study, FK506 eyedrops were used in patients with atopic blepharokeratoconjunctivitis, Mooren's ulcer, ocular pemphigoid, Thygeson's superficial punctate keratitis, nummular adenoviral keratitis, graft-versus-host reaction of the conjunctiva, and steroid response glaucoma after penetrating keratoplasty. The efficacy of the topical treatment was satisfying, but we noted problems with tolerability.[3]

In a prospective, randomized pilot study, we compared the efficacy of FK506 0.06% eyedrops with topical steroids after normal-risk keratoplasties. The efficacy of FK506 was similar to that of topical steroids, but again, there were considerable problems with tolerability.[4,5]

We believe FK506 will play an important role in topical therapy after corneal transplantation. Further prospective, randomized trials with a new eyedrop formula demonstrating better tolerability are needed.

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The authors state that they have no proprietary interest in the products named in this article.

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Reply:

We thank Drs. Birnbaum, Reis, and Reinhard for their comments. We have also selectively used the commercial formulation of 0.03% tacrolimus ointment (Protopic; Fujisawa Health Inc., Deerfield, IL) for inflammatory disorders in addition to the treatment and prevention of corneal graft rejection. In our clinical experience, the off-label use of this 0.03% ointment formulation has been well tolerated by most, but not all, of our patients. Since the publication of our long-term results,[1] we can report the use of 0.03% tacrolimus ointment in >80 patients. Of these subjects, one patient stopped the use of this commercial tacrolimus preparation as a result of "stinging," a very "warm sensation," and discomfort. We have also attempted to use a topical 0.02% tacrolimus eyedrop formulation that was custom-compounded in a pharmacy with a cyclodextran vehicle. Unfortunately, this topical preparation was universally poorly tolerated by our patients due to discomfort. Currently, we have had the greatest success with the Protopic 0.03% ointment formulation of tacrolimus.

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Supported by a grant from the Alliance for Vision Research, Inc.The authors state that they have no proprietary interest in the products named in this article.Reprints: Stephen C. Kaufman, MD, PhD, University of Minnesota, Department of Ophthalmology, MMC 493, 420 Delaware Street SE, 9th Floor, Minneapolis, MN 55455 (e-mail: CorneaMD2000@Yahoo.com).

Photorefractive Keratectomy With and Without Mitomycin-C

I congratulate Dr. Leccisotti[1] for his good and practical study on effectiveness of mitomycin-C (MMC) following photorefractive keratectomy (PRK) and have some comments.

First, the author has performed PRK in myopic eyes with spherical equivalent more than 6.50 D and has applied MMC for 45 seconds in 1 eye and balanced salt solution in the fellow eye. He concluded that there were no significant differences between the two eyes in terms of epithelialization time, uncorrected visual acuity, and best corrected visual acuity. No eye had haze greater than 0.5; however, this low-grade and not clinically significant haze formation was rather more frequent in control group. Then, the question is raised as to whether to reconsider the role of mitomycin-C after PRK if the haze is negligible and the visual acuity is comparable.

Second, the author did not compare contrast sensitivity and wavefront aberrometry and quality of the vision subjectively (the preferred eye in the patients' opinion after surgery). Perhaps, if these modalities had been measured, a better conclusion would have been achieved.

Third, the included patients all had refractive astigmatism less than 1.50 D. There is no clear-cut amount of astigmatism treatment mentioned in the literature that definitely increases the haze formation following PRK. Also, the common approach for application of MMC in surface ablation is usually when the ablation depth was more than 80 microns.[2] However, it is presumed that the more astigmatism is treated, the more haze forms after surface ablation without MMC.[3,4]

The most important concern about application of MMC is its effect on healthy corneal endothelium. Severe endothelial damage is reported after inadvertent long duration of exposure of the ocular surface with MMC during glaucoma surgery,[5] but not after surface ablation. However, it seems wise not to apply mitomycin-C for long durations (more than 50 seconds) as it may have adverse effects on corneal endothelium.[6,7]

Regarding the comparison of outcomes of PRK and laser-assisted subepithelial keratomileusis (LASEK), some previous nonrandomized studies showed better outcomes for LASEK.[4] However, a recent 1-year outcomes from a bilateral randomized prospective clinical trial comparison of LASEK and PRK showed similar levels of postoperative pain, visual acuity, and refractive error following LASEK in 1 eye and PRK in the fellow eye of a homogenous group of patients. Reviewing the literature also shows that LASEK outcomes without MMC had been evaluated in patients with myopia less than 6.50 D to avoid postsurgical haze formation.[8–10] There are also reports of higher corrections of myopia without MMC after LASEK[11]; its prophylactic use after PRK is recommended.[12,13]

In my practice, I usually use MMC in cases with more than 4.0 D of surface ablation, with any ablation depth. I also noticed that even patients with corneal astigmatism greater than 1 D and total spherical equivalent of even less than 4.0 D may develop haze after surface ablation (following performing LASEK on some patients who had been treated for more than 1 D of astigmatism in 1 eye and no astigmatic treatment in the fellow eye and even SE of less than 4.0 diopters and ablation depth of less than 80 microns). After that, I routinely use MMC for all the patients with astigmatic treatment more than 1 D; fortunately, I have experienced no haze thereafter.

Another important issue considering the treatment time of MMC is late-onset corneal haze (LOCH) formation in patients who received MMC less than 20 s—"breakthrough haze" even after short application time of MMC. Considering this untoward haze development, I use MMC at least 30 s whenever it is to be applied. However, the author applied MMC for 45 s for all patients and reported mean 0.47 D of overcorrection. It seems that 45 s is a rather long duration of MMC application; shorter durations may not cause overcorrection and exempt

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the surgeon from adjusting the attempted correction.

It also seems that parameters such as geographic status, the season that the operation has been performed, the patients' occupations and pleasures (like skiing) that may affect the overall exposure time to the ultraviolet light, and different ethnicities may lead to different early and late onset corneal haze formation.

In conclusion, as there is no definite cutpoint for application of MMC after surface ablation, a tailored approach for each patient seems prudent.

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Reply:

I thank Dr. Mohammadpour for having raised some important issues regarding my article.[1]

As indicated by its title, my article was only focused on 2 neglected aspects of intraoperative application of mitomycin-C (MMC) in photorefractive keratectomy (PRK): a possible deleterious effect on reepithelialisation and a possible overcorrection. Other parameters (clinically significant haze, quality of vision, contrast sensitivity, aberrations) were deliberately ignored for 3 main reasons (each of which could suffice):

1. The statistical evaluation of a high number of parameters dramatically increases the chance of false-positive findings[2]
2. As I calculated in the paper, a paired-eye study to assess clinically significant haze difference would need more than 500 patients, which, with the strict criteria used in my study, means that at least 15,000 patients should have been screened
3. The issue of haze has been abundantly addressed by previous literature[3]

The exclusion of preoperative astigmatic errors greater than 1.25 D and a 45-second MMC application in every case were equally chosen to reduce the number of variables and to render all calculations more reliable. I do not believe that a 45-second exposure is so important in causing overcorrection, which has been observed with shorter and longer exposure times.[3] A slight overcorrection is the obvious result of the lack of the "normal" small amount of regression after PRK induced by MMC. Such overcorrection is not necessarily a bad thing: the adjusted nomogram entails less ablated tissue, with the positive implications that can be easily imagined.

Finally, 45 seconds is not a particularly long exposure time. A 2007 review of the American Academy of Ophthalmology states that in surface ablation "it is common practice to apply MMC 0.02% […] for 2 minutes."[4] Being aware of MMC toxicity, I am not an advocate of long exposure times, but I am unsure whether exposures shorter than 30 seconds retain the efficacy we expect.

I therefore fully agree with Dr. Mohammadpour that MMC use should be tailored to refraction, ablation depth, and other risk factors such as previous corneal surgery, skin pigmentation, age, and climate. Unfortunately, we still have a long way before we can draw definitive guidelines on the indications, concentration, and time exposure of MMC after surface ablation, especially because too many variables are involved, beginning from apparently trivial ones (eg, questions of whether the cornea dried before MMC, there is round or ring-shaped sponge, or if sponge materials are delivering the same concentration). Future efforts should aim to standardize the technique, confirm MMC safety, and determine the minimal exposure required to prevent haze in the various situations.

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