Outbreak of Nocardia keratitis after photorefractive keratectomy

Clinical, microbiological, histopathological, and confocal scan study

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Nocardia keratitis occurred in 4 eyes of 3 patients (2 women and 1 man) who had photorefractive keratectomy (PRK) by the same surgeon at the same center. Two eyes of the first 2 patients required lamellar keratectomy to debulk the involved stroma and obtain specimens for microbiological and histopathological evaluation. Light microscopic examination disclosed gram-positive and acid-fast filaments of Nocardia that were confirmed by the microbiological results. Diagnosis of Nocardia keratitis in the third case was not as challenging as in the first 2 cases because of a high index of suspicion. Confocal scans of all cases disclosed hyperreflective and slender, fibril-like structures in the corneal stroma. All eyes responded favorably to topical amikacin and the infection resolved without recurrence. The most probable cause of the outbreak was inadequate attention to sterility during surgery.


Use of the excimer laser in refractive surgery has increased exponentially since the laser was approved by the United States Food and Drug Administration in 1995. Infectious keratitis after keratorefractive surgery is a rare but potentially devastating complication that may be refractory to standard medical therapy. There are several reports of bacterial, viral, fungal, and Acanthamoeba keratitis following photorefractive keratectomy (PRK). In a study by Donnenfeld et al., gram-positive bacteria were the most common cause of post-PRK infectious keratitis and Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and Streptococcus viridans the most commonly cultured organisms. Microorganisms such as S aureus induce acute-onset filamentous keratitis after PRK, but nontuberculous mycobacteria and Nocardia species may lead to late-onset infection. Risk factors for post-PRK infections are corneal epithelial defects, use of extended-wear bandage soft contact lenses, and topical steroids.

Nocardia species are aerobic, gram-positive, and acid-fast filaments that may rarely induce keratitis with a characteristic wreath-like pattern of patchy anterior stromal infiltrates. Predisposing factors to infection include trauma or surgery, contact lens wear, and use of topical corticosteroids. Several sporadic cases and an outbreak of Nocardia keratitis after laser in situ keratomileusis (LASIK) have been reported, but to our knowledge, this is the first report of an outbreak of Nocardia keratitis following PRK that describes the clinical, microbiological, histopathological, and confocal scan features of this rare infection.
Over a period of less than one month, 3 patients with late-onset keratitis following bilateral myopic PRK performed by the same surgeon at the same center were referred to our center. Based on the surgeon’s report, the patients did not have local or systemic predisposing factors and the procedure was uneventful in all eyes. Ethyl alcohol (20%) had been applied for epithelial removal and mitomycin-C (MMC) (0.02%) used for 40 seconds. The entire procedure had been performed under less than optimal sterility; the eyes were not prepared or draped and surgical gloves were not used. After surgery, a bandage soft contact lens had been used for 3 days. Postoperative medications included topical chloramphenicol 0.5% and betamethasone 0.1% eyedrops 4 times a day. No case had developed persistent epithelial defects.

**Case 1**

A 28-year-old woman presented to her surgeon with photophobia, red eye, and reduced vision in the left eye 28 days after PRK. The ocular examination revealed a moderate corneal haze and mild infiltration. The surgeon suspected a sterile infiltration and increased the frequency of topical steroids to every hour. The condition progressively deteriorated, and systemic acyclovir was initiated to treat a presumed herpetic infection. After 2 weeks, dense central corneal infiltration along with satellite lesions appeared. Corneal smear and culture were performed at this stage; the culture was negative. Because of the suspicion of fungal keratitis, topical natamycin 5% was administered but no improvement was noted after 2 weeks. The patient was referred to our center 2 months after the PRK procedure.

The visual acuity in the left eye was 20/400, and slitlamp biomicroscopy revealed a central corneal epithelial defect together with diffuse stromal edema and multiple discrete granular infiltrates with feathery borders in the deep stroma in a wreath-like pattern (Figure 1). A moderate inflammatory reaction was also present in the anterior chamber. A confocal scan (Confoscan 3.4, Nidek Technologies) did not reveal hyphae- or cyst-like structures. After the cornea was scraped for microbiological studies, cefazolin 50 mg/dL and gentamicin 14 mg/dL were started every hour.

Because there was no significant response to the medical regimen, lamellar keratectomy was performed after 3 days to debulk the involved stroma and obtain a specimen for bacteriological and histopathological evaluations. Histopathological examination demonstrated foci of intrastromal...
necrosis with scattered acute and chronic inflammatory cell infiltrates (Figure 2, A). On Gram-Twort staining, small clusters of gram-positive filaments were found in the necrotic areas (Figure 2, B); they were acid-fast on modified Ziehl-Neelson staining (Figures 2, C). Histopathological features were strongly suggestive of Nocardia keratitis, which was confirmed by the results of culture 1 week after incubation (Figure 2, D). The confocal scan was repeated after the new diagnosis and disclosed a few hyperreflective and slender fibril-like intrastromal structures about 9.0 μm in length and 1.5 μm in width (Figure 3). The structures were similar in appearance to the filament-like elements found on the histopathological examination.

Fortified cefazolin and gentamicin were discontinued and amikacin 40 mg/dL eyedrops started based on disk diffusion sensitivity. After 2 days, significant improvement was noted and by day 14, the corneal infiltrates resolved and the epithelial defect healed completely. After 1 month, the best corrected visual acuity (BCVA) was 20/160. At the last follow-up examination, scar formation and corneal thinning were noted (Figure 4).

Case 2

Ten days after the first case was referred to our center, a 24-year-old woman was seen for post-PRK keratitis in the left eye that had developed 3 weeks after surgery and was unresponsive to frequent application of ciprofloxacin 0.3%. The visual acuity was 20/500, and slitlamp biomicroscopy revealed multiple patches of deep stromal infiltrates with a 2.0 mm × 2.0 mm epithelial defect in the left central cornea (Figure 5, A).

The diagnostic and therapeutic approach to this case was similar to the approach in the first case with the exception of a clinical suspicion of fungal keratitis that prompted the initiation of topical natamycin 5%. As in the first case, lamellar keratectomy was performed because of the lack of response; the results were similar to those in the first case. Review of recorded confocal scan images showed one image of hyperreflective and slender, fibril-like elements. The infection responded favorably to amikacin, and at the last follow-up examination, the BCVA was 20/500 and there was no sign of recurrent infection (Figure 5, B).

Case 3

While Cases 1 and 2 were being treated, a 23-year-old man was referred with pain, decreased vision, and redness in the left eye 40 days after bilateral PRK. The visual acuity was 20/40 in the left eye and 20/25 in the right eye. Slitlamp examination disclosed multiple patchy anterior stromal infiltrates in a wreath-like pattern with feathery borders in the left cornea (Figure 6, A). Although the patient had no complaint in the right eye, mild corneal haze was noted in this apparently uninvolved eye.

With a high index of suspicion of Nocardia keratitis, a confocal scan was performed, followed by corneal smear and culture. Amikacin 40 mg/dL was promptly initiated awaiting the microbiological results. The confocal scan and microbiological features of this case were similar to those in the previous cases. The infection responded favorably to therapy, and the stromal infiltrates gradually decreased. During the treatment course in the left eye, the right corneal haze progressed to a focus of anterior stromal infiltration (Figure 6, B), reducing visual acuity. Slitlamp examination was consistent with early Nocardia keratitis, and amikacin 40 mg/dL eyedrops were started. Despite a favorable response to therapy, flare-up of the lesion occurred in the left cornea. This was adequately controlled by increasing the frequency of amikacin eyedrops. At the last follow-up examination, the uncorrected visual acuity was 20/20 in the right eye and 20/25 in the left eye and there was no sign of recurrence (Figure 6, C).
DISCUSSION

*Nocardia* are worldwide inhabitants of soil and water. They are gram-positive and acid-fast to 1% sulphuric acid and stain with the Kinyoun technique, a modification of the Ziehl-Neelson method. They grow slowly on most culture media; therefore, culture plates should be kept for at least 5 to 7 days. 

*Nocardia* keratitis has been reported in immunocompromised patients; following trauma; and after ocular surgery such as LASIK, implantation of intracorneal ring segments, keratoplasty, and cataract surgery. It follows a slowly progressive, indolent, and recalcitrant course. To our knowledge, this report is the first describing an outbreak of *Nocardia* keratitis following PRK, posing a challenging diagnosis in the first 2 cases. *Nocardia* keratitis appears as a well-defined corneal ulcer with a grey sloughing bed and incomplete necrotic boundaries. The superficial stromal infiltrates are pinhead-sized, granular or nodular in shape, and occur in a wreath-like configuration together with “brush-fire” or feathery borders; multifocal or satellite lesions may be seen. The clinical presentation of this rare infection may resemble a fungal or atypical mycobacterial keratitis, possibly delaying the correct diagnosis and management and leading to significant ocular morbidity. The diagnostic confusion was demonstrated in our 2 patients; the infection was considered a mycotic keratitis before the microbiological results were obtained. Although the wreath-like configuration of the stromal infiltrates was noted in all 4 eyes, early treatment was started in only the third patient in whom there was a high index of suspicion.
Possible sources of contamination in post-PRK keratitis are the patient’s skin or conjunctival surfaces, surgical instruments, topical anesthetic agents, and airborne particles. Garg and Sharma report Nocardia keratitis after LASIK surgery in 4 eyes of 3 patients operated on the same day at the same center. Use of the same blade and microkeratome during surgery was considered the most probable route of contamination in these cases. In the current report, although the patients were not operated on the same day, they were operated on by the same surgeon. The most probable source of infection seemed to be inadequate attention to strict sterility rules during surgery; povidone–iodine preparation, draping of the surgical field, and wearing sterile gloves were important issues neglected by the surgeon. Although glove-free surgery may be an acceptable alternative in certain settings, adherence to completely sterile conditions may be more appropriate in communities in which the rate of infectious corneal ulcers is high. Contact lens wear and use of corticosteroids after PRK may also be considered contributing factors but do not seem to induce an outbreak. Application of MMC during PRK is another potential factor because of the predisposition to development of persistent corneal epithelial defects. However, none of our 3 patients developed persistent epithelial defects after surgery; the development of late-onset infection also points to possible inoculation of the microorganisms during surgery. The occurrence of infection in the left eye in all 3 cases may suggest contamination of the instruments during the course of surgery in the right eye.

Nocardia species are highly sensitive to amikacin, sulphamethazole, and imipenem. Monotherapy with amikacin appears to be the treatment of choice in Nocardia keratitis, with favorable prognosis if started early. Based on disk diffusion test results, all the isolates from our cases were sensitive to amikacin and monotherapy with amikacin was successful in all eyes.

A confocal scan is a noninvasive diagnostic tool with high sensitivity and specificity for rapid diagnosis of Acanthamoeba and fungal keratitis. A confocal scan imaging together with appropriate microbiological staining techniques can facilitate early diagnosis, leading to proper management and a favorable response to therapy in Nocardia keratitis.

REFERENCES


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