Post-LASIK Infiltrates and Infection

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CASE PRESENTATION

A 78-year-old man presented after uncomplicated cataract-IOL surgery the previous year. His residual manifest refraction was +0.50 -2.50 X 90 = 20/20, +2.50 J1+ OD, and +0.25 -1.25 X 95 = 20/20, +2.50 J1+ OS. The patient expressed a desire for monovision to improve his reading vision and to reduce his residual astigmatism and dependence on spectacles.

One day after uneventful bilateral iLASIK (Abbott Medical Optics Inc., Santa Ana, CA), the patient had a UCVA of 20/30 with mild flap edema and J3 near vision in his right eye. His postoperative therapeutic regimen consisted of Lotemax and Besivance q.i.d. (both products manufactured by Bausch + Lomb). Two weeks after surgery, he had a UCVA of 20/20 OD and a clear LASIK flap, but a small epithelial defect was visible superiorly. The patient had just completed his use of Besivance but was still instilling Lotemax. At that visit, the latter medication was discontinued.

One week later, the patient presented with a complaint of tearing and foreign body sensation for 1 day. A small infiltrate, which appeared similar to a typical peripheral contact lens-related infiltrate, was located superiorly 1 mm inside the LASIK flap's edge of the right eye. The patient was started on hourly Besivance and bacitracin ointment five times per day. The infiltrate seemed to improve, and re-epithelialization occurred in 48 hours; the interface, however, appeared to have light diffuse lamellar keratitis (DLK) centrally. Lotemax was restarted four times per day. The DLK cleared, but the cornea became increasingly edematous, although the epithelium remained intact. A 48-hour trial of Durezol (Alcon Laboratories, Inc.) every 2 hours produced no improvement.

After diagnosing DLK, the surgeon lifted and refloated the flap (Figure 1). Thereafter, the patient only temporarily showed signs of improvement. Cultures performed during this intervention were negative for growth. Despite the addition of fortified antibiotics to the therapeutic regimen, the course deteriorated (Figure 2).

A week later, culturing during a second lifting of the LASIK flap produced a positive Gram stain for gram-negative rods and gram-positive cocci. After consulting several physicians, the surgeon decided to amputate the flap and send it for pathology, microbiology, and microscopy. Pathology showed no organisms. Gram stains showed gram-positive rods in chains that were acid fast.

How would you proceed from an infectious and clinical standpoint? It is now roughly 3 months after the original surgery, and Figure 3 shows the appearance of the affected eye at the slit lamp.

Figure 1. A slit-lamp photograph of the patient's right eye. Cells in the interface were not responsive to topical medical intervention.

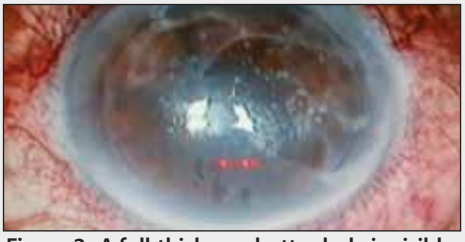


Figure 2. A full-thickness buttonhole is visible superiorly in the area of previous inflammatory debris and ulceration, with an 80% epithelial defect and epithelial ingrowth covering approximately 20% of the nasal interface.

Figure 3. A slit-lamp photograph of the eye 3 months after the original iLASIK procedure.

(Images courtesy of Karl G. Stonecipher, MD.)

ERIC D. DONNENFELD, MD

This case emphasizes several important points in the management of infectious keratitis after LASIK:

- Any focal infiltrate after the procedure must be considered infectious until proven otherwise.
- Any postoperative infiltrate must be cultured, because infections after LASIK are often opportunistic and do not respond to conventional antibiotic therapy. This is particularly true for infiltrates that occur more than 10 days after surgery.
- Patients who have developed an infiltrate while using a prophylactic antibiotic usually will not be sensitive to that antibiotic, so increasing the frequency of the antibiotic is not helpful.
- Corticosteroids will often mask the presentation of infectious keratitis.

The organisms seen in early-onset infectious keratitis are common bacterial pathogens such as *Staphylococcus* and *Streptococcus*. Gram-negative organisms are rare. The organisms seen in late-onset infectious keratitis are usually opportunistic such as fungi, *Nocardia*, and atypical mycobacteria. Because the organisms responsible for infectious keratitis after LASIK often will not respond to empiric therapy, my colleagues on the ASCRS Cornea Clinical Committee and I recommend lifting the flap, scraping and culturing suspicious cases, and selecting appropriate culture medium, including blood agar, chocolate agar, Sabouraud's dextrose agar, and thioglycollate broth. For infectious keratitis occurring 2 weeks or more after LASIK, we suggest a growth media for atypical mycobacteria such as Lowenstein-Jensen medium or Middlebrook 7H-9 broth in addition to the other culture media. If these special media are unavailable, blood agar is a useful alternative, because atypical mycobacteria grow quite well on these plates. At the time of culturing, we also recommend scraping the infiltrate and performing a Gram stain, Gomori methenamine silver stain, and Ziehl-Neelsen stain to rule out unusual pathogens such as *Nocardia*, atypical mycobacteria, and fungi.[1]

For delayed-onset keratitis, the most common organisms are atypical mycobacteria, *Nocardia*, and fungi. For empiric treatment until the results of the culture return, we have patients begin therapy with amikacin 35 mg/mL every 30 minutes alternating with a fourth-generation fluoroquinolone every 30 minutes, start oral doxycycline 100 mg twice a day, and discontinue corticosteroids. This treatment will not affect fungal infections; therefore, treatment for all cases of infectious keratitis should be modified based on culture and scraping results and the patient's clinical response to therapy.[1]

In the presented case, the Gram stain is consistent with atypical mycobacteria, so I would recommend amikacin 35 mg/mL every 30 minutes and would consider switching to clarithromycin if the patient did not respond to initial therapy. To improve penetration of the medication, I would consider scraping the epithelium. This patient may require a therapeutic penetrating keratoplasty for visual rehabilitation.

Future therapeutic intervention that appears promising is riboflavin-ultraviolet cross-linking, which effectively kills resistant organisms.[2]

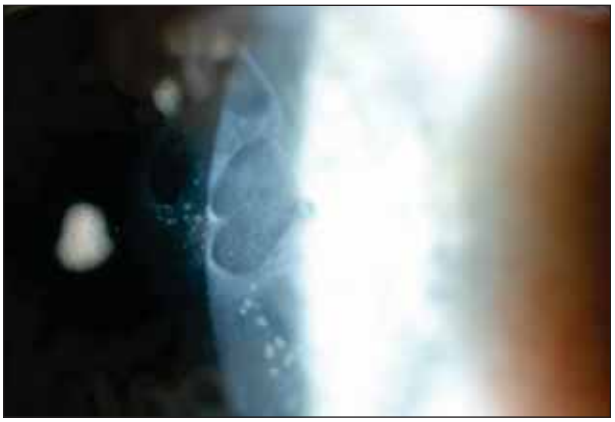
TERRENCE J. DOHERTY, MD, AND JAMES C. LODEN, MD

This unfortunate case demonstrates the need to respond aggressively when infiltrates begin to appear in the flap interface. The infiltrates that are shown in Figure 1 do not seem characteristic of DLK. Their consolidated, dense appearance with indistinct borders in a central location is more indicative of an infectious etiology. Making this assumption and treating accordingly would call for lifting the flap as soon as possible before necrosis or scarring occurred.

> "Respond aggressively when infiltrates begin to appear in the flap interface."
>
> *—Terrence J. Doherty, MD, and James C. Loden, MD*

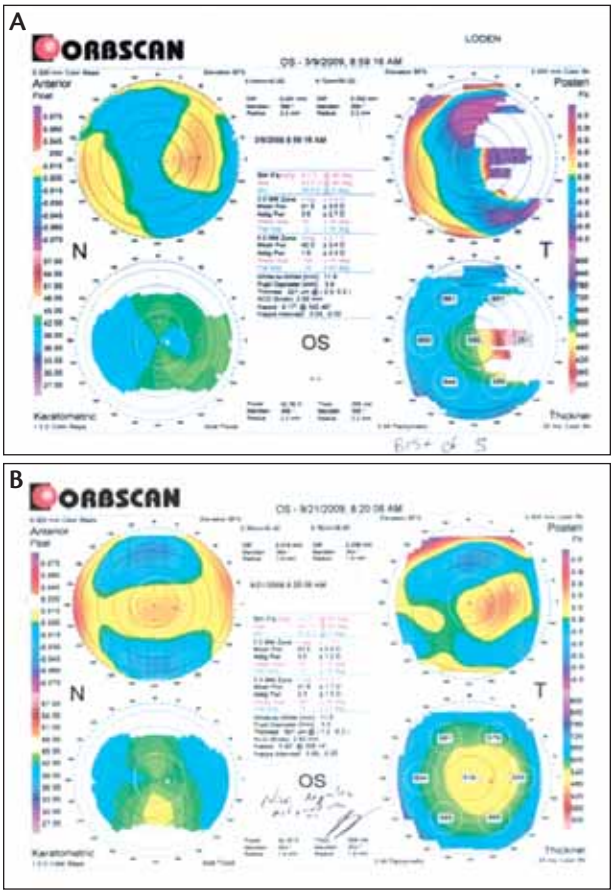
Our typical course of action includes lifting the flap in the OR setting and culturing the infiltrate using chocolate and Sabouraud's agar for bacteria and fungus. We also have slides and a bench microscope in our clinic, which we will use to perform Gram stains in house. We have found this approach particularly helpful in identifying fungus, which may take a week to grow in culture. Ideally, cultures are taken before antibiotics have been started.

We thoroughly scrape the stromal bed and underside of the flap using a Tooke's knife or other blunt instrument. We then place several drops of a fourth-generation fluoroquinolone (Zymar [Allergan, Inc.] or Vigamox [Alcon Laboratories, Inc.]) as well as Tobradex (Alcon Laboratories, Inc.) directly on the stromal bed before repositioning the flap. We prefer these medications not only for their broad spectrum of coverage and anti-inflammatory properties, but also because they are fully dissolved solutions and not suspensions; they are therefore less likely to irritate or leave debris in the interface. We would then start the patient on q1h fortified antibiotics, usually gentamicin and vancomycin to cover gram-positive and gram-negative bacteria.



(Courtesy of Terrence J. Doherty, MD, and James C. Loden, MD.)

Figure 4. The appearance of a post-LASIK eye injured by a holly thorn.



(Courtesy of Terrence J. Doherty, MD, and James C. Loden, MD)

Figure 5. The results of topography on the eye shown in Figure 4 before (A) and 6 months after the amputation of the LASIK flap (B).

Although nontuberculous mycobacteria (NTM) used to be the most common cause of infectious keratitis after LASIK, their incidence has significantly decreased, perhaps in large part due to the common use of fourth-generation fluoroquinolones. As this case demonstrates, however, this infection can still occur and may be hard to identify early. If NTM are suspected, the infiltrate from the lifted flap could be plated directly on several slides for a Gram stain by a pathologist. Because NTM are only weakly gram positive, they would likely be hard to identify with a Gram stain in the office. Additionally, the infiltrate could be plated directly on a special medium such as Lowenstein-Jensen. A conversation with the local pathologist is often helpful in choosing the correct medium and properly collecting a sample.

The recommended treatment for NTM keratitis includes multi-drug therapy, which normally includes macrolide antibiotics, such as clarithromycin or azithromycin. Only recently has this class of antibiotic been available in a topical drop (Azasite; Inspire Pharmaceuticals, Inc.). We are not aware of any published reports on using this medication to treat NTM keratitis after LASIK, but it seems appropriate to consider such therapy, especially since the drug has been shown to remain at high concentrations within ocular tissue after a single dose.[3] We would not recommend using Azasite directly on the stromal bed when lifting the flap, however, because the Durasite vehicle (Insite Vision Incorporated, Alameda, CA) is thick in consistency and may interfere with other medications or destabilize the repositioned flap.

During the past 13 years, we have seen three referred cases in which an injured or damaged LASIK flap required amputation. In one, severe infectious keratitis occurred several years after the LASIK procedure. The infection caused almost complete necrosis of the flap and required its amputation on the patient's first visit to our office. We cut the tissue specimen into small pieces and placed them directly on culture plates. The results yielded a fluoroquinolone-resistant *Staphylococcus aureus* that was sensitive to tobramycin. Aggressive treatment with fortified vancomycin and tobramycin ultimately eradicated the infection. The residual scarring caused poor BCVA, however, and the patient eventually required a penetrating keratoplasty. Although a progression from LASIK to transplant surgery may be considered a worst-case scenario, with the improvements in keratoplasty techniques, including IntraLase-enabled keratoplasty (IntraLase FS laser; Abbott Medical Optics Inc.), even these patients may achieve highly functional vision.

In another of the three cases, a 47-year-old man had undergone LASIK in 2007. The next year, he was hit in his left eye by a holly thorn, injuring the flap and causing scarring (Figure 4). His BCVA was reduced to 20/30-2 with irregular astigmatism, and the patient was contact lens intolerant (Figure 5A). We amputated the flap in March 2009. Six months later, his BCVA was 20/15. The residual manifest refraction was -1.25 -2.00 X 10 OS, and the patient was happy, with no desire to pursue PRK. Postoperative topography is shown in Figure 5B. The keys to success here

were the creation of a smooth stromal bed and the prevention of postoperative inflammation and haze. We trimmed the flap's hinge as close to the stromal bed as possible with Gills scissors and smoothed the stump of remaining tissue with a diamond-tipped burr. We applied mitomycin C (MMC) 0.02% for a full 90 seconds and then thoroughly rinsed the ocular surface. We instilled a drop of bromfenac on the stromal bed and placed a bandage contact lens. Postoperatively, we prescribed Pred Forte q2h and Vigamox q.i.d. and observed the patient closely for the development of haze. No return trips to the OR were necessary.

Our point is that, if the LASIK flap is injured and requires amputation, the patient can still attain a satisfactory visual acuity, provided that the surgeon maintains a smooth stromal bed and takes aggressive measures to prevent haze and inflammation.

STEPHEN G. SLADE, MD

I have removed several LASIK flaps during my career, and the patients have done well. I usually treat the bed with MMC, after the flap's removal, to help avoid haze. Practically, the result is a deeper, rougher PRK. I typically peel or avulse the flap, a procedure that can be performed at the slit lamp, although this setting makes administering MMC tricky. Pulling back on the flap against its base will create a lamellar tear into the base of the flap. It will also produce a smooth, beveled edge and avoid the ridge likely after simply cutting off the flap at its hinge. A helpful test is a gas permeable contact lens overrefraction. If the patient's vision improves, then the problem is likely irregularity and not the blocking effect of haze. If available, the surgeon could consider a topography-based ablation in this case.

In none of my cases has haze developed after the flap's removal. If it did, I

would place a lamellar graft on top of the bed after removal of the haze with the excimer laser.

I have only seen one mycobacterium infection, on referral. It resolved after the LASIK flap's removal and treatment with clarithromycin and amikacin. Fluoroquinolones are not very helpful in these cases. Of course, for suspected mycobacterium, a full culture and sensitivity are required.

Amputating the flap helps to debulk tissue and bacteria, it likely removes a nonoptical element, and perhaps most importantly, it allows the antimicrobial agents direct access to the stromal bed.

TERRY KIM, MD, AND CLAYTON FALKNOR, MD

This patient apparently experienced an infectious keratitis after developing an epithelial defect superiorly in his right eye, with an associated inflammatory response in the LASIK interface. A strong course of topical antibacterials did not quell the intense inflammatory response of the cornea. Epithelial ingrowth and a flap melt ensued. The cultures obtained demonstrated an infection with mycobacteria chelonae.

An underrecognized infectious complication of LASIK is caused by nontuberculous or atypical mycobacteria. Most take several weeks to grow, and these microbes can often be attributed to contaminated sources of water, including steam instrument cleaners and nonsterile ice.

In 2004, Chang and colleagues published a large retrospective review of cases of post-LASIK infections that divided them into early onset (within the first 7 days postoperatively) and later onset (> than 10 days postoperatively). Although the early-onset organisms were mostly gram positive (54%), the majority of infections with later onset were culture positive for atypical mycobacteria (57%).[4] In a 2005 ASCRS white paper, Donnenfeld et al reviewed more than 100 published cases of post-LASIK infectious keratitis and found atypical mycobacteria to be the most prevalent (47%) cause.[1] Half of those cases eventually required amputation of the flap, and antibiotic treatment was needed for at least 2 to 3 months. Moshirfar et al confirmed these findings in a 2007 review.[5] Due to the widespread prophylactic use of fourth-generation fluoroquinolones, cases of atypical mycobacterial keratitis may be decreasing. A recent large study by Llovet et al early this year reviewed 204,586 cases of LASIK. Of the 72 cases of infectious keratitis, none cultured positive for atypical mycobacteria, although appropriate culture media may not have been used, and there were many culture-negative cases in later-onset infections.[6]

Based on the recommendations of the ASCRS Cornea Clinical Committee, an appropriate plan in the presented case would be a long course of frequently administered, topical, fortified amikacin 35 mg/mL, alternating with a fourth-generation fluoroquinolone, and oral doxycycline. Steroids should not be restarted, but a topical cycloplegic such as scopolamine 0.25% b.i.d. should be instituted. The patient's response to treatment would determine if other options are warranted (eg, the flap's amputation, lamellar or penetrating keratoplasty, etc.). ■

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