Sloughing of Corneal Epithelium and Wound Healing Complications Associated With Laser In Situ Keratomileusis in Patients With Epithelial Basement Membrane Dystrophy

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• PURPOSE: To report sloughing of corneal epithelium during laser in situ keratomileusis and subsequent wound healing complications in patients with epithelial basement membrane dystrophy.
• METHODS: In a retrospective study, the surgical procedures, postoperative course, and visual acuities of 16 eyes of nine patients with epithelial basement membrane dystrophy who underwent laser in situ keratomileusis complicated with epithelial sloughing at three centers were reviewed. The mean follow-up period was 23 weeks (range, 4 to 52 weeks).
• RESULTS: In 13 (81%) of 16 eyes with epithelial basement membrane dystrophy, epithelial sloughing occurred during laser in situ keratomileusis. In eight of the 13 eyes, epithelial growth beneath the flap was observed. The flap was lifted and the interface epithelium scraped in six eyes. Flap melt or keratolysis occurred in four eyes. At the last follow-up visit, 13 of 16 eyes had an uncorrected visual acuity of 20/30 or better, and all eyes had a best-corrected visual acuity of 20/30 or better.
• CONCLUSIONS: Patients with epithelial basement membrane dystrophy have poorly adherent corneal epithelium and are predisposed to epithelial sloughing during the microkeratome pass of laser in situ keratomileusis. This may lead to flap distortion, interface epithelial growth, flap keratolysis, and corneal scarring. It is not recommended that laser in situ keratomileusis be performed in patients with classic, symptomatic epithelial basement membrane dystrophy. In patients who present with mild and asymptomatic epithelial basement membrane dystrophy, laser in situ keratomileusis should be performed with caution, or photorefractive keratectomy may be the preferred refractive procedure. (Am J Ophthalmol 2000;130:297–303. © 2000 by Elsevier Science Inc. All rights reserved.)

EPITHELIAL BASEMENT MEMBRANE DYSTROPHY IS THE most common corneal dystrophy, with an estimated prevalence of 5%.1 As with other corneal dystrophies, the disorder is bilateral but it may be asymmetric. The synonym map-dot-fingerprint dystrophy refers to biomicroscopic findings of map-like subepithelial geographic opacities, intraepithelial microcysts (dots), and subepithelial ridges resembling fingerprints.1–5 The primary histopathologic defects in epithelial basement membrane dystrophy are multiple laminations of basement membrane, underdeveloped hemidesmosomes, and an absence of anchoring fibrils.6,7 These findings result in poor adherence of corneal epithelium to Bowman layer. In patients with epithelial basement membrane dystrophy, even minor trauma to the corneal surface may dislodge poorly anchored epithelium. We report sloughing of corneal epithelium during the microkeratome pass of laser in situ keratomileusis and subsequent wound-healing complications in patients with epithelial basement membrane dystrophy.

PATIENTS AND METHODS

IN A RETROSPECTIVE STUDY AT THREE CENTERS, WE REVIEWED the surgical procedures, postoperative course, and visual acuities in 16 eyes of nine patients with epithelial basement membrane dystrophy who underwent laser in situ keratomileusis complicated by epithelial sloughing (Table 1). Two of nine patients (cases 2 and 5) were referred to the centers after additional complications of
epithelial sloughing. One patient with a known history of symptomatic epithelial basement membrane dystrophy (case 6) had been symptom-free for 12 months before undergoing laser in situ keratomileusis. Epithelial basement membrane dystrophy was initially undetected in three patients (cases 3, 4, and 7) in whom dystrophic changes were recognized postoperatively. In the remaining three patients (cases 1, 8, and 9), the dystrophy was judged to be insignificant in its appearance and by its paucity of symptoms.

All patients were examined on the first postoperative day. The frequency of subsequent follow-up examinations was at the surgeon’s discretion, according to the healing pattern of the epithelium, the status of the corneal flap, and the visual acuity. The mean follow-up period was 23 weeks (range, 4 to 52 weeks).

### CASE REPORTS

- **CASE 1**: A 50-year-old woman with epithelial basement membrane dystrophy underwent bilateral, simultaneous laser in situ keratomileusis. Preoperative refractions were $-6.50 + 1.00 \times 082$ (20/20) in the right eye and $-6.75 + 2.25 \times 082$ (20/20) in the left eye. At the time of surgery, a 3-mm by 3-mm area of epithelial defect was noted over the flap edge at the 8 o’clock position in the right eye; otherwise, the procedures were unremarkable. A bandage contact lens was placed in the right eye.

On the first postoperative day, uncorrected visual acuity was RE: 20/20 and LE: 20/50. The epithelial defect persisted in the right eye for 1 week, with mild underlying flap edema. On postoperative day 14, small nests of epithelium were found beneath the flap. The epithelial

### TABLE 1. Postoperative Course in 16 Eyes of Nine Patients With Epithelial Basement Membrane Dystrophy After Laser In Situ Keratomileusis

<table>
<thead>
<tr>
<th>Case/Age/Sex</th>
<th>Preoperative Refraction (BCVA)</th>
<th>Epithelial Sloughing$^a$</th>
<th>Epithelial Ingrowth$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total or Partial Sheet or Nests</td>
<td>Flap Melt$^c$</td>
</tr>
<tr>
<td>1/50/F</td>
<td>RE $-6.50 + 1.00 \times 082$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>LE $-6.75 + 2.25 \times 082$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>2/52/M</td>
<td>RE $-5.00 + 0.75 \times 075$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>LE $-5.25 + 0.75 \times 080$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>3/40/M</td>
<td>RE $-4.00 + 1.50 \times 130$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>LE $-3.25 + 0.50 \times 075$ (20/30)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>4/45/F</td>
<td>RE $-8.00 + 2.00 \times 085$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>5/61/F</td>
<td>RE $-5.00 + 0.75 \times 075$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>LE $-5.25$ sphere (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>6/53/F</td>
<td>RE $-9.25 + 1.00 \times 113$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>7/56/M</td>
<td>RE $-3.00 + 0.50 \times 020$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
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<tr>
<td></td>
<td>LE $-5.25$ sphere (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>8/33/M</td>
<td>RE $-5.50 + 0.75 \times 130$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>LE $-7.00 + 0.75 \times 065$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>9/44/F</td>
<td>RE $-4.00 + 0.50 \times 165$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>LE $-4.25 + 0.75 \times 020$ (20/20)</td>
<td>+ or +</td>
<td>+</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>7 or 6</td>
<td>6 or 2</td>
</tr>
</tbody>
</table>
nests were continuous with the surface epithelium in the region where the epithelial defect had been present.

On postoperative day 42, the interface epithelium was found to cover a larger surface area, and it was approaching the visual axis (Figures 1 and 2). A segment of the flap was lifted, and both surfaces (stromal bed and the posterior surface of the flap) were scraped. The fellow flap (LE) was lifted to correct a residual refractive error of \(-1.75 + 1.00 \times 075\). This treatment was given without incident.

On the forty-fourth postoperative day, epithelium was still present in the same area of the interface in the right eye. On postoperative day 58, the interface epithelium still appeared to be continuous with the flap edge and extended 2.5 mm toward the corneal center. The eye was again treated. This time the entire flap was retracted and a sheet of epithelium was peeled from the stromal bed surface. Both surfaces were then vigorously scraped. On postoperative day 100, rare epithelial nests were noted away from the flap edge, with an uncorrected visual acuity of RE:
20/25, a best-corrected visual acuity of RE: 20/20, and an uncorrected visual acuity of LE: 20/20.

CASE 2: A 51-year-old man with a preoperative refraction of RE: $-5.00 + 0.75 \times 075$ (20/20) and LE: $-5.25 + 0.75 \times 080$ (20/20), underwent bilateral, simultaneous laser in situ keratomileusis. Intraoperatively, it was noted that the corneal epithelium had completely separated from the underlying Bowman layer during the creation of the primary keratectomy flap in the right eye. The laser ablation was completed without incident. The flap was then repositioned without use of a bandage contact lens. The surgeon elected to proceed with the fellow eye, despite this occurrence. During the microkeratome cut, the corneal epithelium completely separated from the underlying Bowman layer again. The laser ablation was completed without incident. The flap was repositioned without use of a bandage contact lens.

On the first postoperative day, a total epithelial defect was present in both eyes. By the seventh postoperative day, both epithelial defects had healed. A large sheet of epithelium was noted in the superior interface of both eyes. This was associated with flap edema. The surgeon attempted to remove the ingrowth from both flaps (Table 1). On postoperative day 11 (4 days after reoperation), recurrent epithelial ingrowth was noted. The epithelial ingrowth was again removed from both eyes. In an attempt to prevent further recurrence, the superior portion of both flaps were sutured with several interrupted 10-0 nylon sutures. On postoperative day 18 (1 week after the third procedure), uncorrected visual acuity was RE: 20/200 and LE: 20/400, correcting to RE: 20/70 and LE: 20/200. There was no evidence of recurrent epithelial ingrowth in the right eye. The interface was noted to have scattered debris and fibrosis. Recurrent ingrowth, involving 70% of the entire flap, was observed in the superior aspect of the left eye (Figure 3). This was associated with 30% necrosis of the superior portion of the flap. Fibrosis and scarring were also present in the region of the previous suture tracks.

The patient was referred for further management. On postoperative day 25, the epithelial ingrowth was removed from both the stromal bed and the posterior surface of the flap in the left eye. Portions of the superior necrotic flap were removed by blunt dissection. The remaining non-necrotic flap was sutured in place with several interrupted 10-0 nylon sutures (Figure 4). On postoperative day 46 (3 weeks after the third postoperative procedure), the surface epithelium was intact. No further melting was observed. The sutures were removed.

On postoperative day 185, the patient underwent un-
complicated laser in situ keratomileusis enhancement in the right eye. At 1 year, there has been no further evidence of recurrent epithelial ingrowth in either eye. The right eye has an uncorrected visual acuity of 20/25 with a best-corrected visual acuity of 20/20. The left eye has an uncorrected visual acuity of 20/40 and a best-corrected visual acuity of 20/25 (see Table 1). The area of previous melt and ingrowth has healed with faint scarring. The patient does not have any glare, halos, or night vision difficulties. Both eyes demonstrate classic map-dot-fingerprint changes in the epithelium over the flap.

**CASE 3:** A 40-year-old man with a preoperative refraction of RE: $-4.00 + 1.50 \times 130$ (20/20) and LE: $-3.25 + 0.50 \times 075$ (20/30) underwent bilateral, simultaneous laser in situ keratomileusis. The diminished best-corrected visual acuity in the left eye was the result of corneal scarring from a foreign body. During the microkeratome cut, poor epithelial adhesion was noted in the inferior cornea (approximately 3 clock hours, 2 mm inside the flap) in both eyes. Bandage contact lenses were placed.

On the first postoperative day, the patient reported a mild foreign body sensation and had an uncorrected visual acuity of RE: 20/30 and LE: 20/40. The epithelium was irregular in the areas described; however, there was no epithelial defect. The bandage contact lenses were removed. On the tenth postoperative day, the epithelium was noted to be intact and smoother.

On the sixty-second postoperative day, uncorrected visual acuity was RE: 20/70 and LE: 20/80. Refractions were RE: $-2.00 + 1.50 \times 120$ (20/25) and LE: $-1.50 + 1.75 \times 117$ (20/30). There was evidence of map and fingerprint lines in the superficial cornea. During bilateral, simultaneous enhancement, a 3-mm by 4-mm epithelial defect was noted at the inferior nasal edge of the flap in the right eye. The procedure was uneventful in the left eye. A bandage contact lens was placed on the right eye. The following day, the patient complained of a mild foreign body sensation in the right eye. Uncorrected visual acuity was RE: 20/80 and had improved to 20/25 in the left eye. On the seventieth postoperative day (1 week after enhancement), the corneal epithelium in the right eye had healed. However, a fold was present in the inferior nasal aspect of the flap, as well as several islands of retained epithelium in the right eye (Figure 5). The flap edge appeared normal, without any apparent connection between the islands of retained epithelium and the surface.

By the three-hundredth postoperative day, the interface epithelial nests as well as the flap fold had resolved. Uncorrected visual acuity at this time was RE: 20/30, correctable to 20/20 with a residual refraction of $-0.50 + 0.50 \times 105$. Uncorrected visual acuity in the left eye was stable at 20/25.

**RESULTS**

SIXTEEN EYES OF NINE PATIENTS WITH EPITHELIAL BASEMENT MEMBRANE DYSTROPHY underwent laser in situ keratomileusis (Table 1). During the microkeratome pass in 13 eyes (81%), partial (six) or total (seven) epithelial sloughing occurred. Subsequent flap distortion was common. This was believed to be the result of the loss of the previously placed ink markings on the corneal surface and minor edema.

Epithelial ingrowth beneath the flap was observed in eight (62%) of 13 eyes with epithelial sloughing. Two eyes had isolated nests of ingrowth that spontaneously resolved.
in one eye (case 3), and was stable in the other eye until the patient was lost to follow-up (case 6). Six eyes had epithelial sheets that were continuous with surface epithelium. In these six eyes, the flap was lifted and the interface epithelium scraped. Four of six eyes (67%) required repeated intervention to remove the epithelial ingrowth. The number of flap interventions for epithelial ingrowth was once in two eyes (patient 4, right eye and patient 5, right eye), twice in three eyes (patient 1, right eye; patient 2, right eye; and patient 5, left eye), and three times in one eye (patient 2, left eye). Flap keratolysis or melt occurred in four (67%) of six eyes with sheets of epithelial ingrowth (patient 2, right eye and left eye; patient 5, right eye and left eye).

Fifteen of 16 eyes had a preoperative best-corrected visual acuity of 20/20. One eye had a preoperative best-corrected visual acuity of 20/30. At the last follow-up examination, 13 of 16 eyes (81%) had an uncorrected visual acuity of 20/30 or better. The worst uncorrected visual acuity (20/60) was in patient 6 at 18 weeks postoperatively. She was subsequently lost to follow-up. She lived 2,000 miles from the treating surgeon and was seen by local physicians for portions of her care. At the last follow-up visit, all 16 eyes had a best-corrected visual acuity of 20/30 or better.

**DISCUSSION**

**THIS REPORT DEMONSTRATES THAT THE PRESENCE OF EPITHELIAL BASEMENT MEMBRANE DYSTROPHY MAY INCREASE THE RISK OF MICROKERATOME COMPLICATIONS WITH LASER IN SITU KERATOMILEUSIS.** In the preoperative evaluation for refractive surgery, it is important to obtain a clinical history of symptoms related to epithelial basement membrane dystrophy and to examine the cornea carefully. The most common symptoms include pain and a foreign body sensation, especially upon awakening; perception that the lid is “sticking” to the cornea, especially upon awakening; and blurred vision. On slit-lamp evaluation, a meticulous examination of the corneal epithelium should be performed by direct, tangential, and retro-illumination. Because this is best performed when the pupil is dilated, we recommend doing this evaluation after the cycloplegic refraction. Observation for negative staining of fluorescein dye with cobalt blue illumination may also be helpful in the diagnosis. The characteristic changes of epithelial basement membrane dystrophy include map, dot, and fingerprint patterns within the epithelium. Map-like and fingerprint patterns represent abnormal multilaminar basement membrane. These abnormal basement membrane deposits occur both in the normal location overlying Bowman layer and within the epithelium. The dot (microcystic) patterns represent degenerated epithelial cells trapped by the abnormal basement membrane.1–3 Bron and Brown5 have also described more unusual bleb-like changes in the corneal epithelium, best seen on retroillumination. It is important to realize, however, that clinical signs in asymptomatic eyes may be absent, and despite meticulous examination, epithelial basement membrane dystrophy may be missed.

In our series, sloughing and/or loosening of corneal epithelium occurred during laser in situ keratomileusis in 13 of 16 eyes in nine patients with epithelial basement membrane dystrophy. These patients were known to have epithelial basement membrane dystrophy before the procedure or were noted to have epithelial basement membrane dystrophy after laser in situ keratomileusis. Because patients with epithelial basement membrane dystrophy have decreased adherence of epithelium to Bowman layer, we propose that they are at an increased risk of epithelial sloughing in laser in situ keratomileusis by mechanical trauma during the sliding motion of the microkeratome over the corneal surface.

Epithelial sloughing may lead to interface epithelial growth, a complication of laser in situ keratomileusis. The few published reports of this complication have an incidence that is highly variable, and there is an uncertain etiology.8–12 Epithelial growth within the flap-corneal stromal bed interface occurred in eight of 13 eyes with epithelial sloughing. We hypothesize that epithelial sloughing may cause mild flap edema with elevation of the flap margin. Distortion at the flap edge may create a potential space within the interface for epithelial cells to migrate from the flap perimeter. A sheet of epithelium, continuous with epithelium from the flap edge, can grow beneath the flap. This hypothesis appears to be clearly supported by the findings in case 1. In this case, the epithelial sloughing occurred in a discrete area (8 o’clock) of the flap edge. Mild flap edema was observed in that area, with subsequent epithelial ingrowth in that location (Figures 1 and 2). When the flap was lifted a second time, the epithelial ingrowth was peeled as a sheet that was continuous with surface epithelium. It is recommended to aggressively remove a sheet of interface epithelium, continuous with and fed by surface epithelium, if the sheet is unreleenting or causing visual symptoms by encroaching on the visual axis, producing irregular astigmatism or flap keratolysis. Isolated nests of interface epithelium may, however, be observed, because they will often spontaneously degenerate without visual sequelae.

Flap keratolysis or melt (Figure 3) was observed in four of eight eyes with epithelial ingrowth. Flap keratolysis may occur with prolonged periods or repeated bouts of epithelium within the interface (case 2, right eye and left eye). Less commonly, flap melt may occur more rapidly in cases of aggressive epithelial ingrowth (case 5, right eye and left eye). To prevent recurrence of epithelial ingrowth, suturing of the flap after epithelial removal may be helpful. Production of enzymes, such as proteases, by the epithelium has been postulated to cause flap keratolysis.10 If this were the only mechanism, one would expect some necrosis
of the stromal bed. This was not observed in any cases. The epithelium within the interface may interfere with metabolic exchange between the aqueous humor and the flap, creating necrosis.

From our series of nine patients, in three patients (cases 3, 4, and 7) epithelial basement membrane dystrophy was undetected despite careful preoperative examination. In another three (cases 1, 8, and 9), epithelial basement membrane dystrophy was judged to be insignificant because of the paucity of signs and symptoms. One patient with a history of symptomatic epithelial basement membrane dystrophy (case 6) had been symptom free for 1 year before undergoing laser in situ keratomileusis. Finally, the two patients referred for complications of epithelial sloughing (cases 2 and 5) were noted to have classic corneal epithelial basement membrane dystrophy changes postoperatively. Because the estimated incidence of epithelial basement membrane dystrophy is 5% in the general population, it is likely that other patients with initially undetected epithelial basement membrane dystrophy may have undergone laser in situ keratomileusis with or without epithelial sloughing but without further complications. The lack of precise information regarding the frequency with which eyes with epithelial basement membrane dystrophy may have undergone laser in situ keratomileusis is a limitation related to the retrospective nature of our study.

In summary, meticulous screening of all laser in situ keratomileusis candidates for epithelial basement membrane dystrophy should be performed. It is not recommended that laser in situ keratomileusis be performed in patients with symptomatic epithelial basement membrane dystrophy. Surgeons should have heightened awareness for potential epithelial sloughing during laser in situ keratomileusis in patients with previously symptomatic epithelial basement membrane dystrophy. Caution should also be exercised in an asymptomatic patient with classic signs of epithelial basement membrane dystrophy. One should proceed with laser in situ keratomileusis with caution, even in those who have minimal signs of epithelial basement membrane dystrophy and no history of symptoms, as well as in those who describe a history of symptoms related to epithelial basement membrane dystrophy who are currently without signs of the dystrophy. It is not recommended that laser in situ keratomileusis be performed in the fellow eye if significant sloughing of the epithelium occurred in the first eye. If significant sloughing has occurred, in an otherwise adequate flap, one option would be to abstain from lifting the flap initially to minimize flap edema and the possibility of epithelial in growth. A bandage contact lens should be placed on the eye and one should wait one to two weeks after complete healing of the epithelium. The patient should be refracted again, only then lifting the flap to perform laser in situ keratomileusis. Alternatively, photorefractive keratectomy may be a good choice to eliminate the risk of epithelial sloughing, ingrowth, and flap melt, at the same time as the abnormal basement membrane is discarded. When an epithelial defect occurs at the flap edge especially in a patient with initially unsuspected epithelial basement membrane dystrophy, and the laser keratomileusis is completed, certain steps should be taken to promote rapid epithelial healing. These include repositioning the loose epithelium on the cornea, the use of a bandage contact lens, and copious lubrication until epithelial healing is achieved. Careful evaluation of the flap edge should be performed at frequent intervals. If epithelial ingrowth occurs in conjunction with flap elevation or distortion, the flap should be repositioned.

REFERENCES