Corneal Epithelial Adhesion Disorders

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Introduction

The normal corneal epithelium maintains its adhesion to the underlying basement membrane, through complex adhesion structures, which are composed of hemidesmosomes, basement membrane components, and structural proteins. Following trauma to the corneal epithelium, new structures are formed as part of the wound healing process. A defect in the appropriate formation of these structures results in inadequate epithelial–stromal attachments, and may lead to localized adhesion problems of the corneal epithelium, manifesting in a distinctive clinical entity entitled recurrent corneal erosion (RCE) syndrome.

Corneal epithelial adhesion problems have many etiologies and are collectively referred to as recurrent corneal erosion syndrome. This disorder is characterized by episodes of spontaneous erosions of the corneal epithelium. These episodes are unpredictable and acute, with symptoms ranging from a mild ocular foreign body sensation, to abrupt sharp pain, usually occurring in the middle of the night or upon awakening. The duration of symptoms may last from minutes to hours. This recurrent disorder can last from a few weeks to several years, creating significant disability and suffering for the patient. It poses a significant therapeutic challenge, since there is no definitive treatment to date. Various treatment strategies have been developed over the years, ranging from various topical medications, which are aimed at prevention of these attacks, to surgical procedures which try to create a new stroma–basement membrane–epithelial environment.

Pathophysiology

NORMAL ANATOMY OF THE EPITHELIAL ADHESION COMPLEX

There are two major adherence mechanisms for corneal epithelial cells to adhere to basement membrane. One mechanism is through direct molecular interaction of receptors with ligands located in the extracellular matrix. Three major families of such molecular interactions have been identified. These include the N-CAM family, the cadherin family, and the integrins, which are a family of integral membrane proteins interacting with an extracellular matrix ligand at cell–matrix interfaces.1

The second mechanism of cell–matrix adhesion is through adhesive junctions, called hemidesmosomes (Fig. 26.1).2 The hemidesmosomes are located on the basal membranes of the epithelial cells. On the external side of the cell membrane at the hemidesmosome, an electron-dense line parallels the membrane and, from it, anchoring filaments extend through the lamina lucida to the lamina densa of the basement membrane (Fig. 26.1). Opposite the lamina densa, anchoring fibrils insert from the stromal side. These fibrils form an intertwining network in the anterior stroma. Distal from their insertions in the basement membrane, anchoring fibrils insert into anchoring plaques, which appear structurally as small segments of basement membrane (Fig. 26.1). Collectively, all these structurally linked components, including intermediate filaments, hemidesmosomes, anchoring filaments, anchoring fibrils and anchoring plaques, are termed the adhesion complex.3

EPITHELIAL CELL ADHESIONS IN RECURRENT CORNEAL EROSIONS

Immediately after the removal of the corneal epithelium, the denuded stroma in the area of the epithelial defect is
coated with fibronectin. This provides a platform for the adjacent viable epithelial cells to slide and migrate to cover the denuded area, and to proliferate to form the superficial cells. The basal cells form adhesion complexes with the underlying structure.

As basal cells of the corneal epithelium begin to migrate to cover a wound, they lose their hemidesmosomes. Re-establishment of the tight adhesion of the corneal epithelium is associated with re-formation of hemidesmosomes and components of the adhesion complex. An interim adhesion junction, termed ‘focal adhesion,’ is constructed along the cell–matrix interface of epithelial cells during migration, as evident by a dramatic increase in protein synthesis during migration to cover a wound.

The status of the basement membrane at the time of initial injury can influence the outcome of epithelial healing. When the basement membrane is involved in the damage, epithelial cell migration and its adherence to the underlying stroma is delayed up to a few weeks. If the basement membrane remains intact, epithelial cells migrate over the old membrane and form adhesion complexes in a few days.

Ultrastructural studies of the cornea in RCE have demonstrated defective junctional complexes following epithelial trauma, resulting in delayed adhesion of epithelial cells to underlying structures (Fig. 26.2). These adhesion complex defects are characterized primarily by the focal absence of the basement membrane and of the hemidesmosomes. The basement membrane may appear multilayered and folded between epithelial cells. In addition, some of the basal corneal epithelial cells appear pale and swollen. Areas of healthy epithelium contain intraepithelial pseudocysts, with collections of cellular and amorphous debris. This cellular debris is probably the result of entrapment of the epithelium by aberrant basement membrane. The abnormal adhesion complexes between the basal epithelial cells and the basement membrane, may lead to focal areas of elevation of the epithelium and the accumulation of underlying cellular debris (Fig. 26.2). This leads to formation of abnormal basement membrane, with further focal detachments of the basal epithelium and accumulation of cellular debris, leading to a vicious cycle of aberrant epithelial adhesion and recurrent erosions.

Figure 26.2 Electron micrograph demonstrating a detached basement membrane (BM) with almost complete absence of hemidesmosomes. Cell membranes are poorly demarcated and interrupted. Cellular debris (G) accumulates between the cells and the basement membrane. (From Tripathi RC, Bron AJ. Ultrastructural study of non-traumatic recurrent corneal erosion. Br J Ophthalmol 1972;56:73, Figure 5, page 79.)

The timing of the erosion corresponds with an abrupt opening of the lids, which is why these episodes occur at night time or while awakening from sleep in the morning. During sleep and lid closure, there is no air between the lids and the tear film, and the surface tension of the tears creates sealing of the lid margins. Abrupt opening the lids creates a shearing force, which is greater than the force of adherence of the epithelium to its basement membrane, and this may result in epithelial avulsion.

MEIBOMIAN GLAND DISEASE AND INFLAMMATORY MEDIATORS

A higher incidence of severe meibomian gland disease (MGD) and acne rosacea was noted in non-traumatic RCE. These patients had inspissation of the meibomian glands, reduced tear film break-up time, conjunctival injection, and facial manifestations of acne rosacea, including facial erythema, flushes, papules, and pustules. The location of the corneal erosions was at the inferior cornea, which was explained by a longer contact with the tear film, containing its inflammatory mediators, typical of MGD.

MGD is associated with higher levels of inflammatory cytokines and matrix-degrading enzymes in the tear film, which may potentially disturb the normal healing process, by interfering with the formation of normal hemidesmosomes and adhesion complexes. Increased bacterial lipase has been demonstrated in patients with MGD, which is responsible for the production of free fatty acids, which can interfere with the assembly of the adhesion complexes. In addition, inflammatory cytokines and matrix-degrading enzymes, such as interleukin-1 and MMP-9 were found to be elevated in the tears of patients with MGD, further contributing to the damaged healing patterns of the corneal epithelium in RCE.

Elevated levels of MMP-2 and MMP-9 have been observed in the tear fluid of patients with RCE. These matrix-degrading enzymes were found to be up-regulated in human epithelia affected by recurrent erosion. These enzymes are concentrated in basal epithelial cells where they may play an important role in degradation of the epithelial...
anchoring system and result in recurrent epithelial slippage and erosion.¹⁴

**Etiology**

Recurrent corneal erosions are the clinical end result of multiple disorders of the corneal epithelium and basement membrane. Although most of the patients with unilateral RCE will present after a history of acute trauma to the cornea with sloughing or erosion of the corneal epithelium (Fig. 26.3), careful consideration must be given to a wide spectrum of causes, specifically in patients with a bilateral disease, having no prior injury to the cornea.

The etiology of RCE may be classified into primary and secondary disorders (Box 26.1).⁹ Primary disorders include genetic disorders, chiefly the corneal dystrophies that involve the epithelium, basement membrane or anterior stroma. Primary disorders are usually bilateral, symmetrical, and may occur in multiple locations in the cornea. The most common of these etiologies is the map-dot fingerprint dystrophy (Figs 26.4, 26.5). RCE is a common manifestation in lattice dystrophy, which involves the anterior stroma (Fig. 26.6).¹⁵

The secondary basement membrane disorders leading to RCE are more common. They are usually acquired disorders, appear in one eye, and are often limited to a single location in the cornea. Of these, minor trauma to the corneal epithelium is the most common cause for RCE.

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**Box 26.1  Etiology of RCE**

**Primary**
- Genetically related basement membrane abnormalities (dystrophies)
  - Anterior epithelial basement membrane dystrophy
  - Map-dot-fingerprint dystrophy
  - Cogan’s dystrophy
- Bowman’s layer
  - Reis-Bückler’s dystrophy
  - Type I: marked visual loss early in life
  - Type II: visual loss late in life
- Stromal dystrophy
- Lattice dystrophy (RCE common)
- Macular dystrophy
- Granular dystrophy (RCE rare)

**Secondary**
- Acquired basement membrane abnormalitie
- Traumatic epithelial abrasions
- Salzmann’s nodular degeneration
- Band keratopathy
- Herpetic infection
- Following bacterial ulcers
- Meibomian gland dysfunction
- Keratoconjunctivitis sicca
- Diabetes mellitus
- Epidermolysis bullosa
- Following refractive surgery

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membrane dystrophy (EBMD). The macroform erosions are associated with a traumatic etiology, and persist for several days. 17 Although little is known about the epidemiology of RCE, it is thought to be a relatively common problem in specialized cornea services. The incidence of RCE was reported to be 1:150 cases following trauma. 9 Careful slit lamp examination is needed to find the subtle signs of this syndrome, since the epithelium in many cases had already healed. The delicate signs of basement membrane dystrophy (Fig. 26.9), the sites of a previous erosion, or clusters of small epithelial microcysts, may be seen with either a broad slit beam or with retroillumination (Fig. 26.10). Examination of the cornea after pupil dilation, against the red reflex, may disclose subtle changes in the corneal epithelium. Gentle pressure applied to the cornea through the eyelid may demonstrate wrinkling of loosely adherent epithelium. In many cases, no signs are found, and then the patient should be instructed to

**Clinical Manifestations**

Sharp pain, tearing, photophobia and redness that occur abruptly upon awakening, when opening the lids, or during sleep, mainly due to rapid eye movements, are the hallmark of RCE. The combination of a previous history of minor trauma to the involved eye, episodes of pain on awakening, and a rough irregular area of healing epithelium, is diagnostic of RCE.

Two main forms of erosion have been identified: microform and macroform. The microform erosions are small epithelial breaks, while the macroform erosion is larger and surrounded with a loosely adherent epithelium. Typically, the microform erosions are less severe, occur more frequently, sometimes every night or morning, occur spontaneously and are associated with epithelial basement membrane dystrophy (EBMD). The macroform erosions are associated with a traumatic etiology, and persist for several days. 17

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return immediately after the next episode of pain, without allowing time for the epithelium to heal and cover the erosion. This will facilitate proper diagnosis and correct location of the lesion for the purpose of treatment.

During the acute attack or during the first few days following the attack, the affected corneal epithelium can present as a loosely adherent and elevated epithelium, or as epithelial microcysts, or as corneal epithelial defects. Stromal infiltrates and opacities may also develop at the site of the erosions. The location of most of the corneal erosions is in the lower half of the cornea. The midline below the horizontal meridian is usually the last area to re-epithelialize, and the closure lines at this area are predisposed to frequent breakdown. In addition, this is the area of maximal exposure, since it opposes the line of lids closure.

A possible complication of RCE is infectious keratitis, occurring as a result of prolonged bandage contact lens use and topical steroids.

When no obvious signs of RCE are evident in the slit lamp examination, the presence of impaired epithelial adhesion is detected by use of a dry cellulose sponge, which is gently rubbed over the area of suspected epithelial erosions. If the intact epithelial sheet is moveable by the sponge, then the lack of adequate epithelial–stromal adhesion must be suspected.

The duration of symptoms may vary, and the frequency and number of attacks are also extremely variable. The frequency of recurrence may range from a minor recurrence every morning to a major recurrence every several months. Recurrences typically last from 1 to 4 hours in the microform condition and 1 to 21 days in the macroform erosions. A more recent study in a large cohort of RCE
patients demonstrated that after 4 years of follow-up, 59% of all patients were still symptomatic, and most of them complained of symptoms occurring upon waking in the mornings. The median frequency of the attacks was every 60 days; however, 24% of symptomatic patients suffered with an attack at least every week, and 51% of the symptomatic patients suffered an attack at least every month.

Comparing patients with a traumatic etiology with patients who had RCE secondary to EBMD, patients with EBMD were significantly more likely to be symptomatic: 75% of patients with EBMD were symptomatic compared with 46% of patients with traumatic etiology.21

Management

The management of RCE is challenging, and to date, not one single therapy was found to be definitive and sufficiently effective. Over the years, multiple treatment strategies were developed, including topical conservative treatments, such as hypertonic lubricants, soft bandage contact lenses, and various aggressive surgical modalities, such as anterior stromal puncture and photorefractive keratectomy, which aim at creating a new basement membrane—epithelial interface (Box 26.2).

The primary goals of management of RCE during the acute attacks include pain relief and promotion of fast and prolonged epithelialization. Stabilization of the healed epithelium and prevention of subsequent erosion episodes are the long-term goals of RCE management. These goals are not easily achieved, and the chronic course of resistant cases of RCE may be frustrating for both patient and physician.

MEDICAL MANAGEMENT

Topical Lubricants and Hyperosmotic Agents

Most patients with an acute episode of RCE can be managed initially with patching and a topical antibiotic ointment.16,17 To prevent recurrences, the most widely used therapies include topical lubrication and hypertonic saline.10,16,17,22

Topical lubrication can be administered as drops, gels or ointment. The bedtime application of an ointment will reduce the amount of friction between the tarsal conjunctiva and the corneal epithelium overnight, during the rapid eye movements (REM), and will protect the corneal epithelium from the shearing action of the eyelids upon awakening, which is the major trigger of recurrence.

Hyperosmotic agents are also routinely used in RCE. During sleep there is a relative hypotonicity of the tear film as a result of decreased tear fluid evaporation. The reduced tear osmolarity at night will cause a shift of water from the tear film into the cornea, resulting in a relative corneal epithelial edema and decreased epithelial adhesion. Hypertonic (5%) sodium chloride, either drops or ointment, will promote epithelial adherence by increasing the tear osmolarity, thereby, decreasing epithelial edema and promoting epithelial adherence. These agents should be continued for a few months after the last attack, as it takes a few months for the adhesion complexes to build up.

Most patients will do well with these conservative treatments, which are effective in relieving the pain and promoting the initial epithelial growth.22 However, these modalities will not reduce the likelihood of recurrences.16

Useful advice for patients is to instruct them to move their eyes slowly to the left and right before opening them, and to gradually retract the lower lid, to facilitate gradual separation between the tarsal conjunctiva and the corneal epithelium. This slower separation of the cornea from the tarsal conjunctiva will prevent the shearing force created on the corneal epithelium during abrupt lid opening, and will prevent the erosion.

Therapeutic Bandage Contact Lenses

Therapeutic bandage contact lenses promote epithelial migration and regeneration of the basement membrane by protecting the corneal epithelium from the friction created by the upper tarsal conjunctiva.21 To be effective, a bandage contact lens should be worn for a few weeks to several months,16 replacing it every 2 weeks. This may enable the formation of stable adhesion complexes between the corneal epithelium and the basement membrane.

These contact lenses should be used under close supervision, since long-term continuous use of contact lenses may predispose to bacterial keratitis and neovascularization.16,24 However, the introduction of the silicon hydrogel extended-wear contact lenses, in recent years, has significantly increased the safety of long-term use of bandage contact lenses.25,26

Autologous Serum

Autologous serum has been used effectively in RCE, significantly reducing the incidence of recurrence.27,28 It is composed of substances that are essential for epithelial healing, such as vitamin A, epidermal growth factor, transforming growth factor β and fibronectin. Fibronectin promotes epithelial cell migration and participates in the adhesion process.29 The lipids in the serum may act as a substitute for the lipids produced by the meibomian glands. When appropriately prepared and used, autologous serum is safe and no adverse effects have been reported with its use.28

Managing Lid Disease

Meibomian gland disease (MGD) and chronic blepharitis are associated with RCE.10 The tear film in MGD may
have increased levels of bacterial lipases, fatty acids, interleukins and MMPs, which can interfere with corneal epithelial healing. Therefore, the usual therapeutic measures employed in the treatment of MGD should be used in RCE as well. These include lid hygiene and oral tetracyclines. Oral tetracyclines were shown to be beneficial in reducing episodes of RCE by reducing the free fatty acids in the tear film of MGD, by inactivating the MMPs, and by reducing the number of colony forming units from lid cultures. Low doses of oral tetracyclines should be continued for a few months.

The corneal epithelium produces matrix-degrading enzymes, such as MMP-2 and MMP-9. These enzymes have roles in the wound healing process, and are part of the inflammatory activity in many ocular surface disorders. Increased production of these enzymes, specifically MMP-2, was demonstrated in RCE. Therefore, MMPs may be responsible for the degradation of anchoring molecules in the adhesion complexes of the basement membrane during epithelial healing. This is the basis for the use of inhibitors of MMP in the treatment of resistant RCE. Indeed, a combination of oral doxycycline and topical steroids was successfully used in recalcitrant cases of RCE. Both topical steroids and oral doxycycline were reported to decrease the frequency of RCE in a randomized, controlled clinical trial. In addition, doxycycline and corticosteroids have significant anti-inflammatory properties. Doxycycline decreases the synthesis and bioactivity of interleukin-1, produced by cultured human epithelial cells. The combination of steroids and doxycycline can inhibit the inflammatory cytokines and MMPs and promote rapid resolution and prevent further recurrence in RCE.

SURGICAL MANAGEMENT

When the various medical treatment options fail, surgical therapy can be highly effective. Over the years, a series of surgical procedures have been described for RCE, including diamond burr polishing of Bowman’s membrane, anterior stromal puncture with an insulin needle or with YAG laser, and excimer laser phototherapeutic keratectomy (PTK). As these procedures result in high success rates and carry low risks, it is advisable not to defer the surgical options if the medical treatment is not effective.

Debridement of Loose Epithelium

Epithelial debridement is probably indicated when a large area of the epithelium is loose and mobile with lid movements. Debridement of this large area of loose epithelium is necessary for pain relief, and can promote healing from the healthy adherent edges of the intact epithelium. Epithelial debridement may be performed under topical anesthesia with the slit lamp, by removing the loose epithelium with a sterile sponge. A therapeutic bandage contact lens should be placed if the epithelial defect is large. Topical antibiotics and cyclopentolate drops may be added. Epithelial debridement alone cannot reduce the recurrences of epithelial erosions.

Anterior Stromal Puncture

Anterior stromal puncture is a highly effective and widely used office technique, involving the use of a straight 25-gauge needle to make multiple shallow penetrations through the epithelium into anterior corneal stroma, thus, improving epithelial adhesion. It is theorized that this procedure incites reactive fibrosis and scarring, and production of extra cellular matrix proteins, that are responsible for proper adhesion of the epithelium to its substrate. The procedure is performed with topical anesthesia with a bent 25 gauge (0.1–0.3 mm turned end) needle attached to a 3-ml syringe. Topical nonsteroidal drops, such as ketorolac or diclofenac should be instilled prior to the procedure to reduce postoperative pain. Fluorescein can be instilled topically before the treatment to better define the affected area (Fig. 26.11). The angled tip of the needle is kept perpendicular to the surface of the cornea, and multiple superficial punctures are placed approximately 0.5 mm apart in the affected area (Fig. 26.11). Treatment is extended to 1–2 mm into the normal epithelium bordering the lesion, because the loose epithelium usually extends beyond the visible limits of the erosion. Treatment within the pupil area should be minimized if possible. Since anterior stromal puncture may result in subepithelial scars (Fig. 26.12),
its use is not advisable if the erosion directly involves the visual axis, since a central scar may result in glare and a reduction in visual acuity. Immediately after the treatment, a bandage contact lens is placed and antibiotics are given for 1 week.18,22

Success rates of up to 80% have been reported in recalcitrant RCE.18 Treatment failure is associated with a too small treatment area, and erosions then develop outside of the treated area. A second, larger treatment can often resolve the erosions in patients in whom the initial procedure was unsuccessful.

Anterior stromal puncture can also be performed with a short-pulsed Nd:YAG laser.14 Energy levels ranging of 1.8–2.2 mJ can be used. The advantage of laser puncture over needle puncture is that the laser puncture is more reproducible, shallow, and translucent.

**Phototherapeutic Keratectomy (PTK)**

Studies have shown that partial ablation of Bowman’s layer, with the excimer laser, provides a smooth bed for migrating epithelium, and results in new hemidesmosomal adhesion complexes.15,36 Human studies have shown that the basal epithelial layer forms hemidesmosomes and new basement membrane within 2 weeks of laser photoablation.12 Thus, new hemidesmosomes, anchoring fibrils, and epithelial basement membrane are synthesized rapidly and in increasing amounts after PTK. In addition, removing the basement membrane allows the epithelium to come into direct contact with stromal elements, stimulating the synthesis of new anchoring fibrils and hemidesmosomes.18

The safety and efficacy of PTK for RCE have been well established.18,39 The advantages of PTK are removal of corneal tissue with extreme precision, without damage to the non-ablated area, and simultaneous treatment of wider areas. The aim is to remove a 6.0-mm diameter of thick anterior stromal layer. The defective epithelium is removed with a cellulose sponge and a 7.0–8.0-mm diameter flat beam is programmed to ablate a 6.0-mm diameter layer of the anterior stroma. The eye is usually padded after cycloplegic and antibiotic drops. Bandage contact lenses may be needed during the postoperative period. The success rate of PTK is between 60% and 100%.40,41 PTK results in a higher rate of success for RCE following trauma than corneal dystrophies.40,41

The main disadvantages of PTK are the postoperative discomfort and the hyperopic shift caused by the central flattening of the cornea. More advanced PTK treatments, based on flying spot beam profiles, are associated with fewer undesirable refractive changes, compared to those with older, broader beam lasers.

**Diamond Burr Superficial Keratectomy**

Epithelial debridement and diamond burr polishing of Bowman’s membrane is another, less commonly used option in the treatment of RCE. This procedure includes the debridement of loose sheets of epithelium from the cornea, using a combination of peeling with forceps and gentle wiping with a cellulose sponge. If the erosion is within the visual axis, the entire corneal surface is polished with a fine diamond burr, using multiple circular movements to prevent an irregular surface. The limbal epithelium is left intact in the 1–2-mm circumferential periphery. Treatment is limited to the anterior part of Bowman’s layer. A bandage contact lens is applied and antibiotics are given following the treatment.

The results of diamond burr are comparable to those of PTK.42 A subtle granular subepithelial deposit is initially noticed. The haze clears in up to 3 months postoperatively. A study on cases with RCE and anterior basement membrane dystrophy showed significantly less haze after diamond burr polishing compared to PTK. Diamond burr polishing is a simple, less expensive procedure with a smaller incidence of haze and fewer recurrences compared to PTK. In addition, it can be used to treat RCE involving the visual axis.

**Conclusion**

Epithelial adhesion disorders are common problems encountered by most cornea specialists. Recurrent corneal erosions occur most commonly after mild trauma to the corneal epithelium, but may also result from various inherited dystrophies of the corneal epithelium, basement membrane and anterior stroma. RCE is symptomatic with episodes of pain upon awakening, and can cause considerable impairment of the quality of life. Careful slit lamp examination is needed to find subtle changes associated with either mild trauma or EBMD. The majority of cases are mild and respond to simple, conservative medical treatment, such as lubricants and hyperosmotic agents. However, a minority of patients will develop a more persistent course of RCE and will require surgical intervention, including anterior stromal puncture or PTK. Tailoring the proper treatment strategy to each patient is the key to a successful control of these disorders.

**References**
