Compensatory Epithelial Hyperplasia in Human Corneal Disease

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ABSTRACT
Compensatory hyperplasia of the corneal epithelium (CEH) has been observed histopathologically in animal and human eyes after excimer laser photoablative keratectomy, and has been implicated as a cause of variable refractive results and refractive regression after this procedure. Retrospective histopathologic analysis of routine keratoplasty specimens revealed CEH in 85 of 130 (65%) corneas with keratoconus, 18 of 36 (50%) corneas with chronic herpes simplex virus (HSV) keratitis, and 14 of 25 (56%) corneas coded as nonspecific scars. Mild CEH occurred apically and/or peripherally in keratoconus. Massive CEH (up to 200 \(\mu\)m thick) occurred in chronic HSV keratitis with irregular stromal loss. Our data indicate that CEH occurs frequently in several corneal diseases marked by stromal ectasia or loss. We postulate that stromal loss may contribute to CEH by providing relative protection against exfoliative shearing forces of superior eyelid closure. Our study complements previous reports that imply that CEH is a contributory factor in refractive regression after excimer laser photoablation.

Since its first description by Trokel et al, the 193-nanometer excimer laser has generated great excitement for its potential application in surgical procedures designed to alter the shape of the anterior corneal surface. It has been used experimentally in both peripheral radial keratectomy and central-optic-zone ablative procedures to correct a variety of refractive problems. Additional therapeutic applications for anterior corneal scarring, superficial dystrophies, and recurrent erosions also are under investigation.

A recent clinical report has suggested that compensatory hyperplasia of the corneal epithelium (CEH) may be a factor in refractive regression and variation in refractive results after excimer laser photoablative procedures. This conclusion is based in part on data from histopathological studies that have shown thickening of the corneal epithelium after excimer laser photoablation in animal and human eyes.

CEH is also observed during routine histopathologic examination in a variety of common corneal diseases marked by stromal loss or ectasia. To better assess the frequency and histopathologic features of CEH in several human corneal diseases, we conducted a retrospective histopathologic review of a large series of keratoplasty specimens excised from patients with keratoconus, chronic herpes simplex virus (HSV) keratitis, and nonspecific corneal scarring.

MATERIALS AND METHODS
A list of all corneal buttons coded as keratoconus, chronic HSV keratitis, and nonspecific corneal scarring recorded in the computerized diagnostic retrieval system of the Ophthalmic Pathology Laboratory, Wills Eye Hospital, between May 1987 and May 1990, was generated. Routine histologic slides and pathology reports from all cases were retrieved from laboratory archives and reviewed retrospectively. All corneas had been fixed in neutral-buffered formaldehyde and embedded in paraffin.

Six-micrometer sections routinely stained with hematoxylin and eosin and periodic acid-Schiff were reviewed.
To assess for the presence of epithelial hyperplasia, the thickness of corneal stroma was measured centrally and peripherally with a calibrated ocular micrometer inserted as a reticle in the eyepiece of a standard laboratory microscope. Conversion figures for the microscope’s several objective lenses were available, permitting thickness measurements at various magnifications. In general, the measurements were performed at the highest magnification possible. In cases with irregular stromal thinning or epithelial thickening, the thinnest or thickest area was measured and recorded. The number of cell layers comprising the epithelium in each case also was estimated.

Slides from 15 eyes enucleated for posterior segment uveal melanoma that had no known or apparent corneal pathology or glaucoma were used as normal controls to evaluate the degree of tissue shrinkage caused by fixation and processing.

RESULTS

In the control material, the corneal epithelium was 5 to 6 cells thick and measured 30 to 40 μm centrally and 40 μm peripherally. The stroma of the control corneas measured 500 to 550 μm centrally and 600 to 650 μm peripherally.

As expected, the corneal stroma was markedly thinned in most of the cases of keratoconus. In 87.7% (114/130) cases, the central stroma measured between 100 to 300 μm; most were approximately 200 μm. Peripherally, the stroma of the corneas with keratoconus was marginally thicker. In half (65/130) of the cases, the peripheral stroma measured less than 400 μm.

In 20% (26/130) of the cases of keratoconus, the corneal epithelium at the apex of the cone was 60 to 100 μm thick, and was composed of 7 to 12 layers of cells. Mild to moderate compensatory hyperplasia of the peripheral epithelium also occurred frequently. Overall, compensatory hyperplasia involving either the central or peripheral corneal epithelium, or both, was observed in more than half (85/130 or 65.4%) of the
cases of keratoconus (Figs 1-4).

Among the 36 cases of chronic HSV keratitis examined, 7 (19.4%) had stroma of normal thickness and epithelium that was either of normal thickness or attenuated. The variation in stromal thickness in the remaining 29 herpetic corneas was markedly irregular (Figs 5-9). Usually the stromal thickness varied from 200 to 450 μm. In 62% (18/29) of the cases with variable stroma thickness, the epithelium had undergone varying degrees of facet-like hyperplasia that “filled in” the areas of anterior stromal loss. In selected cases, epithelial facets were 1 to 2 mm long and at least 60 μm thick. In the most remarkable case, the hyperplastic epithelium was more than 20 cells and 200 μm thick.

In 56% (14/25) of the buttons coded as nonspecific corneal scars, hyperplastic epithelium covered areas of irregular stromal thinning. In these cases, the hyperplastic epithelium was 100 to 200 μm thick. The thickened epithelial plaques in all three categories of specimens contained scattered rounded cells with pyknotic nuclei (Fig 9). These cells were interpreted as reflecting the intraepithelial necrosis of single cells rather than dyskeratosis.

DISCUSSION

This retrospective histopathologic review of corneal epithelial morphology in corneas excised for keratoconus, chronic HSV keratitis, and nonspecific corneal scarring indicates that CEH occurs frequently in several corneal diseases that often are marked by stromal ectasia or loss. Approximately half of the corneas in our series that had either nonspecific scarring or chronic HSV keratitis showed epithelial thickening. In these cases, the epithelium measured up to three to four times the normal thickness, and frequently formed facets that often extended 1 to 2 mm
COMPENSATORY EPITHELIAL HYPERPLASIA

FIGURE 9: Compensatory epithelial hyperplasia. Arrows mark nonviable epithelial cells with pyknotic nuclei in thickened epithelial plaque (hematoxylin and eosin, original magnification × 250).

across the corneal surface. In 25% of the corneas with keratoconus, the epithelium was thicker than normal, overlying the apex of the cone, corresponding to the area of greatest stromal ectasia. In addition, nearly one third of the keratoconus specimens showed mild epithelial thickening on the order of 60 to 90 μm in the periphery of the specimen. Bowman’s membrane was intact in most of these specimens.

We believe that the mechanisms normally responsible for the maintenance of the corneal epithelium are operative in the pathogenesis of CEH. Toth and Friend have suggested that corneal epithelial maintenance depends on a balance between basal cell proliferation, the centripetal migration of cells from the limbus, and the exfoliation of older surface cells.12 Eyelid closure may be a major driving force in epithelial cell migration and turnover.13,14 According to Lemp and Mathers, shearing forces generated by upper-eyelid closure causes exfoliation of older superficial epithelial cells.15 This mechanism is somewhat analogous to a palpebral “snowplow.” Lemp also indicates that the exfoliation of superficial epithelial cells appears to be decreased in depressed areas of the cornea, where the cells are relatively protected from the shearing forces of the lid.14 Accordingly, the relative protection against eyelid-induced cellular exfoliation afforded by irregular areas of anterior stromal ectasia and loss may be a crucial factor in the genesis of CEH.

We infer that corneal epithelial cells that have migrated into depressed areas in the stroma continue to proliferate until the depressions are filled by epithelial plugs or facets. Exfoliation of the superficial cells (the major factor that determines epithelial thickness) commences when the anterior surface of the epithelial facet roughly approximates the level of the neighboring normal corneal surface, and consequently becomes subject to the shearing forces of upper-eyelid closure.

Thickening of the corneal epithelium has been shown histopathologically in both human and animal eyes after excimer laser photorefractive keratectomy.3,10 The results of our study imply that this cellular hyperplasia is a normal response of the corneal epithelium to stromal loss and is not intrinsically related to excimer laser therapy. We found that the degree of CEH appears roughly to correlate with the extent of corneal stromal loss. Extensive epithelial plaques generally occurred in corneas that had focal stromal loss. However, 65% of our cases of keratoconus, a disease that tends to be characterized by a more diffuse pattern of stromal loss, also had mild to moderate CEH. The presence or absence of Bowman’s membrane did not appear to influence the development of CEH. Our data complement previous reports that imply that compensatory hyperplasia of the corneal epithelium contributes to refractive regression and variation in refractive results after 193-nanometer excimer laser photorefractive keratectomy.

REFERENCES