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Epithelial and fibrous downgrowth: mechanisms of disease

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Epithelial invasion is a rare, but devastating, complication of anterior segment surgery or penetrating trauma. In 1832, MacKenzie first described epithelial cells invading the eye with the case of a semitransparent cyst growing in the anterior chamber after a perforating injury [53]. In 1937, Perera classified epithelial invasion into three forms: epithelial pearls, epithelial cysts, and diffuse sheets of epithelium, also known as epithelial downgrowth [65]. This classification scheme remains useful today, as these distinct entities have separate management and prognostic implications. Pearl tumors are the least common, usually seen after trauma when skin or hair follicles are implanted into the eye [84]. The epithelial wall may be keratinized, which creates a pearly or opaque appearance. These lesions are generally small, and most remain quiescent. Occasionally, they may expand to fill the anterior chamber, and if necessary, they may be completely excised, generally with good results [80].

Epithelial cysts are typically translucent to grayish, and are often attached to the anterior surface of the iris. It is thought by some that cysts and sheet-like downgrowth differ only in the mechanism by which the epithelial cells were introduced into the eye [36,54]. Histologically, the epithelium appears the same, but cysts tend to behave in a more benign fashion than epithelial downgrowth. It is important to recognize that cysts may be converted to the more devastating diffuse downgrowth if incompletely excised [36], so that most authors recommend surgical removal only if glaucoma, iritis, or significant growth impairing vision develop.

Finally, epithelial downgrowth represents the most common form of epithelial invasion, causes the most destruction, and is most likely to lead to intractable glaucoma. The management of this entity remains problematic, and this form of epithelial invasion is the focus of this article.

Incidence

The true incidence of epithelial downgrowth is difficult to determine, as most of the literature is comprised of case reports or very small series. Given the rare nature of this disease, large series are rare, and the majority of these are histopathologic series, with limited clinical data available.

There is a general impression in the literature that the incidence of epithelial downgrowth has declined with the advent of microsurgery, improved instrumentation, surgical technique, sutures, and the operating microscope. In the past, 7–26% of all enucleations following cataract extraction were attributed to this complication [1,6,55,61,65,75] with an overall incidence of 0.1–1.1% of all cataract extractions [6,19,88,89]. A more recent 30-year review showed a decline in the incidence from 0.12% of all cataract extractions between 1953 and 1983, to 0.076% when the last decade of the study was analyzed independently [90]. This was attributed to improved surgical techniques, instruments, and sutures, resulting in improved wound closure. However, the most recent large series of 207 histopathologic cases published in 1996 showed no significant decline in the number of cases [42]. This could simply be attributed to a rise in

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the total number of surgeries and improved salvaging of traumatized eyes that previously could not have been repaired. It is interesting to note, however, that in the last 15 years of their study there was a significant increase in the number of "clinically missed" diagnoses. Perhaps the impression of a decline in incidence may be due in part to a decreased index of suspicion for this entity. While it is expected that modern-day cataract surgery with small self-sealing wounds should reduce the incidence of epithelial downgrowth, sutureless cataract incisions also have the potential to gape open slightly. There have already been several reports of epithelial invasion following sutureless cataract surgery [37,42,46]. Long-term follow-up will be needed to determine if the incidence of epithelial downgrowth truly is declining. With new techniques such as laser refractive surgery, the invasion and proliferation of epithelium into a wound such as epithelial invasion into a LASIK flap, presents a new post-surgical problem of epithelial invasion.

Risk factors

The most common event leading to epithelial downgrowth is cataract extraction [6,42,54,64] followed by penetrating injury, and penetrating keratoplasty [42,90]. Other predisposing events described in the literature include perforated corneal ulcer, IOL exchange or secondary IOL, lensectomy, pterygium excision, anterior chamber aspiration, transcorneal sutures, and keratoprosthesis. It is notable that epithelial invasion of the anterior chamber is rarely attributed to penetrating keratoplasty and is almost never described following glaucoma surgery alone, particularly since inadvertent filtering blebs and fistulas are found on presentation and considered to be a significant risk factor for downgrowth [87].

In our review of the existing epithelial downgrowth literature (see Table 1), cataract extraction was by far the most common event leading to the development of downgrowth, with 334 cases of diffuse downgrowth reported after cataract surgery alone. Trauma was the next most commonly reported event and the event most frequently associated with the development of epithelial cysts. Many patients in the post-surgical literature had secondary procedures such as penetrating keratoplasty or glaucoma surgery in addition to cataract extraction, but penetrating keratoplasty without antecedent cataract surgery was only described in 23 cases. There were only two cases of downgrowth after glaucoma surgery alone, and twelve cases due to perforated corneal ulcers. A significant number of the post-surgical cases involved either multiple surgeries or complications at or soon after surgery, including wound leaks, tissue incarceration, or hypotony.

Table 1
Review of epithelial downgrowth literature

Ethology	Number	% of total
Traumatic		18
Penatrating trauma	96	
And cataract extraction	2	
And excision of cyst	1	
Non-traumatic		82
Cataract alone		
Unspecified	83	15
ICCE	191	35
ECCE	55	10
Phacoemulsification	5	1
Cataract + PK	14	3
Cataract + trabeculectomy	1	
Cataract + PK + trabeculectomy	2	
Cataract + PK + IOL exchange	2	
Cataract + IOL (secondary or removal)	16	3
Cataract + other (cyst, discission, etc)	12	2
PK alone	23	4
PK + corneal ulcer	10	2
PK + other	9	2
Glaucoma surgery alone	2	
Perforated corneal ulcer	12	2
Miscellaneous		
Unknown	5	
Pterygium excision	1	
Aqueous humor aspiration	1	
Iris cyst resected	1	
Vitrectomy/lensectomy/ACIOL	1	
Total	545	

[1,3,5,6,10,11,16–18,21,22,24,26,28–32,36,37,39–44,46,48–51,57–59,61,65–67,69–72,74,76,78,81,82,85,86,88,90,91,94]

Pathogenesis

Many studies have attempted to identify the risk factors and necessary conditions for the development of epithelial downgrowth. While much knowledge has been gained from clinical observation and experimental studies, a precise understanding of the pathogenesis is still unknown. It has been difficult to experimentally reproduce epithelial downgrowth as it occurs in humans [65,68,85,89]. The fact that epithelial downgrowth occurs so infrequently and unpredictably suggests that multiple, or as yet unidentified, factors may play a pathogenetic role.

Route of entry

Epithelium cannot develop within the eye by metaplasia; it must be introduced in one of three scenarios: implantation, tissue flap, or ingrowth along a tract [88]. The invading epithelial cells are thought to originate from either conjunctival or corneal epithelium. Histopathologic studies of epithelial downgrowth reveal non-keratinized stratified squamous epithelium consisting of 1–12 cell layers [38,40,42, 57,90,91] (see Fig. 1). Studies vary with regard to the origin of the invading epithelium, with several ultrastructural studies of downgrowth occurring after cataract surgery suggesting a conjunctival source of the epithelium [39,40,94], while others have suggested a corneal origin [69,91].

Implantation of epithelial cells could occur via surgical instruments or during trauma. However, early experiments have demonstrated that the mere presence of epithelium in the anterior chamber appears insufficient to cause downgrowth. Many attempts at creating experimental models of downgrowth by implanting tissues in the anterior chamber have failed to produce sheets of downgrowth similar to that seen clinically [20,65,68], except in special circumstances, such as a murine model which required the addition of a carcinogen to stimulate cell proliferation [63]. Experimental reverse corneal transplantation, where the epithelium faces the anterior chamber, has not led to the development of epithelial downgrowth [4,93]. Epithelial downgrowth did not develop in two case reports of epithelium retained within the anterior chamber following penetrating keratoplasty. One case involved an inadvertently reversed corneal graft which was left in place for 13 days [62], while another case involved a recipient corneal button retained in the anterior chamber under the graft for five months [9]. Neither case subsequently developed epithelial downgrowth.

In the second scenario, a flap of conjunctiva could be incorporated into the surgical wound, providing a continuous source of epithelium. Attempts at creating epithelial downgrowth using a flap technique, where a conjunctival or corneal flap or wick provide continuous source of epithelium, have also been tried. These earlier efforts, however, resulted only in the formation of cysts in a few cases, and again, epithelial downgrowth could not be reproduced [65]. Most recently, a feline model of downgrowth using a corneal transplant with a conjunctival flap into the anterior chamber has successfully produced epithelial ingrowth [12].

Inadequate tissue closure, providing a route for invasion into the eye, is generally thought to be the predisposing event for epithelial downgrowth. Indeed, a wound leak is observed on initial presentation in 16–56% of patients [42,55,83,90]. Corneoscleral suture tracks have been proposed as potential sites

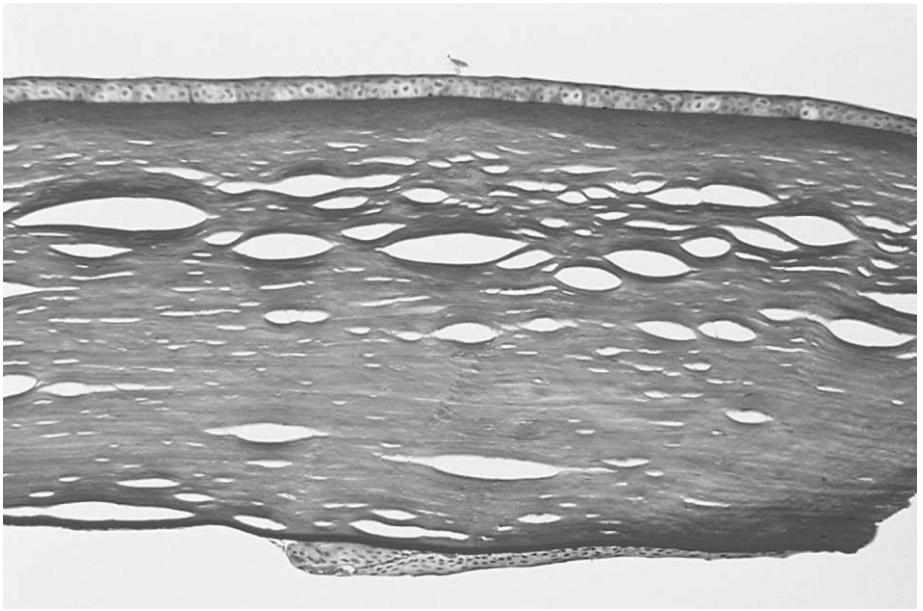

Fig. 1. Histopathology demonstrating non-keratinizing stratified squamous epithelium on the posterior corneal surface (See also Color Plate 5.) (Courtesy of Claes H. Dohlman, MD, Boston, MA).

for fistula formation [7,25,65], with several cases of downgrowth developing post-keratoplasty attributed to excessively tight PK sutures which gaped open an old cataract wound [78]. However, histologic studies have shown epithelium extending 1mm into the anterior chamber but without the clinical or histologic picture of true epithelial invasion [68]. Furthermore, recent studies have not demonstrated an increased risk for epithelial downgrowth as a result of multiple corneoscleral sutures [2,90]. Suture tracks may be less of a concern today, with modern suture material and instruments.

Factors promoting growth

In addition to a source and route of entry for epithelial cells, several clinical observations have led investigators to examine the biochemical and nutritive requirements of epithelial downgrowth. First, eyes with epithelial downgrowth often have a significant degree of inflammation, and studies have shown that uninflamed aqueous humor alone is insufficient to support the growth of epithelium [68]. Perhaps uninflamed aqueous humor lacks vital growth factors needed for the development of downgrowth. Many pathologic and experimental studies have also demonstrated that the invading epithelium almost always grows more rapidly and several layers thicker over uveal tissue than when growing over cornea [40,54,90], suggesting an important nutritive role from the richly vascular uvea. In addition, vascularization of the corneal stroma has been identified in many cases, and is thought to provide an important source of nutrition for the invading epithelium [12,14]. In one large study, stromal vascularization was seen in 89% of post-surgical cases and 94% of trauma patients, with the majority of vascularization along the wound tract [90]. Other investigators have had similar findings, with stromal vascularization seen clinically in half of Calhoun's cases [14], and pathologically in all specimens of Gundersen [35] and Bernardino [6].

Endothelial-epithelial interactions

While wound fistulas and vascularization appear to be risk factors promoting epithelial downgrowth, other authors have suggested that pathologic endothelium is an important risk factor for epithelial downgrowth. This is based on the histopathologic observation that in many cases of downgrowth, the corneal endothelium is either missing or severely attenuated. It has been suggested that healthy endothelium prevents epithelial migration by contact inhibition [15,23,33,88,92], and that damaged corneal endothelium may be a prerequisite to allow epithelial migration via the loss of contact inhibition [15,23, 45,73]. For example, when rabbit corneas in organ culture have had their endothelium removed, epithelium rapidly covers Descemet's membrane, presumably due to the loss of contact inhibition [85]. On the other hand, others have noted that epithelium can advance directly over endothelium [40,91,92], and a cat model of downgrowth has shown epithelium sliding over intact endothelial cells and subsequently exerting a cytotoxic effect on the underlying endothelium [13].

While several important factors have been identified by clinical and experimental studies, the pathogenesis of epithelial downgrowth is still unclear.

Clinical presentation

Clinically, the majority of patients present within 6–12 months after surgery or trauma [42,90], but case reports have described a range from 4 days [60] up to 38 years [42]. The most common symptoms described, in decreasing order of frequency, include decreased vision, red eye, pain, tearing, and photophobia [90]. In Weiner's 30-year review of 124 cases, the most common presenting signs include a retrocorneal membrane (45%), glaucoma (43%), a positive Seidel test (23%), and corneal edema (21%) [90]. The characteristic retrocorneal membrane appears as a gray line, best seen on retroillumination (see Fig. 2). When growing on the posterior corneal surface, the epithelium tends to progress circumferentially first, and then centrally. Iris involvement may be seen as effacement of the usual stromal contour, or pupillary distortion. Glaucoma is present on presentation in over half of cases [47], and will develop in the majority of eyes [27], representing the most common cause for enucleation following epithelial downgrowth. Initially, intraocular pressure may be low or normal due to the presence of a fistula, but these eventually close and can cause a suddent rise in intraocular pressure. The mechanism of glaucoma is most likely multifactorial, including epithelial growth over the trabecular meshwork, angle closure from PAS, clogging of the meshwork with epithelial cells or mucus, and pupillary block [47,52,80,90].

Diagnosis

In addition to the history, symptoms, and clinical examination, several adjunctive non-invasive diag-

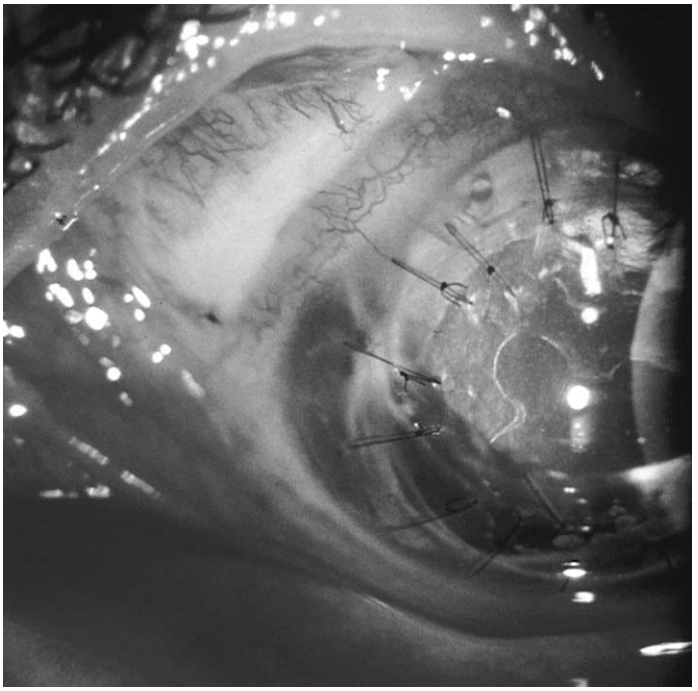

Fig. 2. The retrocorneal membrane is best seen on retroillumination (See also Color Plate 6.) (Courtesy of Dimitri T. Azar, MD, Boston, MA).

nostic tests may aid in diagnosis. The Seidel test, in which fluorescein 2% applied to the globe reveals a lighter yellow-green stream of diluted fluorescein, may identify a fistula, which may be present in up to one-third of cases [38]. Specular microscopy may show a sharp demarcation between endothelium and invading epithelium [37,45,79], with small epithelial cells showing a reversed image, with dark centers and bright margins [37]. Perhaps the most dramatic test involves argon laser photocoagulation, in which photocoagulation of epithelium overgrowing the iris produces a pathognomonic fluffy white reaction, while photocoagulation of iris mesoderm fails to produce a demonstrable change [55,83]. Suggested settings are 500 micrometer spot size, with 100 mW of power, at 0.1 seconds. In addition to diagnosis, photocoagulation may be used pre-operatively to delineate the extent of ingrowth. This should be performed within 24 hours of surgery due to a significant inflammatory reaction which may ensue. Fluorophotometry has also been used, demonstrating a delayed disappearance of fluorescein in the area of the downgrowth [37]. Invasive diagnostic procedures include anterior chamber paracentesis [34], curettage of the posterior corneal surface [55], and biopsy [38].

Treatment

The treatment of epithelial downgrowth remains a difficult problem. Methods which have been tried in the past include radiation, stripping of the membrane, swabbing with alcohol, diathermy, cryotherapy, photocoagulation, and surgical excision [27,38,80]. Currently, the most widely accepted treatment modality is surgical removal with adjunctive cryotherapy, as first reported by Maumenee [56] and later modified by Stark [83]. Maumenee reported encouraging results in a series of 40 eyes with epithelial downgrowth treated in a step-wise surgical fashion [56]. However, these cases were identified very early, and likely enjoyed success secondary to the ability to entirely eradicate the invading epithelium. Despite these advances, the prognosis in general is poor, with secondary glaucoma, recurrences, and corneal decompensation dominating the long-term management.

Fibrous downgrowth

Fibrous downgrowth, also termed stromal downgrowth or retrocorneal membrane, involves the invasion of connective tissue elements into the eye [8].

Although distinct from epithelial downgrowth, fibrous downgrowth shares the same risk factors for development and is often found concurrently with epithelial downgrowth in post-surgical cases [90].

Much less has been written about fibrous downgrowth. Unlike epithlelial downgrowth, it is often self-limited or minimally progressive, causing few if any symptoms. Diagnosis is often made only histopathologically [8,38,80]. The cellular origin of fibrous downgrowth is still a matter of debate, possibly originating from metaplastic endothelium, keratocytes, fibroblasts, or invading conjunctival connective tissue [8,80]. Using a rabbit model of fibrous downgrowth, three important factors have been identified in promoting fibrous downgrowth: healthy keratocytes, a large Descemet's break, and damaged endothelium surrounding a wound [77].

Clinically, fibrous downgrowth is most commonly recognized as a retrocorneal membrane developing after penetrating keratoplasty, but has also been reported after cataract surgery, trauma, goniotomy, and filtering surgery [80]. On examination, the membrane may be vascularized, which is not seen in epithelial downgrowth. Unlike epithelial downgrowth, there are no adjunctive tests to confirm the diagnosis of stromal downgrowth. Fortunately, medical management of the glaucoma, inflammation, and corneal edema is often sufficient, and if surgical intervention is required, removal of all the fibrous proliferation is not required as it is in epithelial downgrowth [47].

Summary

Epithelial downgrowth is a rare, but potentially devastating, complication of intraocular surgery and trauma. It has been suggested that the incidence is declining with modern surgical techniques, but further long-term analysis is needed to determine whether this in fact is true. While clinical observations and experimental studies have helped to elucidate factors involved in the development of this disease, a precise understanding of its pathogenesis is unknown. Given the difficult management and poor prognosis of this disease, further study and heightened clinical awareness are needed to better understand this disease process.

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