Diffuse Keratoconjunctival Proliferation
A Novel Clinical Manifestation

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Objective: To report a previously unrecognized benign bilateral widespread conjunctival and corneal proliferative condition with a potential to affect vision.

Methods: A gradually progressive diffuse conjunctival proliferation extending on the cornea was noted in 14 patients (28 eyes). These patients were followed up for a mean of 6 years for the site, extent, and progression of the condition. Six eyes had these lesions removed and studied histopathologically.

Results: Patients included 6 men and 8 women (mean age, 57 years). Two patients had bilateral nasal lesions only, 1 patient had bilateral temporal lesions only, 6 patients had both nasal and temporal lesions, and 5 patients had lesions that extended circumferentially. Pathology reports showed dense collagenous tissue, a moderate number of active fibroblasts, numerous blood vessels, and no elastotic degeneration in 3 of the 6 eyes. Two eyes showed mild subepithelial elastotic degeneration, and 1 lesion was difficult to interpret because of excessive intraconjunctival hemorrhage. None showed any inflammatory activity.

Conclusions: The lesions appear to be a clinical variant of classic pterygium with the corneal encroachment being wider, irregular, and more extensive. Histologically, a non-inflammatory nonelastotic collagenous accumulation appears to be a predominant feature unlike in classic pterygium where elastotic degeneration is the predominant feature.

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Pterygium is a wing-shaped fibrovascular growth of the bulbar conjunctiva and underlying subconjunctival tissue of the interpalpebral fissure that may encroach onto the cornea. The lesion is characterized by centripetal growth of a leading edge of altered limbal epithelial cells followed by squamous metaplastic epithelium with goblet cell hyperplasia, an underlying stroma of active fibroblasts, neovascularization, inflammation, and extracellular matrix remodeling. The pathophysiology of pterygium remains ill understood; however, features suggesting disordered growth have been found by many authors. Chronic irritation and/or inflammation occurring at the peripheral cornea and limbal tissue caused by dust, low humidity, microtrauma secondary to smoke or sand, human papillomavirus infection, and genetic and environmental factors, as such excessive exposure to UV irradiation, have all been suggested as risk factors for pterygium.

Limbal epithelial stem cell deficiency has also been proposed as an etiological factor. Histologically, pterygia exhibit subconjunctival accumulation of amorphous material interpreted as elastotic material, resembling that seen in actinic degeneration of the skin, interspersed with coiled or fragmented abnormal elastic fibers. Fibrocyte proliferation is often associated and interpreted as a response to injury. Aggregation of proteinaceous substances, acid mucopolysaccharide, and calcification are sometimes seen in older lesions. The accumulated stromal material was found to stain with Weigert and with Verhoeff elastic-tissue stains; therefore, it was considered to be a form of degenerated elastic tissue. However, incubation of excised lesions with the nonproteolytic enzyme elastase has produced no evidence of elastolysis; hence, the terms elastoid and elastotic degeneration were used to describe the presumed origin of this material from degenerated collagen.

Pterygia are predominantly located in the interpalpebral area more nasal than temporal. A pterygium is composed of an apex or head that is slightly elevated but...
firmly adherent to the underlying tissue and a body that can be readily lifted from the epibulbar surface. The advancing apex may be preceded by a gray-white avascular zone located in the subepithelial tissue; sometimes round, gray, coinlike extensions of the cap precede it, termed Lots of Fuchs.16 Sometimes, a golden-yellow iron line is seen in the corneal epithelium bordering the corneal side of the head, also known as the Stocker line.16

Progressive pterygia are usually thick and fleshy and heavily vascularized with a broad base and an apex that may progress slowly toward the middle of the visual axis. Active pterygia are known to show numerous inflammatory cells.17

We report a series of patients with a diffuse form of keratoconjunctival proliferative change that resembled a pterygium but with distinct clinical and histological differences.

**METHODS**

Our series included 14 white patients, 6 men and 8 women with 28 affected eyes, who attended the Cornea Service of the Queen’s Medical Centre since 2004. The Cornea Service of the Queen’s Medical Centre is a specialist tertiary referral center serving a population of approximately 1 million people but also attracting tertiary referrals from afar. These patients were referred for an atypical fibrovascular pterygiumlike change extending from the conjunctiva onto the cornea. The referring ophthalmologists had used the terms *pterygiumlike*, *pseudopterygium*, or *stem cell deficiency* to describe the lesions. All patients had full medical and ocular history taken and underwent a detailed ocular examination. None of them had any previous surgery or biopsy of their lesions. The lesions were reviewed for the site, extent, and progression of their condition. Slitlamp photographs were obtained. In 6 eyes of 5 patients where the lesions encroached on the visual axis, surgical excision (with autologous conjunctival graft in 5 eyes and a rotation conjunctival graft in 1 eye [patient 7 in the Table]) was carried out using a slight variation of the standard technique described for pterygium.18 (The subconjunctival fibrovascular tissue was less abundant and thin; hence, the excision of the subconjunctival tissue was less extensive. Extra sutures with 10-0’ nylon were taken along the limbus to anchor the transplanted or rotated graft because the extent of exposed limbus was relatively larger.) For autotransplantation, care was taken to use bulbar conjunctiva that appeared normal and located away from the limbus. Excised tissue was histologically examined following formalin fixation and wax embedding, supplemented by hematoxylin-eosin staining and elastic–van Gieson staining. All patients were followed up for visual acuity, progression of the lesions, or evidence of recurrence in cases in which the lesions were removed.

**RESULTS**

**OBSERVATIONS**

The mean age of patients was 57 years (range, 35-89 years). No patient had a history of conjunctival inflamm-

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**Table. Showing Clinical Details Including Visual Acuity, Clock Hours of Limbal Involvement, and Associated Conditions**

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Eye</th>
<th>Visual Acuity</th>
<th>Limbus Involvement</th>
<th>Associated Conditions</th>
<th>Eyes With Lesion Removed</th>
<th>Results of Histopathological Examination</th>
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*Limbal involvement is indicated in clock hours.*
matory conditions, such as Stevens-Johnson syndrome, chemical injury, or chronic conjunctivitis. One patient had associated primary acquired melanosis (patient 12 in the Table). Only 1 patient had a history of contact lens wear (rigid lenses, patient 13 in the Table). Two patients had Crohn disease (patients 3 and 13 in the Table) and 1 had systemic lupus erythematosus and rosacea (patient 8 in the Table). The main presenting complaint was that of intermittent redness, sore eyes, and unsightly appearance of their eyes. Three patients had chronic anterior blepharitis. One patient with more extensive lesions complained of blurred vision especially at night. Visual acuity ranged from 6/9 to 6/4 (Table).

CLINICAL FEATURES

Limbal changes in the form of an opalescent elevation, like a circumferential “roll” extending from 4 to 12 clock hours, were seen in 6 eyes of 3 patients (Figure 1A and B). In both eyes of 2 patients, a fibrovascular pannus was seen to “break through” the limbal elevation and extend onto the cornea nasally (Figure 1C and D), temporally (Figure 1E), and both nasally and temporally (Figure 1F). This was associated with a patch of dilated conjunctival vessels adjacent to the limbus, with fine vessels encroaching onto the cornea across the elevated limbus (Figure 1A and B). In 3 eyes, small aneurysmal dilatations of the ves-
sels were also noted. All other eyes had a diffuse widespread fibrovascular pannus that extended from the adjacent conjunctiva across the limbus onto the cornea for varying length and width. In 2 eyes, the pannus was associated with a circumferential limbal opacity suggestive of a preexisting limbal elevation (Figure 2). The pannus itself was vascular but thin and superficial.

The fibrovascular proliferative keratoconjunctival lesion was the dominant feature in most of the eyes. The lesions affected the conjunctiva diffusely, crossed the limbus over an average of 6 clock hours (range, 3-12 clock hours) (Table), and tended to be very broad at the apex (Figure 3A and B). Small and large conjunctival cysts were seen in 3 eyes (Figure 3C). Lesions were firmly adherent to the underlying tissue as illustrated in Figure 3D. Small subepithelial circular dotlike opacities, which were located central to and often not connected with the limbal lesion or fibrovascular pannus, were seen in all eyes (Figure 3E and F).

Two patients had bilateral nasal lesions only, 1 patient had bilateral temporal lesions only, 6 patients had both nasal and temporal lesions, and 5 patients had lesions that extended circumferentially around the cornea. These lesions were very slowly progressive.

All lesions removed were examined histologically. Three of the 6 lesions showed subepithelial nonelastotic collagenous proliferation with a moderate number of active fibroblasts (Figure 4A and B). All lesions showed some degree of vascularity but not such that this ever dominated the histological impression of collagenosis. Two samples showed elastic degeneration in which a proteinaceous substance identified as so-called elastotic degenerate material was seen on a granular background (Figure 4C and D). Inflammation was not identified as a significant process in any case. One sample was impossible to interpret histologically because of subepithelial hemorrhage that effaced stromal changes. The epithelial covering was nonkeratinized stratified epithelium, which was thinner than regular conjunctival epithelium. There was a paucity of goblet cells, with 1 specimen showing no goblet cells at all.

Follow-up of lesions was for a mean of 6 years and median of 2 years (range, 2 months-12 years). Follow-up of patients with excised lesions ranged from 2 months to 2 years following surgery. No recurrence was noted in any case (Figure 5).

**COMMENT**

We describe a novel lesion that clinically resembles a pterygium but that can be identified by distinctive clinical and histopathological features. Its clinical significance is that, although it resembles a pterygium, it has distinctive features that include the diffuse nature of the process, a more extensive corneal component compared with classic pterygium, a very thin fibrovascular pannus, and the presence of discrete sentinel dotlike opacities that appear to precede the advancing edge of the pannus. Furthermore, in all cases, it was very slowly progressive over the follow-up period.

Another important feature is that these lesions can arise from any site along the limbus and are not confined to nasal or nasal and temporal aspects like most pterygia. In one of our patients, the lesions were only temporal. In several others, they were circumferential. The lesions have different patterns with a dominant diffuse involvement and, unlike classic pterygium, have no distinct apex or body. Once lesions encroach on the cornea, they can appear broader at the advancing edge than the limbus.

We have named this lesion diffuse keratoconjunctival proliferation (rather than degeneration) to distinguish it from classic pterygium and to acknowledge the present lack of understanding of its pathogenesis. There has been a historic view to classify lesions such as pinguecula and pterygium as “degenerate.” However, we feel that this is a wrong biological perspective given the active growth and clinical evolution of pterygium. The discrepancy in the description of a pterygium has also been commented on by others.19

Histologically too there are differences. In 2 eyes, histological findings were similar to those seen in a classic pterygium, with significant accumulation of so-called elastotic degenerate material. In the other 3 eyes, the pathological process was dominated by a predominantly collagenous accumulation associated with corneal encroachment by conjunctival and subconjunctival tis-
Inflammatory cells were not a striking feature of the lesions, making an inflammatory etiology very unlikely. However, the sentinel dots seen with all lesions were clinically reminiscent of subepithelial infiltrates but active infiltrates were never seen in any case. These dots may represent fibroblastic proliferation. The lesions were covered by a stratified nonkeratinized epithelium that typically lacked goblet cells. This is likely to reflect changes in the conjunctival epithelium, possibly reflecting a change toward squamous metaplasia, and contrasts with the goblet cell hyperplasia observed in pterygia.

Based on our slitlamp examination and follow-up of these 28 eyes, we propose the following stages in the evolution of the pathological features that might be useful in clinically identifying similar lesions at an early stage. It must be emphasized that this is a preliminary attempt based on a small clinical series that will require further validation.

Stage 1 (Figure 1A and B): Limbal changes (elevation and vascularization) associated with subepithelial rounded opacities that occur preferentially but not necessarily in the nasal and temporal bulbar conjunctiva.

Stage 2 (Figure 1C-F): Encroachment of a fibrovascular pannus from the conjunctiva across the limbal elevation, on the corneal periphery, preceded by dotlike subepithelial opacities.
Stage 3A (Figure 2): Increased vascularization and encroachment of the fibrovascular pannus with regression of the limbal “roll-like elevation.”

Stage 3B (Figure 3A and B): Extensive encroachment of the fibrovascular pannus not confined to the nasal or temporal limbus that gradually creeps toward the center of the cornea.

Our series does not allow us to propose the rate of corneal encroachment because this requires a much longer-term follow-up.

Though diffuse keratoconjunctival proliferation has similarities to pterygium, when the clinical and histological features are considered together it stands out as a distinct entity. For example, in 1 patient (patient 7) whose lesion showed elastotic degeneration, the clinical appearance in both eyes (Figure 2) was very unlike a pterygium. The extensive involvement of the limbus, as demonstrated by several cases, would lead one to suspect that these patients may manifest symptoms and signs of limbal stem cell deficiency over the long-term. Furthermore, in vivo confocal microscopy of active pterygia has demonstrated numerous inflammatory cells, but these were lacking in our patients with diffuse keratoconjunctival proliferation where histological examination was performed. These patients were subjected to surgery because the lesions were slowly progressive and invading the papillary area and thus could be classed as active.

The management implications of these lesions are related to the natural history of encroachment onto the cornea. In our limited clinical series, there was an excellent prognosis following surgical removal, with no recurrence of the abnormal proliferation during follow-up of up to 2 years.

Further studies to reveal the etiology of these lesions and the nature of the preceding subepithelial opacities and relationships to classic pterygia are needed. It is possible that there is a common initiating point for both classic pterygium and diffuse keratoconjunctival proliferation as represented in our proposed stages 1 and 2. The reasons for diffuse encroachment and propensity for development of subepithelial collagenization in the absence of elastotic material in some cases in stages 3A and 3B of diffuse keratoconjunctival proliferation remain to be established.

Figure 4. Histopathological examination of lesions. A and B, Subepithelial nonelastotic collagenous proliferation. C and D, Elastotic degeneration. Arrows point to the area of the elastotic degeneration. Ep indicates epithelium covering the lesion (hematoxylin-eosin, original magnification ×100 [A and C] and ×400 [B and D]).

Figure 5. One year postoperative picture of the left eye of patient 2 showing no recurrence of the lesion. The preoperative picture for the same eye is shown in Figure 3D.
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Author Contributions: Prof Dua had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

REFERENCES


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