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.

Arch Ophthalmol. 2008;126(9):1226-1232

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.1 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.2 The pathophysiology of pterygium remains ill understood; however, features suggesting disordered growth have been found by many authors.3-7 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, such as excessive exposure to UV irradiation, have all been suggested as risk factors for pterygium.8-12 Limbal epithelial stem cell deficiency has also been proposed as an etiological factor.5,6 Histologically, pterygia exhibit subconjunctival accumulation of amorphous material interpreted as elastotic material, resembling that seen in actinic degeneration of the skin,14 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.13

Pterygia are predominantly located in the interpalpebral area more nasal than temporal.9 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 epithelial surface. The advancing apex may be preceded with a gray-white avascular zone located in the subepithelial tissue; sometimes round, gray, coinlike extensions of the cap precede it, termed Lots of Fuchs.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. Serial 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.\textsuperscript{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 inflam-

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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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</table>

\textsuperscript{a}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).

Figure 1. A and B, Circumferential limbal elevation with a patch of dilated conjunctival vessels in the left eyes of patient 11 (A) and patient 10 (B). C and D, Fibrovascular pannus extending beyond the limbal elevation nasally in both eyes of patient 14. E and F, Pannus extending beyond the limbal elevation temporally in the right eye (E) and both nasally and temporally in the left eye (F) of patient 9.

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 wide-
spread fibrovascular pannus that extended from the ad-
jacent conjunctiva across the limbus onto the cornea for
varying length and width. In 2 eyes, the pannus was as-
associated with a circumferential limbal opacity sug-
suggestive of a preexisting limbal elevation (Figure 2). The
pannus itself was vascular but thin and superficial.

The fibrovascular proliferative keratocconjunctival le-
sion was the dominant feature in most of the eyes. The
lesions affected the conjunctiva diffusely, crossed the lim-
burs on an average of 6 clock hours (range, 3-12 clock
hours) (Table), and tended to be very broad at the apex
(Figure 2A and B). Small and large conjunctival cysts
were seen in 3 eyes (Figure 3C). Lesions were firmly ad-
herent 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 lim-
bal lesion or fibrovascular pannus, were seen in all eyes
(Figure 3E and F).

Two patients had bilateral nasal lesions only, 1 pa-
tient had bilateral temporal lesions only, 6 patients had
both nasal and temporal lesions, and 5 patients had le-
sions that extended circumferentially around the cor-
nea. These lesions were very slowly progressive.

All lesions removed were examined histologically. Three
of the 6 lesions showed subepithelial nonelastotic collag-
enous proliferation with a moderate number of active fi-
broblasts (Figure 4A and B). All lesions showed some de-
gree of vascularity but not such that this ever dominated
the histological impression of collagenosis. Two samples
showed elastotic degeneration in which a proteinaceous sub-
stance identified as so-called elastotic degeneration was seen
on a granular background (Figure 4C and D). Inflamma-
tion was not identified as a significant process in any case.

One sample was impossible to interpret histologically be-
cause of subepithelial hemorrhage that effaced stromal
changes. The epithelial covering was nonkeratinized strati-
fied epithelium, which was thinner than regular conjunc-
tival 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 pte-
ygium but that can be identified by distinctive clinical
and histopathological features. Its clinical significance is
that, although it resembles a pterygium, it has distinc-
tive features that include the diffuse nature of the pro-
cess, a more extensive corneal component compared with
classic pterygium, a very thin fibrovascular pannus, and
the presence of discrete sentinel dotlike opacities that ap-
pear to precede the advancing edge of the pannus. Fur-
thermore, 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 involve-
ment and, unlike classic pterygia, 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 keratocconjuncti-
val proliferation (rather than degeneration) to distin-
guish 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 pin-
gueca and pterygium as “degenerative.” 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, his-
tological findings were similar to those seen in a classic
pterygium, with significant accumulation of so-called elas-
totic degenerate material. In the other 3 eyes, the patho-
logical process was dominated by a predominantly col-
lagenous accumulation associated with corneal encroach-
ment 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.

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.

**Figure 3.** A, An extensive lesion not confined to the nasal and/or temporal limbus, extending onto the cornea with only a small island of central corneal epithelium remaining in the right eye of patient 7. B, The left eye of the same patient showing an extensive lesion fanning out onto the cornea and covering a third of the pupillary area. C, Large cyst within the lesion in the right eye of patient 8. D, Illustration of firm adhesion of the lesion to the underlying tissue in the left eye of patient 2. E and F, Subepithelial circular and geographical opacities are shown central to the advancing edge of the lesions in the right eye of patient 9 (E) and left eye of patient 10 (F).
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.
Submitted for Publication: March 13, 2008; final revision received May 21, 2008; accepted May 26, 2008.

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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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