

CORNEAL AND CONJUNCTIVAL INTRAEPITHELIAL NEOPLASIA

A Clinical and Histopathological Analysis

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ABSTRACT

A retrospective study identifying 306 patients (326 pathology samples; 59.74% of whom were males) with a corneal and conjunctival intraepithelial neoplasia (CIN) was performed. The neoplasia was conjunctival in 213 (69.6%) and corneal in 94 (30.7%) of the cases studied. Mean age in the conjunctival group was 48.2 ± 16.2 years, while in the corneal group it was 59.2 ± 14.8 years ($p = 0.0001$). There was a predominance for the CINs to locate on exposed interpalpebral areas.

Mean follow-up time was 21.9 months. Among the mild-moderate dysplasias, 2.9% recurred, compared to 8.06% of the severe-*ca in situ* dysplasias. The resection border was more frequently involved in the 18 cases that recurred (61%) than in the 308 that did not recur (37.9%).

Overall, there were 18 recurrences (5.52%) in a mean time of 20 months. This group was statistically different regarding male sex, prolonged sun exposure, more advanced dysplastic stage, and resection border involvement. Thus, a complete resection and appropriate anatomical reconstruction are considered essential for the proper management of this entity.

INTRODUCTION

Corneal and conjunctival intraepithelial neoplasia (CIN) is being increasingly recognized in ophthalmology because of its oncological as well as its functional implications. The term CIN was first employed during the 70s in gynecology referring to cervical intraepithelial neoplasia. Its main objective was to include all intraepithelial dysplastic le-

sions in one group with similar risk factors, management, and prognosis.¹ In 1978 Jakobiec and Pizarello used such a denomination for the first time in ophthalmology referring to conjunctival intraepithelial neoplasia.² Later on, Waring, Roth, and Elkins used it to describe corneal intraepithelial neoplasia,³ so that nowadays the term CIN in ophthalmology means essentially dysplasia at the limbal junctional zone.

CIN usually appears in the 5th to 6th decades, more frequently in caucasian males,^(2,4-7) unilaterally, and predominantly in the interpalpebral zone.⁽⁸⁻¹¹⁾ An actinic^{2,4,10,12-17} as well as a traumatic influence^{2,18} has been proposed. A viral etiology has also been suggested (HPV type 16),¹⁹⁻²³ like that of uterine cervix CIN, in which this etiology is more firmly established.²⁴

Considering that monoclonality is a fundamental neoplastic characteristic, cellular genome alterations will perpetuate only when taking place in stem cells, since these are the only ones capable of self renewal. The stem cells of the ocular surface are located at the basal cell layer on the limbus. This explains why the CINs are connected to the limbus, comprising the corneal and conjunctiva simultaneously, although asymmetrically.

MATERIALS AND METHODS

This was a retrospective study done through the Pathology Laboratory at the Instituto Barraquer de America in Bogota. The study checked on all cornea and/or conjunctiva specimens previously classified as squamous cell carcinoma, CIN, papilloma, keratotic plaque, solar keratosis, and pseudoepitheliomatous hyperplasia, either clinically or histologically, between 1964 and 1994. The clinical records were reviewed regarding patient's age, sex, job, symptoms, previous treatments, physical examination findings, result of the anterior segment angiography, treatment, and follow-up.

Semiological analysis was based on slit-lamp pictures taken preoperatively, looking for:

- Growth pattern:
 - Gelatinous: Gray-whitish, somewhat raised outgrowth, less brilliant than the normal epithelial surface (Fig. 1).
 - Leucoplasic: White, dry, or creamy outgrowth with an irregular surface (Fig. 2).

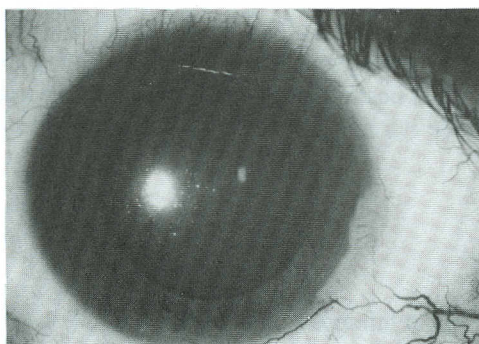


Figure 1. Gelatinous growth pattern.

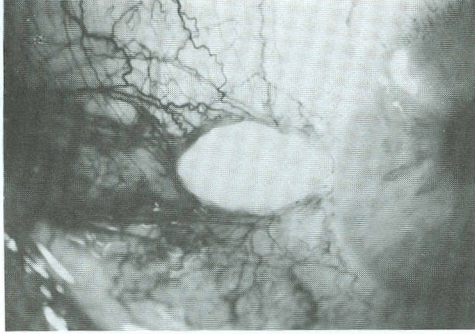


Figure 2. Leucoplakic growth pattern.

- Velvety: Pink-reddish convex outgrowth with a delicate vascular supply (Fig. 3).
- Papillomatous: Pink-whitish, vaulted, multinodular outgrowth (Fig. 4).
- CIN Location: Corneal or conjunctival, according to which side comprised a grater percentage of the lesion, by ocular surface quadrants.

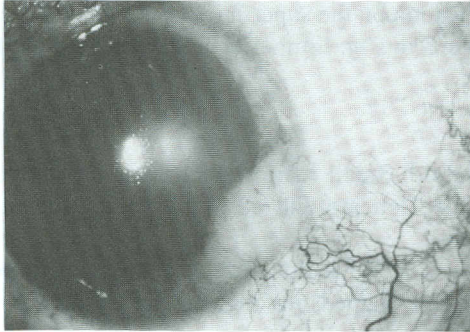


Figure 3. Velvety growth pattern.



Figure 4. Papillomatous growth pattern.

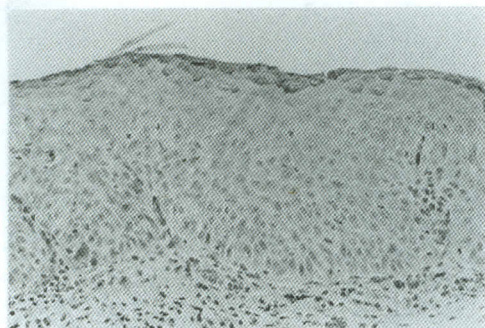


Figure 5. Mild-moderate dysplasia. Epidermoid fusiform cellularity. Magnification 63x.

- Advance Border: Convex or fimbriated
- Vascularity: Avascular, slight pannus, fibrovascular pannus, vertical vessels and vertically branching vessels.

Hematoxilin and eosin (HE) and periodic acid of Schiff (PAS) stained slides were reviewed, considering:

- Dysplasia Stage
 - Mild-moderate: Involvement of up to 2/3 of epithelial thickness. There is appropriate maturation on the superficial layers (Fig. 5).
 - Severe carcinoma *in situ*: Epithelial involvement greater than 2/3 of its thickness (Fig. 6).
- Cellularity:
 - Fusiform Basaloid: Small fusiform cells oriented perpendicularly to the basement membrane; delicate and eosinophilic cytoplasm; ellipsoid, moderately chromatic nuclei.
 - Epidermoid Fusiform: Medium-sized cells; more copious, eosinophilic cytoplasm; more vesicle-shaped, although elongated nuclei.

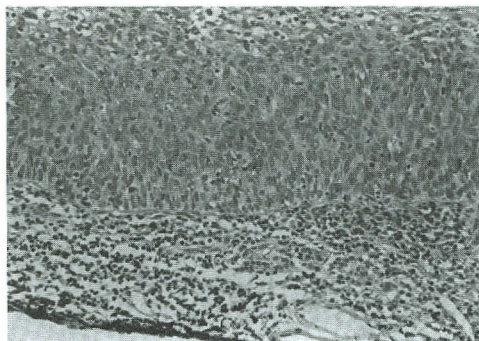


Figure 6. Severe-Ca "*in situ*" dysplasia. Epidermoid fusiform cellularity. Note basal mononuclear cell infiltration. Magnification 63x.

Table 1. CIN related consultation causes (n= 188)

Sign/symptom	Number	Percentage
Pterygium/Pinguecula/mass	142	75.53
Red eye	66	35.10
Ocular burning sensation	59	31.38
Foreign body sensation	30	15.95
Poor visual acuity	18	9.57

- Epidermoid: Epithelioid cells, pleomorphic and bizarre with an eosinophilic and extensive cytoplasm; large nuclei and prominent nucleoli.
- Presence of suprabasal mitosis (\geq per 100x field), basal mononuclear cell infiltration, hyper- and parakeratosis, vascularization type, and resection border status.

RESULTS

This study identified 326 samples corresponding to CIN, pertaining to 306 patients. The mean patient age was 51.7 ± 16.5 years (range 10–88 years) and 59.74% were males. Daily activities were related to a prolonged sun exposure in 18.25% of the cases. The initial consultation complaint was CIN-related in 188 patients (61.43%), as illustrated in Table 1. Frequently the patient had more than one of the signs/symptoms. Symptoms had been present for a mean of 8.3 ± 12.4 months, and in most cases (75.16%) patients had received no treatment at all. Among the 76 patients (28.84%) who had received some treatment, 20 had been operated on—most with a diagnosis of pterygium—the remaining 56 patients had received multiple medical treatments without improvement.

The CIN was conjunctival in 213 (69.6%) and corneal in 94 (37.7%) patients; in one patient it was symmetrically corneal and conjunctival. Mean age of the patients in the conjunctival group was 48.2 ± 16.2 years, while in the corneal group it was 59.2 ± 14.8 years ($p = 0.0001$). The initial clinical diagnosis was corrected in 71.5% of cases. The most frequent misdiagnoses (undiagnosed CIN) were pterygium, pinguecula, and papilloma. Quadrant distribution of the CINs on the ocular surface evidences an exposed area predominance; often a lesion comprised more than one quadrant (Table 2).

When the quadrant distribution was analyzed according to patient age it was evident that the younger group had a nasal zone predominance while the older one has a superior quadrant predominance (Table 3). This pattern was statistically significant in the conjunctival group ($p = 0.0001$).

In the conjunctiva, the most frequent growth pattern was leucoplasic (43.19%), followed by gelatinous (22%), papillomatous (20.9%), and velvety (14%). In the cornea, the most frequent type was gelatinous (64.13%), followed by leucoplasic (15.5%), papillomatous (11.8%), and velvety (8.5%). These differences probably correspond to the variable

Table 2. Quadrant distribution

CIN	Nasal	Temporal	Superior	Inferior
Conjunctival	64.3%	29.5%	5.1%	11.2%
Corneal	61.9%	39.1%	16.3%	38.0%

Table 3. Age (yrs)—CIN location relationship

CIN	Nasal	Temporal	Superior	Inferior
Conjunctival	46.0	52.7	65.0	54.1
Corneal	56.5	61.9	57.4	57.2

difficulty with which the lesion is perceived against its background. The most frequent advancing border found, both in conjunctiva and in cornea, was the fimbriated one (80.1% and 92.4%, respectively).

One of the most characteristic semiological images of the CINs was the presence of blood vessels not reaching the lesion's advancing border. In early stages, when still avascular, 16.4% of the conjunctival and 10.6% of the corneal CINs were identified. This was probably due to the nutrition of the conjunctival neoplasia from the lamina propria, which lets them grow larger while still avascular. In addition, it was harder to identify early fine blood vessels against the white scleral background. The presence of a slight pannus and fibrovascular pannus was recognized slightly more frequently in the cornea than in the conjunctiva. However, when the vertical vessels began to appear — reflecting a greater volume — these percentages grew closer (11.7% in the cornea and 8.9% in the conjunctiva) and in the case of vertically branching vessels, it was greater in the conjunctiva (19.2%) than in the cornea (17%).

A similar operative technique was used for all patients: the CIN was dissected with Westcott scissors from bulbar conjunctiva up to the limbus, and intraepithelially from the cornea towards the limbus with a fine flat spatula. Once both slopes had been dissected, the CIN was sectioned with curved Vannas scissors at the limbus. When the limbus was irregular it was leveled with an aerotor; a free conjunctival graft or limbal-conjunctival graft (if the resection border was greater than 120°) was used to obtain an adequate anatomical reconstruction.²⁵ Postoperatively, patients were given antibiotic/steroid drops t.i.d. for 10 days, at which time the sutures were removed.

Mean follow-up time was 21.9 months. Mean visual acuity at first follow-up visit was 0.72 ± 0.37 , and at the last one it was 0.81 ± 0.29 ($p = 0.0001$). There were 18 recurrences (5.52%) at a mean time of 20 months. This group was statistically different regarding sex (83.3% males), sun exposure (44.4% had prolonged sun exposure) and poorer final visual acuity (0.57 ± 0.32 ; $p = 0.04$).

Histopathological Analysis

A total of 326 samples were processed at the pathology laboratory. Conjunctival CINs were associated to a pterygium or pinguecula in 54% of cases. There was a slightly greater percentage of lesions showing an earlier stage in the corneal group, as was expected due to its easier clinical detection. Hence, the incidence of mild-moderate dysplasia was 46.1% in the cornea and 42.2% in the conjunctiva; the incidence of severe CA *in situ* dysplasia was 54.9% in the corneal and 60.4% in the conjunctiva. Sometimes there was more than one dysplastic pattern in the sample. No relationship between age and dysplastic stage was found. The more advanced the dysplasia, the greater the probability of recurrence. Thus, only 2.9% of the mild-moderate dysplasias recurred compared to 8.06% of the severe CA *in situ* dysplasias. The cellularity type was similar in the corneal and conjunctival groups, as follows: epidermoid fusiform in 83.6%, epidermoid in 22.1%, and

Table 4. Dysplasia stage-cellularity type relationship

Dysplasia	Fusif. Basaloid	Epiderm. Fusif	Epidermoid
Cornea			
Mild-moderate	100%	44.28%	36.36%
Severe-"in situ"	0%	55.72%	63.63%
Conjunctiva			
Mild-moderate	42.85%	23.37%	42.22%
Severe-"in situ"	57.15%	76.62%	57.77%

fusiform basaloid in 2.6% of cases (mean corneal and conjunctival values). The marked predominance of the epidermoid fusiform cellularity is sound, as it represents an intermediate stage in the benign morphological alteration sequence that begins with the more benign fusiform basaloid type and is most advanced with the epidermoid one.

When analyzing the association between a specific type of cellularity and the dysplastic stage, there was a trend towards a more severe corneal dysplasia associated with the epidermoid cellularity while in the conjunctiva this was associated with epidermoid-fusiform cellularity as shown in Table 4. The resection border was involved in 124 samples (38.03%); this number was significant when discriminating between the incidence of border involvement among the 18 cases that recurred (61%) and in the 308 that did not recur.

CONCLUSIONS

CIN has a multifactorial etiology, with different external influences partly depending on the age group. Hence, the predilection for exposed areas in young people and for the superior one in older groups suggests two different etiologies. It is likely that in younger patients there is a greater relation to the actinic factor, while in the older group it corresponds to the mutagenicity directly related to aging.

Although some groups have suggested the use of conjunctival²⁶⁻³⁰ and exfoliative^{27,31,32} cytology for the diagnosis of these lesions, a good physical examination complemented with an anterior segment angiography when deemed necessary should be enough to correctly diagnose most CIN.

Classifying the CINs in different dysplastic stages is useful from both the pathological and prognostic standpoint. The dysplastic stage initially found is an important prognostic factor as 2.9% of the mild-moderate dysplasias recurred, while 8.06% of the severe-CA *in situ* dysplasias recurred.

A clear relationship was found between the resection borders status and the recurrence rate; so, 61% of recurring cases showed resection border involvement in the initial surgical sample, while 37.9% of those who did not recur showed it. Most of these recurrences appeared during the first two years, which denotes the necessity of a strict control of these patients for at least such a period.

No clinical sign that might allow prediction of the dysplastic stage of the lesion was found. Therefore, a careful follow-up and the verification of growth will determine the appropriate moment for resection. The basis for the surgical management of this entity is the complete resection of the anomalous tissue³³ with a subsequent adequate reconstruction of the ocular surface. Thus, a superficial keratectomy is not considered necessary in the man-

agement of this entity. Likewise, the use of adjunctive procedures or drugs such as cryotherapy,^{5,34-36} radiotherapy,³⁷⁻³⁹ Thiotepa,⁴ or 5-Fluorouracil⁴⁰ are not considered necessary when employing a sound surgical technique.

While relatively low in virulence, the CIN has shown a tendency to recur. In this series, the recurrence rate was 5.52%, but in other series it varied between 10% and 40%,^{5,7,13,33,41,42} usually being around 20%. Several studies have shown the mean age of patients with *in situ* squamous cell carcinoma to be 5 to 9 years less than that of patients with invasive squamous cell carcinoma,^{4,7} which suggests a temporal relation between these two entities. However, their course should not be considered analogous to that of cervical intraepithelial neoplasia where 50% of cases progress to invasive carcinoma in 6 to 9 years,⁴³ compared to only 4.8% of the conjunctival CINs² and an even small number of the corneal CINs (0.3%-0.6%).^{3,33}

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