

An Unexpected Incidence of Ocular Surface Neoplasia on Pterygium Surgery. A Retrospective Clinical and Histopathological Report

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Purpose: To report the unexpected finding of ocular surface neoplasia (OSSN) on conjunctival tissue removed during pterygium surgery and subjected to histopathology analysis.

Methods: This is an observational, descriptive retrospective study in which all the samples removed during surgery between 1997 and 2020 with a clinical diagnosis of pterygium were sent for histopathology analysis in which an unexpected OSSN was found.

Results: There were 461 cases with a preoperative diagnosis of pterygium, with a mean age of 30.14 ± 10.6 years. In this group, there was an unexpected finding of OSSN in 69 cases (14.96%) of the surgical samples, with a mean age of 46 ± 8.2 years (31.86 ± 12.13).

Conclusions: The unexpected coincidence of pterygium and OSSN is frequent, although varies depending on the geographical location. We recommend performing a histopathology analysis on every pterygium removed.

Key Words: pterygium, dysplasia, neoplasia

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Pterygia have been considered a benign disease of the ocular surface, characterized by a centripetal conjunctival growth on the cornea, because of limbal stem cells dysfunction mainly secondary to chronic ultra violet (UV) radiation and microtrauma.¹

Previously, they were considered degenerative lesions, but nowadays, they are better considered a proliferative disease secondary to an aberrant cicatricial response,² influenced by the joint action of cytokines, matrix metalloproteinases, and several growth factors; histologically, they are characterized by the Bowman layer dissolution, the presence of inflammation, neovascularization, and matrix remodeling and activated fibroblasts.^{2–9}

They have a prevalence of 0.3% to 1.2%, being more frequent on equatorial zones; Cameron described what is

called the “pterygium belt” located at ± 35 degrees north and south of the Ecuador.^{10–12}

The ocular surface squamous neoplasia (OSSN) is the most frequent ocular tumor,^{13,14} with a variable incidence between 0.5% and 1.8% of the general population^{15,16}; the term comprises a wide range of epithelial neoplastic lesions of the cornea and conjunctiva, ranging from mild dysplasia, passing through Ca in situ, up to invasive squamous cell carcinoma. These lesions are typically of interpalpebral location, where there is greatest UV radiation exposure, and a strong relationship to human papilloma virus and HIV (human immunodeficiency virus)¹⁷ has also been described.

It is to be expected that having very similar predisposing factors, pterygia and OSSN sometimes coincide on the same lesion. Such a coexistence is closely related to the geographical zone, with reports varying between 0%¹⁸ and over 20%.^{19,20}

Considering pterygium a benign degenerative entity, ophthalmologist remove them only when cosmetically bothersome to the patient or when approaching the visual axis.

The purpose of this report is to increase the awareness on the unexpected coincidence of pterygium and OSSN, and the need to perform a histology analysis in all pterygia resected.

MATERIALS AND METHODS

This is an observational, descriptive, secondary sources retrospective study, where the pathology results of patients operated on with a diagnosis of primary pterygium without any suspicion of associated OSSN between 1993 and 2020 were reviewed at Medellín (Colombia), a city located 6 degrees north of the Ecuador. The study adheres to the Helsinki Declaration principles and was approved by the ethics committee of CES University.

All the clinical records with a diagnosis to pterygium (made by one senior ophthalmologist, L.F.M.) and operated on by one surgeon (L.F.M.) without any suspicion of associated OSSN in the lapse described were reviewed. The surgical technique consisted of complete removal of the anomalous tissue, limbal smoothing, and conjunctival autograft sutured with 7 10-0 Nylon sutures, finalized by closure of the graft donor site with 2 10-0 Nylon sutures²¹; sutures were removed at the 12th postoperative day.

All resected pterygia were sent for histopathology study at the same pathology laboratory, where the samples were cut periodically a 4 μ m thickness, stained by hematoxylin and eosin and periodic acid-Schiff, and studied by a pathologist.

Classic pterygium pathology comprises a proliferative front, elastosis, vascularization, and local invasiveness on the

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cornea with the Bowman membrane fragmentation and abrupt ending.

OSSN is characterized by epithelial maturation disorganization, epithelial proliferation with an incomplete differentiation, and alteration of the nucleus/cytoplasm ratio; on the finding of an OSSN, it was further classified as mild dysplasia (less than 1/3 epithelial thickness involvement), moderate dysplasia (up to 2/3 epithelial thickness involvement), severe dysplasia/carcinoma in situ (more than 2/3 epithelial thickness involvement), or invasive squamous cell carcinoma when the basement membrane was compromised. Dubious cases were evaluated by a second pathologist at the same laboratory (Figs. 1–3).

Statistical Analysis

Owing to the descriptive and observational nature of this study, an analysis of the data from the medical records of all the patients selected were reviewed, recollecting the necessary variables. As dependent variable, we considered the presence or not of OSSN, which was specified in all the clinical records reviewed. Other nondependent variables such as age, pterygium location, and pterygium recurrence were also evaluated.

Data were tabulated on Microsoft Excel v 16.37 for Macintosh, and the analysis was performed using SPSS v 21.0 for Macintosh.

Categoric variables are presented in percentage and absolute value, and numerical variables are presented in mean and standard deviation, based on normal distribution according to the Kolmogorov–Smirnov Test.

We also performed a bivariate analysis with analysis of variance tests for independent samples and with the χ^2 test looking for possible associations.

An alfa value of 0.05, a potency of 80%, and confidence of 95% were considered acceptable.

RESULTS

A total of 461 clinical records pertaining to patients who were operated on with a clinical diagnosis of primary

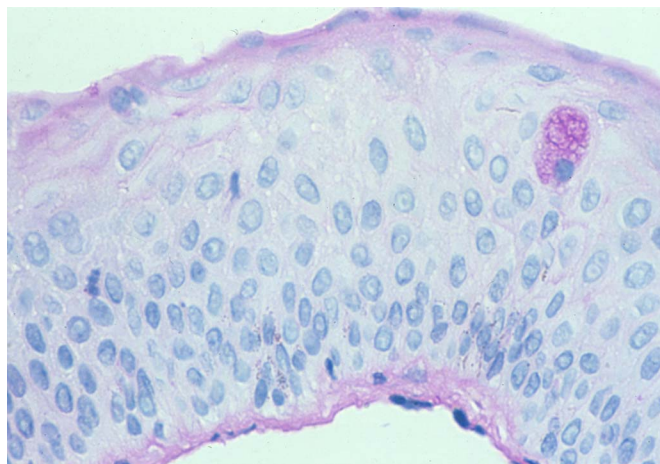


FIGURE 1. Mild dysplasia. PAS staining. PAS, Periodic Acid-Schiff. (The full color version of this figure is available at www.corneajrnl.com.)

pterygium during the time lapse above mentioned were reviewed. If the patient had more than 1 pterygium (not recurrence) during these years, each 1 was counted as a new case.

In this initial group, there were 318 male and 143 female patients, with a mean age of 30.14 ± 10.6 years (range 18–61 yrs); there were 426 nasal pterygia and 35 temporal pterygia; 297 patients were Hispanic, 100 patients were White, and 64 were of Black race. There were 9 pterygia recurrences (1.95%), all of nasal pterygia, in 7 men and 2 women.

In these 461 tissue samples, we unexpectedly found 69 cases of OSSN (14.96%) pertaining to 48 men and 21 women with a mean age of 31.86 ± 12.13 years (range 18–61 yrs); these OSSN were located on 62 nasal and 7 temporal pterygia. The OSSN grade was mild in 46 cases (picture 1), moderate in 16 cases (picture 2), and severe/Ca in situ in 7 cases (picture 3). There were no cases of invasive squamous cell carcinoma. One patient with moderate dysplasia was HIV (+). In the OSSN group, there were no recurrences during the follow-up; the mean follow-up time in OSSN cases was 6.5 years (range 2.6–15.3 yrs).

On bivariate analysis, there was no association between the presence of dysplasia and variables such as gender, age, pterygium anatomical location, or eye involved.

Differences between groups with and without OSSN are shown on Table 1 and positive OSSN cases dysplasia severity on Table 2.

DISCUSSION

Pterygia and OSSN have common characteristics such as the interpalpebral location, a strong association with a common etiologic factor—which is UV exposure—and the prevalence for male gender.^{1,3}

Both pterygium and OSSN are secondary to limbal stem cells dysfunction. With chronic UV exposure and recurrent inflammation, these cells are affected and subsequently altered, giving rise to pterygium or an OSSN. In this process, a coincident role for a mutation of a tumor suppressor gene on the ocular surface²² can originate an overexpression of it producing pterygium^{23–25} or an OSSN.²⁶

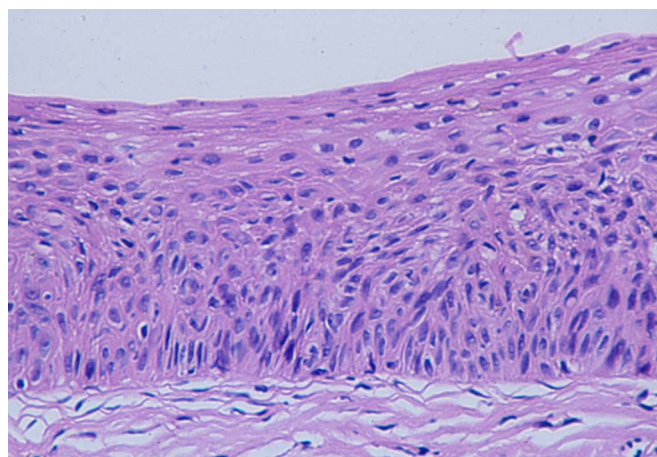


FIGURE 2. Moderate dysplasia. HE staining. HE, hematoxylin and eosin. (The full color version of this figure is available at www.corneajrnl.com.)

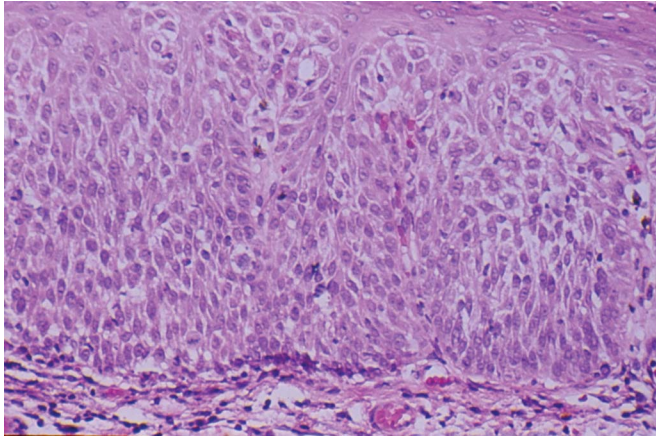


FIGURE 3. Severe dysplasia. HE staining. HE, hematoxylin and eosin. (The full color version of this figure is available at www.corneajrnl.com.)

In OSSN cases in young patients, there is an established association with HIV, much more evident in Africa than elsewhere, which is why we should always discard HIV in any patient younger than 40 years with OSSN¹⁷; our HIV-positive patients with OSSN was 29 years old at the time of diagnosis.

Therefore, the pathology reports of coincident pterygium and unexpected OSSN in patients operated on with a clinical diagnosis of pterygium are not to be unexpected; such pterygium-OSSN association varies widely worldwide depending on the geographical location of the studies.

So, in higher latitudes such as Canada, this unexpected finding is reported as 0%¹⁸ but increases to 4.1% in the United States,²⁷ 9.8% to 12% in Australia,^{28,29} and even greater than 20% in Malawi and South Africa,^{19,20} reflecting a clear association with greater solar exposure and therefore UV radiation (Table 3).

In our series, we found a 14.96% incidence of unexpected OSSN in surgical samples resected with a clinical diagnosis of pterygium. As opposed to what has been published by other authors,^{16,19} we did not find the group of patients with OSSN to be statistically older than pterygium-

TABLE 1. Pterygium-Only and OSSN Groups Characteristics

	Pterygium Without OSSN	Pterygium With Unexpected OSSN	P
No. of cases	392/461 (85.03%)	69/461 (14.96%)	—
Mean age (yr)	32.06 ± 10.36	31.86 ± 12.13	0.14*
Male	68.8%	69.5%	0.91†
Female	31.1%	30.5%	
Nasal location	92.6%	89.85%	0.38†
Temporal location	7.4%	10.15%	
Pterygium recurrence	2.2%	0%	0.2†
HIV (+)	0/392 (0%)	1/69 (1.69%)	—

*ANOVA test for independent samples.

†Chi square test.

ANOVA, analysis of variance.

TABLE 2. OSSN Cases Distribution

Dysplasia Grade	N (%)	Age (yr)	P*
Mild	46 (66.66)	33 ± 13	0.46
Moderate	16 (23.18)	31 ± 11	
Severe/Ca in situ	7 (10.14)	28 ± 11	

*Kruskal–Wallis test for independent samples.

only group (31.86 ± 12.13 vs. 32.06 ± 10.36 yrs). Neither we found a statistically significant difference on the recurrence rate, which is not that rare as our surgical technique is oriented at an adequate reconstruction of the dysfunctional limbus and most of these OSSN are of the mild dysplasia type which—as we have seen previously—can even regress spontaneously.

The presence of an unexpected OSSN in a resected pterygium poses several problems such as the greater risk of recurrence among OSSN^{34,35} compared with pterygia²¹ with comparable surgical techniques, the direct association of border involvement with recurrences in OSSN cases, and the difference in the postoperative follow-up.

We use a similar surgical technique for pterygium and OSSN removal: complete anomalous tissue removal with adequate ocular surface reconstruction with a free conjunctival autograft and closure of the donor site; however, we have some variations based on the clinical diagnosis:

1. In pterygium surgery, we level the limbal area with a high speed flat diamond blur,²¹ whereas in those with a previous OSSN diagnosis, we do not level the limbal area to avoid disrupting the Bowman membrane and therefore lessen the risk of stromal corneal invasion by the tumor.
2. In pterygium surgery, we limit the surgical intervention to the removal of the macroscopically evident anomalous tissue, whereas in OSSN surgery, we leave a 2-mm security border. The importance of having tumor-free borders is well-known because the recurrence rate is directly linked to their status; Tabin et al³⁴ showed recurrences in 56% of OSSN cases with border involvement versus 33% in those with free borders. Other authors have published lower recurrence rates³⁵ with tumor-free borders.
3. In addition, also very important, postoperative follow-up is different depending on the diagnosis. In both cases, we remove sutures at 12 days, but after doing so, we see patients with pterygium again at 12 months, whereas those with diagnosis of OSSN are seen every 4 months for 2 years; this is because we know from previous experience that most OSSN recurrences occur during the first 24 postoperative months.³⁵

The association of pterygium and OSSN has been mentioned for some time, but it has not received the emphasis and transcendence it deserves. It is imperative to have a pathology report of every pterygium removed because an incorrect or late management of an OSSN associated to pterygium can have dire consequences, sometimes even requiring an enucleation or evisceration

TABLE 3. Studies With Unexpected OSSN Associated to Pterygium

Study	Year	Sample Size	% of OSSN	Latitude	Country
Clear et al ¹⁹	1979	167	21	13.25 degrees S	Malawi
Hirst et al ²⁸	2008	533	9.8	30 degrees S	Australia
Yeung et al ¹⁶	2009	1227	0	43 degrees N	Canada (Toronto)
Chui et al ²⁹	2011	100	5	34 degrees S	Australia
Galor et al ²⁷	2012	2005	4.1	37 degrees N	USA
Artornsombudh et al ³⁰	2013	498	1.8	14 degrees N	Thailand
Segev et al ³¹	2014	682	0	31 degrees N	Israel
Furuya-Kanamori et al ³²	2014	3021	0.65	9.19 degrees S	Peru
Zoroquiain et al ³³	2016	215	2.33	49 degrees N	Canada (Vancouver)
Hung et al ¹⁷	2020	1787	0.22	25 degrees N	Taiwan

to solve the problem.³¹ There should be a greater awareness about this association as Pterygium surgery is one of the most common surgeries performed by ophthalmologists worldwide.

Differentiating pterygium from OSSN is not always easy, and the definitive diagnosis can be established only by a pathology analysis.

This is why we recommend to always send the surgical specimen removed during pterygium surgery for pathology analysis, especially when working in areas with a high UV exposure, such as the “pterygium belt” zone.

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