The Unexpected Association of Pterygium and Ocular Surface Squamous Neoplasia. Something to be Aware Of.

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Abstract

Pterygia and Ocular Surface Squamous Neoplasia (OSSN) have worldwide distribution with wide variations, their prevalence being much greater around the Equatorial parallel; they share a main common cause which is Ultraviolet Radiation. As is to be expected, these two pathologies present simultaneously and unexpectedly on a same patient with a prevalence proportional to the prevalence of each one of them separately.

This unexpected coincident presentation varies between 0% at Toronto (Canada) and 20% at Malawi (central Africa); their coincidence at Medellín (Colombia) is 14.9%. This coincidence is not associated to the size, aspect, or location of the lesion, nor the age, race or sex of the patient.

Anterior segment Optical Coherence Tomography (OCT) and Ultrasound Biomicroscopy (UBM) may help establish such association preoperatively at those referral Centers where available. If not available, all pterygia should be surgically removed and sent for histopathological analysis.

Keywords: Pterygium, Ocular Surface Squamous Neoplasia, UV Radiation

Introduction

What we Knew

A pterygium is an entity characterized by a triangular fibrovascular growth of the adjacent conjunctiva over the cornea; it is present worldwide with a mean prevalence of 12%, ⁽¹⁾ but with a wide variation ranging between 0.07% ⁽²⁾ to 53% ⁽³⁾ depending on the geographic location where the study is done.

For many years it was considered a strictly degenerative lesion with a benign behavior, but that concept has been slowly changing so that nowadays it is considered a reactive and proliferative entity secondary to an initial injury on the limbal pluripotential cells (Stem Cells).⁽⁴⁾

The main cause of a pterygium is the ultraviolet (UV) radiation; this is why its prevalence is greater on the Equatorial zone (Taiwan 53%, ⁽⁵⁾ Brazil 52%, ⁽⁶⁾ Southern China 33%, ⁽⁷⁾ Japan 30%, ⁽⁸⁾ Northern India 13%, ⁽⁹⁾ Caribbean Islands 23% ⁽¹⁰⁾) and diminishes progressively the farther it is from there (British Columbia, Canada 2%, ⁽¹¹⁾ Southern Australia 7%, ⁽¹²⁾ Great Britain 0.3% ⁽¹³⁾). **(Figure 1) (Table 1)**

This UV radiation not only is greater on the Equatorial Zone due to the perpendicular incidence of the solar rays but is also greater at higher altitudes over the sea level, and its incidence is stronger on the nasal

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Location	Prevalence	Latitude
Taiwan	53%	N 23
Brazil	52%	S -3
Southern China	33%	N 22
Japan	30%	N 26
Caribbean Islands, Barbados	23%	N 13
Northern India	13%	N 20
British Columbia, Canada	2%	N 43
Toronto, Canada	1.3%	N 43
Southern Australia	7%	S -31
Great Britain	0.3%	N 51

limbus where the cornea focusses the incoming rays concentrating them up to 20 times similar to a loupe; therefore, the higher incidence of pterygia on the nasal side of the cornea.

Other causative factors are repeated physical microtrauma such as sand and wind, and alterations on the tumor suppressor gene p53.

An Ocular Surface Squamous Neoplasia (OSSN) is an entity characterized by an uncontrolled

proliferation of dysplastic epithelial cells derived from genetically altered limbal pluripotential stem cells, which in some cases maybe compromise the basal membrane giving rise to a squamous cell conjunctival carcinoma with variable invasive potential both, on site and in the orbit.

The main cause of these lesions is, as with pterygia, the UV radiation; and its primary focus of compromise is, once again, the limbal pluripotential cells (Stem Cells). Other associations and etiological



agents are the Human Papilloma Virus (HPV), and the Human Immunodeficiency Virus (HIV), as well as chronic inflammation, petroleum derivatives and tabaquism.⁽¹³⁾

Concordantly with the above mentioned, the OSSN incidence varies widely: between 1.5-3.4 cases per 100,000 persons/year in the equatorial zones such as Central Africa ⁽¹⁴⁾ to 0.03-1.9 cases per 100,000 persons/year in Center United States and Great Britain ^(13,15) including Europe with 0.05 cases per 100,000 persons/year. ⁽¹⁶⁾ (Figure 2)

So, looking at the zones of greater incidence of both pterygia and OSSN it is evident its predominance on the zone named by Cameron as the "Pterygium Belt" ⁽¹⁷⁾ located at ± 35 degrees of the Equatorial Parallel, where the solar radiation falls perpendicularly on the earth thereby producing a greater UV radiation.

The association of pterygia and OSSN is low outside the "Pterygium Belt" with an incidence of 0% at Toronto, Canada, ⁽¹⁸⁾ 1.7% at Florida, USA, ⁽¹⁹⁾ and 4% at central United States, ⁽²⁰⁾ while inside the abovementioned belt, it is greater varying between 7% at Bogota, Colombia, ⁽²¹⁾ 9.8% at Brisbane, Australia ⁽²²⁾ and greater than 20% at Malawi, Central Africa. ^(23,24) (Figure 3) (Table 2)

Our Experience

We did a retrospective observational study reviewing the results of the histo-pathological analysis of all pterygia resected in a private practice located at Medellín, Colombia (Latitude 6 degrees North and 1,600 meters above sea level) during the last 27 years.

All cases were diagnosed and operated on as pterygia by one surgeon, without suspicion of associated OSSN.

The surgical technique employed in all cases was the complete removal of the anomalous tissue, limbal leveling with a high-speed handheld diamond mill (Aerotor), superficial episcleral hemostasis, suture of an autologous limbal conjunctival autograft with seven interrupted 10-0 nylon sutures, and closure of the donor site with two 10-0 nylon sutures; and all sutures were removed at the 12th postoperative day, as has been previously published.⁽²⁵⁾



Table 2: Pterigium – OSSN Coincidence				
Location	Coincidence	Latitude		
Toronto, Canada	0%	N 43		
Miami, Florida, USA	1.7%	N 25		
Central USA	4%	N 36		
Bogota, Colombia	7%	N 4		
Brisbane, Australia	9.8%	N -27		
Northern India	10%	N 20		
Central Australia	12%	N -23		
Malawi	>20%	S -13		

All surgical samples were sent to a pathology laboratory to be studied with serial cuts stained with Hematoxylin-Eosin and Schiff Periodic Acid.

We found 461 cases operated with a diagnosis of primary pterygia, pertaining to 318 man and 143 women, with a mean age of 30.14 ± 10.6 years. Pterygia location was nasal in 426 cases and temporal in 35. Most patients were Hispanic (n= 297), followed by Caucasian (n=100) and afrodescendants (n=64).

There were 9 pterygia recurrences (1.9%), none of which were associated with OSSN on its initial presentation or recurrence.

Of these 461 cases, we unexpectedly found 69 cases of associated OSSN (14.97%), in 48 males and 21 females, with a mean age of 31.18 ± 12.13 years. ⁽²⁶⁾ Of these 69 cases, 62 were associated to a nasal pterygium and 7 to a temporal one. **(Table 3)**

OSSN stage was determined as Mild in 46 cases,

Table 3: Patients Operated with Diagnosis of Primary Pterigium Without and With Unexpected Associated OSSN ⁽²⁶⁾						
	Main Group	Without OSSN	With OSSN	Р		
Ν	461	392 (85.03%)	69 (14.97%)			
Male	318 (68.9%)	271 (69.1%)	48 (69.6%)	0.91		
Female	143 (31.1%)	121 (30.9%)	21 (30.4%)	0.91		
Mean Age	30.14+10.6	32.06+10.36	31.18+12.13	0.14		
Nasal	426 (92.4%)	364 (92.9%)	62 (89.9%)	0.38		
Temporal	35 (7.6%)	28 (7.1%)	7 (10.1%)	0.38		

Table 4: OSSN Distribution of the Group with Unexpected Pterygium + OSSN Association $^{(26)}$					
Dysplasia Stage	Number (%)	Age (Years)			
Mild	46 (66.67%)	33+13			
Moderate	16 (23.19%)	31+11			
Severe/Ca in situ	7 (10.14%)	28+11			

Moderate in 16 cases and Severe/Ca *in situ* in 7 cases. **(Table 4)** None of these cases had a recurrence of the associated primary pterygium. Mean follow up time was 6.5 years.

On the bi variate analysis, we did not find any correlation between dysplasia staging and variables such as age, sex, pterygium location, pterygium degree or eye involved.

Discussion

Pterygia and OSSN are entities with a common main causative factor which is the UV radiation. This UV radiation is greater over the Equatorial line because of the perpendicular incidence of the solar rays, and increases with the elevation above sea level; this is why the most objective way to measure the UV radiation is by means of the UV Index (UVI) which is reported at every meteorological station around the world, and gives us a clear indication of the amount of UV radiation that a specific geographical area receives; an UVI greater than 4 is considered harmful for human health; in Medellín (Colombia) the mean UVI is 10. This is why, when interpreting studies referring to the association of pterygia and OSSN it is crucial to know the UVI of the area being reported, as this may vary considerable between countries and even between cities of one same country.

Another very important issue regarding the pterygia/OSSN association is the complete lack of correlation between the pterygium aspect and the chance of having an OSSN associated; this is crucial, as many ophthalmologists send for histopathological analysis only those pterygia they consider "suspicious" or "ugly"; It is imperative to send all pterygia samples for histo-pathological analysis regardless of their clinical aspect as there can be big surprises finding not only advanced stage dysplasia but even microinvasive squamous cell carcinomas on apparently harmless lesions. **(Figures 4 and 5)**

It is important to highlight the role the ultrabiomicroscopy (UBM) and Anterior Segment OCT (AS-OCT) have been slowly gaining in the study of proliferative conjunctival lesions. ⁽²⁷⁾ While their sensitivity and specificity have improved during



Figure 4. Ocular Surface lesion with aspect of pterygium, and its respective histo-pathological analysis. Diagnosis: Pterygium.



Figure 5-A. Ocular Surface lesion with preoperative aspect of pterygium, and its respective histo-pathological analysis. Diagnosis: Microinvasive Squamous Cell Conjunctival Carcinoma.

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Figure 5-B. Ourgery performed: Complete resection, partial keratectomy and sclerectomy and placement of a partial thickness lamellar corneal graft with an overlying limbal conjunctival autograft. Early postoperative aspect

the last few years thanks to better equipment and greater operator experience, we still get widely variable reports depending on which Center they are done; furthermore, in Latin America the access to such exams is limited both, because of limited availability, and because of its cost to our strained health systems.

Finally, our approach to pterygia must change; they should not be seen as benign degenerative lesions anymore, but as proliferative lesions with a variable risk of containing unexpected OSSNs associated; such risk is clearly linked to the UVI of a particular geographical location, which the practicing ophthalmologist should know.

At those referral Centers with last generation technology UBM and AS-OCT equipment and wide experience in their use, all pterygia should be subjected to their analysis in order to establish the association with OSSN and therefore decide the most appropriate management; if there is no availability to such technology, it is better to resect the pterygium and always send it for histopathological analysis. Every resected pterygia must be sent for histopathological analysis regardless of its aspect, location and patient 's age.

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