Pterygium: Epidemiology, Pathophysiology and Evaluation

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Abstract:

Pterygium is a relatively common ocular surface disease. The clinical aspects and the treatment options have been studied since many years ago, but many uncertainties still exist. The core pathologic pathway and the role of inheritence in the development of pterygium are still attractive fields for the researchers. The role of pterygium in corneal irregularities, in addition to the refractive properties of pterygium removal, has been increasingly recognized through numerous studies. The association between pterygium and ocular surface neoplasia is challenging the traditional beliefs regarding the safe profile of the disease. The need for a comprehensive clinical classification system has encouraged homogenization of trials and prediction of the recurrence rate of the pterygium following surgical removal. Evolving surgical methods have been associated with some complications, whose diagnosis and management are necessary for ophthalmic surgeons. According to the review, the main risk factor of pterygium progression remains to be the ultraviolet exposure. A major part of the clinical evaluation should consist of differentiation between typical and atypical pterygia, where the latter may be associated with the risk of ocular surface neoplasia. The effect of pterygium on astigmatism and the aberrations of the cornea may evoke the need for an early removal with a purpose of reducing secondary refractive error.

Keywords: Pterygium**,** conjunctiva, UV.

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Introduction:

A pterygium has been defined as a triangular-shaped, elastotic degeneration of the conjunctiva, consisting of bulbar conjunctival epithelium and hypertrophied subconjunctival connective tissue, occurringmedially and laterally in the palpebral fissure, and encroaching onto the cornea, pterygia (Greek word) is described as a proliferative disorder resembling an aberrant wound healing response. Pterygium

is one of the common ocular surface disorders. From two Greek words, the word "pterygium" has been derived: (pteryx) meaning wing and (pterygion) meaning fin. **(1).**

Pterygium has a predilection for the nasal limbus and affect only humans, compared with nonhuman primates and other animals. Although there is no consensus regarding the pathogenesis of pterygia, epidemiological evidence, support the concept that UV radiation plays a major role in development of pterygium. Furthermore, the limbal predilection may be explained by the phenomenon of peripheral light focusing, in which incidental light passes through the anterior chamber and is focused at the distal (nasal) limbus where limbal stem cells (LSCs) reside.***(1).***

Epidemiology:

The prevalence rates are different in various parts of the world. It is highest in the "pterygium belt" where people are more exposed to UV rays from the sun compared to other parts of the world. It lies between 37° northand south of the equator. The prevalence of pterygium was stated to vary widely from 0.3 to 29 percent in the world. In India, the prevalence ranges from 9.5 to 13%. It is more commonly found in rural parts of the country.**(2)**

Increased incidence of pterygium is noted in the tropics and in an equatorial zone between 30° north and south altitudes. Higher incidence is associated with chronic sun exposure (ultraviolet light), older age, male sex, and outdoor activity. **(3)**

The predominance of pterygia on the nasal side in the interpalpebral zone is speculated to result from the following mechanisms: **(4)**

- Light passes through the cornea medially, concentrating on the nasal limbus region, while the nose shadow decreases the strength of light transmitted to the temporal limbus.
- Longer temporal upper lid eyelashes and outer two-third bowing of these lashes filtering light falling on temporal conjunctiva and cornea.
- The natural flow of tears is from the temporal to the nasal side towards the punctum, and any amount of dust that reaches the conjunctival sacirritates the nasal conjunctive further.
- Since there are two anterior ciliary arteries on the nasal side while there is

only one on the temporal side, any irritant may result in increased nasal hyperemia.

Males work outdoors much longer than females, so it has been shownthat pterygium is found more often in males compared to females.

Etiology:

The various known risk factors are:

- Immune mechanism. **(4).**
- Genitic predisposition.
- The most common is the increased time of exposure to UV raysof the sunlight, followed by chronic eye irritation from dry, hotweather and dusty conditions.

Ultraviolet exposure

The association between development of pterygium and UV radiationcan be concluded from numerous epidemiological studies. The "pterygiumzone" has been described as the area between 40° north and south of the equator, where a higher intensity of UV radiation influences the population of the region. **(4)**

UVA and UVB are the primary subtypes of solar UV rays that reach the ocular surface. UVB causes DNA damage and alteration of intracellularsignaling in ocular surface disease. UVA causes indirect damage to DNA and activation of transcription factors. (**5).**

UV light can induce the development of pterygium through damagingLSCs, altering the function of stromal fibroblasts, or inducing inflammatory responses. Among them, inflammatory responses may be of least importance. A two-stage hypothesis has been proposed for the role of UV inpterygium development; initiation of the process relies on the damage of LSCs and formation of pterygium cells, and the progression is conducted by disrupted limbal barrier, upregulation of inflammatory cytokines, andproduction of growth factors and MMPs. (**6).**

Heredity

Several familial genes and pathways have been proposed to be involved in

the inheritance of pterygium. Familial defects in most of the pathways predispose affected individuals to an abnormal fibrovascular response to UV radiation. As a candidate gene, MMP-1 has been proposedto be involved in familial pterygium. **(5)**

MicroRNAs have also been implicated in the pathogenesis of pterygium. These are small noncoding RNAs that indirectly regulate special protein levels and gene expression. The presence of these molecules is related to anti-neoplastic properties in ocular tissues. Recently, it has been revealed that microRNA-145 level is negatively correlated with more extensive and thick pterygia. In addition, reduced level of the microRNA has been detected in recurrent pterygium. Accordingly, microRNAs may draw attention as they can serve as prognostic factors, therapeutic targets, and even the clue of pterygium inheritance. **(7).**

- **Viral etiologies**

The prevalence of Human Papilloma Virus infection in pterygium hasbeen reported to range from very low to 100%. In a meta-analysis, an overall prevalence of 18.6% has been reported for HPV infection inpterygia. **(8).**

Pathophysiology:

UV rays cause the insufficiency of the limbal stem cells of the cornea.It causes activation of the tissue growth factors, which further lead to angiogenesis and cell proliferation. The limbal stem cells are damaged by the UV rays that cause conjunctivalization of the cornea, and the cornea is invaded by aggressive fibroblasts. UV radiation may cause mutations in the p53 tumor suppressor gene, resulting in the abnormal pterygial epithelium. **(9)**

Recurrent Pterygium Pathophysiology:

Pathophysiology of recurrence is the reactivation of the inflammatoryprocess, which is present in the primary form. Sometimes the surgical trauma serves as an enhancer of the inflammatory response. Proliferative cytokines and growth factors (including vascular endothelial growth factoror VEGF) can increase after surgery if the limbal stem cells remain activated, and fibroelastic tissue is also involved. Because of this, there is an acceleration of fibrovascular proliferation and an increase in metalloproteinase synthesis that destroys the Bowman membrane and the stromal collagen that may increase the progression of pterygium. **(10)**

Histopathology:

Microscopically, pterygium is considered to be composed of elastoticfibro-vascular tissue. Leaving the top, mostly, the pterygium is covered byconjunctival epithelium. Extensions of fibrous tissue are seen on the top of pterygium, and as the head encroaches on to the cornea, the Bowman's layer gets involved and is fragmented. **(1)**

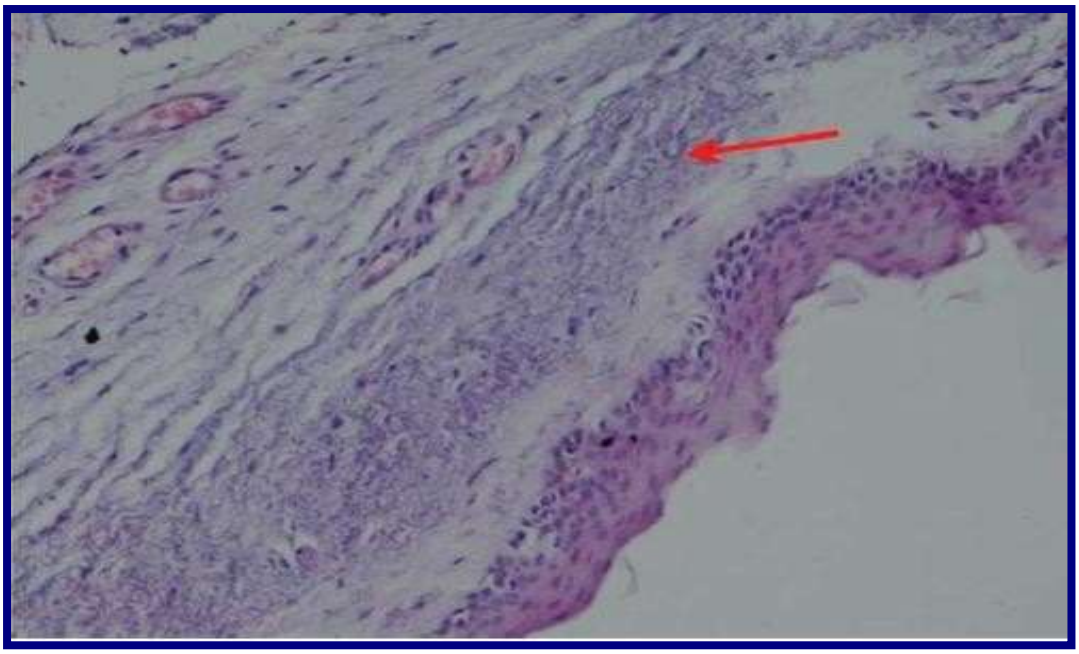

Figure (1): Histological Features of Pterygium. The conjunctiva showed within normal epithelium; the substantia propria showed marked fibrosis and solar elastosis (red arrow) (Hematoxylin and Eosin, X200). **(11).**

The fibrous connective tissue fills these cavities. Histopathological hallmarks of chronic inflammation can also be seen. There is the presence of lymphocytic infiltration consisting of plasma cells, mastocytes, and T-lymphocytes. There may be an increase of newly formed blood vessels, degenerative collagen fibers, and abnormal elastic fibers. The pathognomonic feature in histopathology is elastotic degeneration of conjunctival stroma, and also, there is an excessive fibro-proliferative reaction. **(4)**

Clinical considerations and grading systems:

The anatomy of pterygium can be divided into three parts: apex or head, neck, and body.

- The body is: the conjunctival portion with a base toward the medial canthus.
- The head is: the invading portion which contains the apex of the tissue.
- The neck is: the communicating part between the body and the head,which overlies the limbus.

There may be a superficial corneal haze in front of the apex (cap or halo),even in early stages of pterygium growth.

Differential diagnoses of pterygium include corneal phlycten, elevated pinguecula, limbal dermoid, limbal squamous cell carcinoma (SCC) or ocular surface squamous neoplasia (OSSN), papilloma, and nodular scleritis. Among them, the most important is to diagnose OSSN. **(4).**

OSSN is usually diagnosed clinically, where feeder vessels, positive staining for rose bengal, and leukoplakic or papilliform appearance are evident. Neoplastic lesion sometimes lacks some symptoms, making it impossible to distinguish them from a benign ocular surface condition suchas pterygium, pannus, or papilloma. Histopathologic analysis remains the gold standard for the diagnosis of OSSN. **(4).**

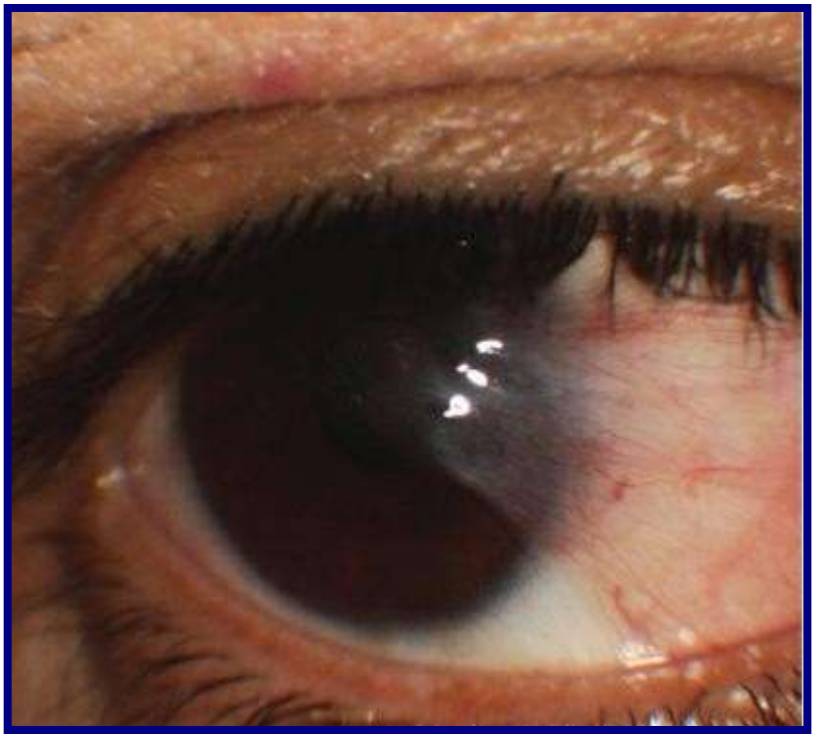

Figure (2): Right Primary nasal pterygium. **(12).**

Chronic and severe ocular surface inflammation or trauma, marginal corneal ulcer, or surgery may cause adhesions between conjunctiva and superficial cornea, which are known as pseudopterygium. As a distinguishing feature, it is believed that pseudopterygium is not attached to the underlying cornea throughout its full length, where a probe can be passed beneath the adhesive tissue (Bowman's probe test). It is notable that pseudopterygium is mainly an inflammatory process, while pterygium is considered as a degenerative response. In addition, pseudopterygium is a stationary condition, while true pterygium is a progressive ocular surface disease. (**12**).

Grading of Pterygium :

Pterygium can be evaluated aaccording to its size from the limbus,extent over the cornea, morphological classification and recurrency.

- **According to size from the limbus**, it has 3 grades:

- **Grade 1**:0-2 mm.
- **Grade 2**:2-4 mm.
- **Grade 3**:>4 mm. **(4)**.

- **According to its extent over the cornea**, it has 3 grades:

- **Grade 1:** refers to the pterygium whose head is located between limbus and a point midway between limbus and pupil.
- **Grade 2** indicates the pterygium with the head located between a point midway between limbus and pupillary margin and pupillary margin itself.
- **Grade 3**, the head crosses the pupil margin**. (4)**.

- **According to its morphological classification based on its transparency under the microscope**, it has 3 grades:

- **Grade T1:** Consists of atrophic pterygia, whose episcleral blood vessels which are present under the body of pterygium are clearly visible.
- **Grade T2:** Consists of intermediate pterygium which has characteristics

between atrophic and fleshy pterygium.

- **Grade T3:** Consists of fleshy pterygia with episcleral vessels completely obscured. **(4**).

➢ **According to recurrency**, different grading systems are proposed with the purpose of predicting the success of surgical intervention. Based on the external appearance, the recurrent pterygia were divided into four grades:

- **Grade 1** consists of cases with a normal operative site.
- **Grade 2** indicates the presence of fine episcleral vesselswithout fibrous tissue.
- **Grade 3** represents cases with fibrous tissue not invading the cornea.
- **Grade 4** indicates true recurrent pterygia with a fibrovascular tissue invading the cornea**. (13)**.

Pterygium complications:

1. Corneal astigmatism:

Although physical obscuration of the visual axis by pterygium is an absolute indication for surgical intervention, the visual function of the patient may be affected far earlier in the course of the disease, persuading the ophthalmologist to intervene before reaching the end stage. Pterygium can have a noteworthy impact on the corneal surface regularity indices through inducing astigmatism and surface asymmetry. Pterygium usually results in a with-the-rule astigmatism due to the flattening of the horizontal meridian along its leading head. The formation of a tear meniscus between the corneal center and the pterygium apex has been proposed for the underlying mechanism of horizontal corneal flattening. The change of corneal curvature caused by pterygium cannot be evaluated by refraction or conventional keratometry because this change occurs over the nasal paracentral cornea in the horizontal meridian. Therefore, computerized videokeratography seems to be the best tool in evaluating corneal topographic changes in pterygium patients.**(13).**

The effect of pterygium on the high-order aberrations of the cornea has also been described. Through the analysis of Placido disk data or anterior segment OCT outputs, it has been revealed that exacerbation of high-order aberrations due to pterygium progression alters with the size of the pterygium and diameter of the analysis. Anterior segment optical coherence tomography (AS-OCT) and Zernike analysis may facilitate objective grading of pterygium progression based on

changes in corneal optics. **(14)**

2. Ocular surface squamous neoplasia

OSSN refers to a spectrum of ocular surface conditions ranging frommild dysplasia to invasive SCC. There are same risk factors for OSSN and pterygium, so these two conditions can coexist or are even related. These common risk factors include UV radiation, chronic inflammation, chronic exposure to ocular surface irritants (such as dust), and oncogenic viruses (such as HPV). (**15**).

Two studies from Australia and three studies from North America have evaluated the coexistence of OSSN and pterygium in pathological studies of surgically removed pterygia. This discrepancy observed in studies is attributable to variations in UV exposure across geographic regions. It is possible that pterygia diagnosed in regions with high UV exposure are more susceptible to carry neoplastic features. Another factor that confounds the prevalence of atypia associates with pterygium is the criterion used for surgical removal by different studies. **(15).**

Evaluation of a case of pterygium:

Comprehensive ocular examination, including visual acuity, extraocular movements (EOM), and anterior segment evaluation is to be done. Detailed refraction should be done to note down the amount and type of astigmatism. Dry eye should be ruled out by conducting Schirmer's test or tear film break-up time. Pterygium should be evaluated under the following criteria: location, size, vascularity, extent, and area of corneal involvement [chord at limbus and extent of corneal encroachment from limbus is measured using Castroviejo's calipers] can be carried out by oblique illumination by torchlight and further substantiated by slit-lamp examination. The presence or absence of Stocker's line is noted, which is a punctate, brownish, subepithelial line passing vertically in front of the invasive apex of the pterygium and consists of corneal linear iron deposition**. (4).**

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