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Analysis of Histopathological Characteristics and Incidence of Dysplasia in Surgical Specimens of Pterygia

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ABSTRACT: Pterygium is a common ocular surface lesion thought to originate from limbal stem cells altered by chronic UV exposure. Traditionally regarded as a degenerative condition, pterygia also display tumor like features such as propensity to invade normal tissue and a high recurrence rate following resection. This study was undertaken to analyze the histopathological features and to determine the rate of dysplasia in 68 specimens of clinically benign primary pterygia during the time period of January 2019-June 2020. 56% of the patients in the study were male while 44% of the patients were female. Histopathological features noted were epithelial pigmentation, dysplasia, inflammatory reaction, stromal elastosis,vascular proliferation more than stromal fibrosis and hemorrhages. Dysplasia was noted in 4.41% specimens. The features of chronic inflammatory reaction noted in the majority of the specimens provides an insight into the etiopathogenesis of pterygium. Also, the presence of dysplasia in some specimens reiterates the importance early surgical intervention in patients even with clinically benign pterygia, and the need to send the excised pterygium sample for meticulous histopathological analysis.

KEYWORDS: Pterygium, OSSN, dysplasia, UV exposure, histopathology

I. INTRODUCTION

Pterygium is an ocular condition which takes its name from the Greek word “pterygos” for wing. It is a horizontally oriented triangular growth of abnormal tissue invading the cornea. The symptomatic association of pterygium is documented to be variable, but an outsized proportion of the cases may even be asymptomatic at presentation. Pterygium has been by various authors based on the amount of encroachment of the lesion on the cornea. Surgical excision of pterygium has been advocated for complaints including cosmetic blemish, foreign body sensation, visual defect. Traditionally thought to be a degenerative condition, pterygia also display tumor-like features, like a propensity to invade normal tissue and high recurrence rates following resection. Although the etiology of pterygium remains unclear, various factors resulting in the occurrence of pterygium including ultraviolet radiation, chronic eye inflammation, toxic effects of chemical substance. Some viruses are proposed to play a role in the development of pterygium. Histopathologically, pterygia are characterized by a hyperplastic centripetally directed growth of altered limbal with Bowman’s layer dissolution, epithelial-mesenchymal transition and an activated fibroblastic stroma with inflammation, neovascularization and matrix remodeling mediated through concerted actions of cytokines, growth factors and matrix metalloproteinases[1]. The collagen at the region of elastic degeneration gives it a basophilic staining pattern with Hematoxylin and Eosin staining. The pterygium also shows lymphocytic infiltration consisting predominantly of T lymphocytes, plasma cells and mastocytes. The newly formed blood vessels, number of fibroblasts and presence of abnormal elastic fibers also indicate the presence of chronic inflammation[2]. Currently once the pterygia are excised, they are commonly discarded without histological evaluation. This practice is not recommended because of reported cases of potentially malignant secondary disorders in association with pterygia. Also, in case the histopathological analysis of a specimen reveals a dysplastic lesion, the further managementwould require longer follow ups, as subjecting these

lesions to surgical excision is documented to have high recurrence rates.

II. MATERIAL AND METHODS

Patients having clinically benign pterygia admitted to Department of Ophthalmology, GRMC and JA Group of Hospitals, Gwalior for pterygium excision surgery between January 2019 to June 2020 constituted material for the study.

INCLUSION CRITERIA

• All the patients having clinically benign pterygium, willing to sign an informed consent for their involvement in the study and undergoing pterygium surgery.

EXCLUSION CRITERIA

• Patients refusing to participate in the study.
• Patients having atrophic pterygium.
• Previous medical treatment for pterygium including topical steroids or non- steroidal anti- inflammatory drugs.
• Patients with conjunctival cicatricial disease, systemic autoimmune disease, and untreated dry eye disease.
• Patients having lesions clinically suspicious of Ocular squamous surface Neoplasia.

All the patients were subjected to complete ocular examination, and underwent routine screening for hypertension, diabetes, HIV, HBsAg reactivity status. Pterygia were graded according to the extent of corneal involvement as follows: Grade I- between the limbus and a point midway between the limbus and pupillary margin, Grade II- head of the pterygium reaching the pupillary margin, and Grade III- crossing the pupillary margin[3]. They were then treated using the same surgical technique, pterygium excision with conjunctival limbal autograft application under local anesthesia. (Figure 1)

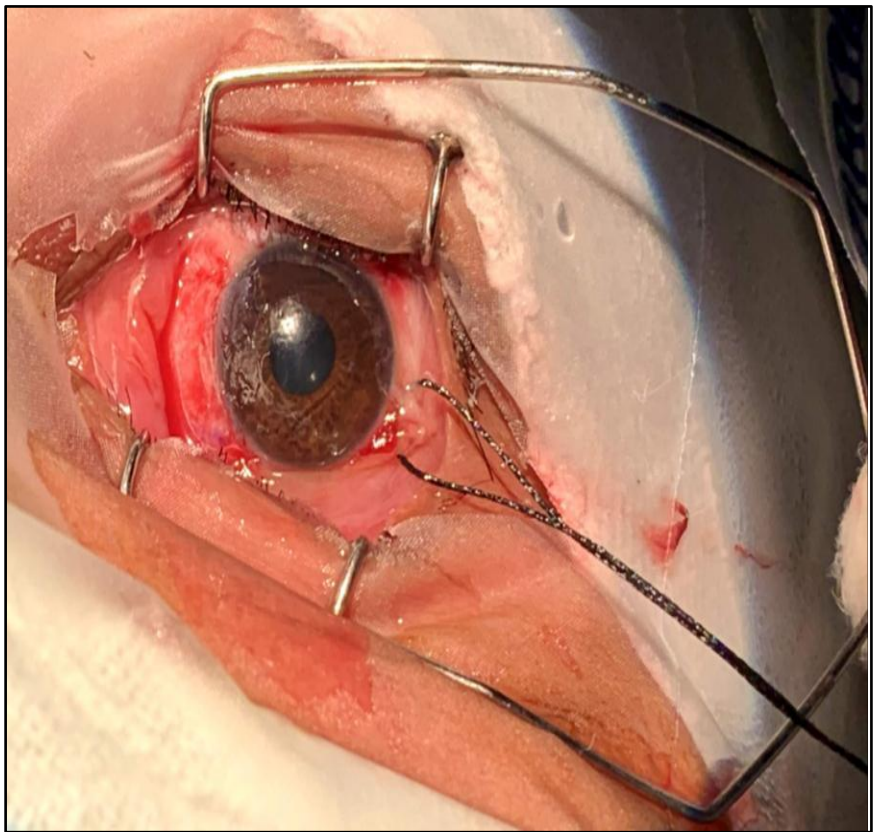

Figure 1 Appearance after pterygium excision and conjunctival limbal autograft stabilization

The obtained tissue was preserved in formalin and sent to Department of Pathology, GRMC and JA Group of Hospitals, Gwalior for histopathological analysis by light microscopy.

Statistical data was entered in Microsoft Excel for Windows and analyzed using SPSS, Chi square test.

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III. OBSERVATIONS AND RESULTS

This study included sixty-eight eyes of sixty-eight patients over the study period. The age of the patients ranged from 20 to 82 years with the mean age at presentation being 52.90 ± 15.39 years. The gender distributionshowed a slightly greater affliction for male patients (Table 1).

TABLE 1 Gender distribution

	Gender	Number of patients	Percentage
1	Male	38	55.88%
2	Female	30	44.12%
Total Patients		**68**	**100%**

Interestingly the a marginally higher number of individuals were found to be engaged in an indoor based profession (52.94%).The location of the pterygiumwas found to predominantly found to be nasal (94.12% patients) (Table 2)

TABLE 2 Location of pterygium

	Location of pterygium	Number of patients	Percentage
1	Nasal	64	94.12%
2	Temporal	4	5.88%
Total Patients		**68**	**100%**

There was no significant difference in the laterality of affliction (Table 3).

TABLE 3 Laterality of the pterygium

	Eye to be operated	Number of patients	Percentage
1	Right Eye	36	52.94%
2.	Left Eye	32	47.06%
Total Patients		**68**	**100%**

At the time of presentation, the pterygium was Grade I in 3 patients (4.41%), Grade II in 31 patients (45.59) and Grade III in 34 patients (50%).

Histological analysis of the specimens showed the presence of a conjunctivo-epithelial structure with the overlying epithelium appearing as a stratified squamous epithelium without keratinization, being similar to that of the bulbar conjunctiva. Prominent epithelial pigmentation (Figure 2 A) was present in 35 samples (51.47%), while 33 specimens didn't show any increased epithelial pigmentation. Epithelial dysplasia (Figure 2 B) was present in 3 specimens (4.41%) out of which 2 specimens had mild dysplasia and 1 specimen had moderate dysplasia. All the samples demonstrated the presence of inflammatory cells, where 1 sample had features of acute moderate inflammation (1.47), 49 specimens (72.06%) had chronic inflammation while 18 specimens (26.47%) had mixed mild inflammation. All the specimens had increased elastic fibers (Figure 2 C) in the subepithelial layers, forming the major mass of the pterygium specimen. 57 specimens (83.82%) showed prominent stromal vascularity while the remaining 11 specimens (16.18%) showed vascular proliferation being equal to or less than elastotic changes. An overwhelming 58 specimens (85.29%) demonstrated the presence of hemorrhages (Figure 2 D).

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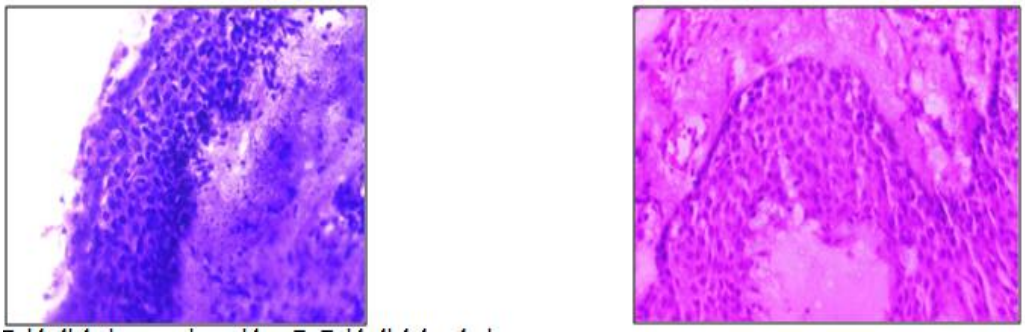
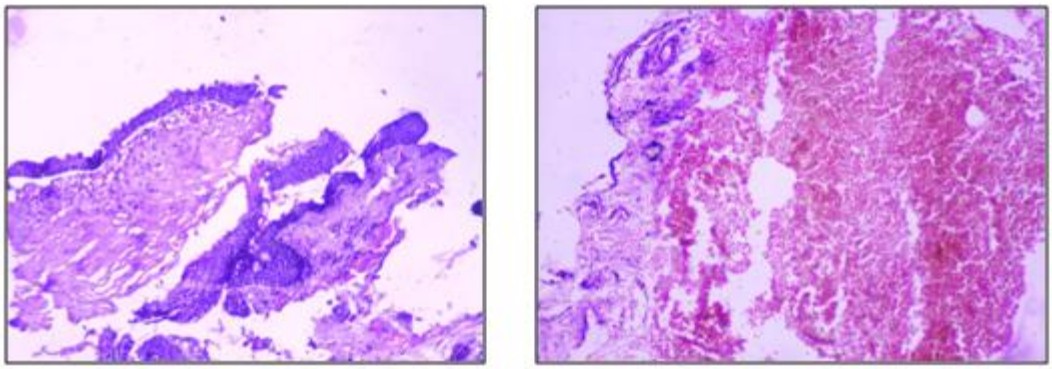


A. Epithelial pigmentation with chronic inflammatory cells

B. Epithelial dysplasia



C. Subepithelial fibrosis

D. Hemorrhages

Figure 2 Histopathological features of pterygia

The grade wise distribution of the observed histopathological features is summarized in Table 1

TABLE 1 Grade wise distribution of the observed histopathological features

	Total number of specimens	**Grade I** (n=3)		**Grade II** (n=31)		**Grade III** (n=34)		**P value**
		Number of specimens	%	Number of specimens	%	Number of specimens	%	
Epithelial Pigmentation								
Present	35	2	66.67%	20	64.52%	13	38.24%	0.668
Absent	33	1	33.33%	11	35.48%	21	61.76%	
Dysplasia								
Mild	2	0	-	1	50%	1	50%	0.406
Moderate	1	0	-	0	-	1	100%	
Inflammation								
Acute moderate	1	0	-	1	100%	0	-	0.0001
Chronic mild	49	3	6.1%	28	57.1%	18	36.7%	
Mixed mild	18	0	-	2	11.1%	16	88.8%	
Connective Tissue changes								
Predominant	68	3	4.4%	31	45.5%	34	50%	--

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elastosis								
Vascular changes								
Vascularity>elastosis	57	2	3.5%	25	43.8%	30	52.6%	0.266
Vascularity≤elastosis	11	1	9.1%	6	54.5%	4	36.3%	
Hemorrhages								
Present	58	3	5.2%	24	41.3%	31	53.4%	0.036
Absent	10	0	-	7	70.0%	3	30.0%	

IV. DISCUSSION

The present study demonstrated male predilection for pterygium occurrence, which is consistent with most of the reported literature, although female preponderance has also been reported[4]. The mean age at presentation in this study was 52.90 ± 15.39 years, which was close to the mean age of patients reported in the study done by Sun LL et al[5] and Zoraquin P et al [6], but was higher than that reported by Reda AM et al[7].Thepatients in the current study showed nearly equal distribution of professions on comparing indoor and outdoor based professions. The observations of Detels R et al[8]about a high prevalence of pterygium in sawmill workers (traditionally considered as an indoor based profession) has been used to strengthen the importance of ocular irritation as a causative agentand play down the case for UV light. It is however possible that even when working indoors, these workers were exposed to albedo[9]. Such high incidence of pterygium in pterygium in patients with an indoor based profession might be due to unknown causative agent resulting in ocular irritation. Concurrently, a higher incidence of pterygium amongst patients with indoor based profession in the present study might be coincidental and could be attributed to a small sample size.

The observation of overwhelmingly high occurrence of pterygium on the nasal side was in agreement with the findings of previously available literature [10-14]. This has been ascribed to the proposed phenomenon that the anterior eye acts as a side on lens which focuses light from the side to nasal limbus after transcameral travel. This explanation has also been attributed to the occurrence of other ocular conditions where UV light exposure has been attributed, such as pinguecula and initial site of critical cataract. Although the degree of limbal focusing was further determined by corneal shape and anterior chamber depth, leading to quantifiable risk factors to identify at risk individuals.

Histological examination revealed epithelial pigmentation in 48.53% samples in the present study which was similar to the study done by Reda AM [7].Epithelial pigmentation is considered to be present if it is prominent along basal keratinocytes or suprabasal keratinocytes, also referred to as primary acquired melanosis (PAM) of conjunctiva or conjunctival hypermelanosis[15,16]. These lesions are a form of melanocytic lesions that fall between nevus and invasive melanoma and have been related to sun exposure [17]. Hence findings of increased melanin pigment in pterygium epithelium that is related to UV exposure is expected. Primary acquired melanosis as a histological finding is important due to the fact that PAM with atypia progresses to melanoma and lesions with epithelioid features are associated with invasion and metastasis, a potentially fatal disease if undetected, whereas PAM without atypia does not progress to melanoma.

In the present study epithelial dysplasia was noted in 4% samples, a finding which was in agreement with the study done by Gaton et al [18] and Reda et al [7] in which mild dysplasia was reported in 6.6% samples and 8.5% samples respectively. Although none of these studies reported the presence of moderated or severe dysplasia in the examined specimens, whereas the current study noted the presence of moderate dysplasia in 1 sample. The reposted rate of concomitant OSSN in pterygia specimens varies from 0% to 9.8%. This wide range of variation is probably due to the difference in study population, as the occurrence of OSSN has been strongly linked to the amount of UV exposure, which varies in different regions of the world. The decadal UV index (July 2002-June 2012) has showed that the UV exposure in most parts of India falls in high to extreme categories in most parts of the year (mean UV index >8) [19]. Study done by Sankar S et al

[20]in Kerala cohort found epithelial dysplasia in 14% of the samples, which was significantly higher than what was found in the current study. Although, this difference might be due to the fact that Sankar S et al included specimens excised for all the conjunctival lesions whereas specimens included in current study were taken from clinically benign pterygia only. Although the role of HIV infection has also been proposed in the occurrence of OSSN [21-23], none of the patients diagnosed with OSSN on histopathology in the present study were found to be seropositive for HIV.

The pattern of inflammation found in the present study was predominantly chronic mild inflammation (72.06%) followed by mixed mild inflammation (26.47%) whereas acute moderate inflammatory reaction was seen in only one sample. The distribution of type of inflammatory reaction amongst various grades of pterygia in the present study was found to be similar tothat observed in the available literature [7,24] This finding also correlates with the proposed chronic inflammatory pathway in the pathogenesis of pterygium. The current study also found a significant correlation between the grade of pterygium and the type of inflammatory reaction in the specimens (p=0.0001).

The presence of an overwhelmingly high amount of elastic fibers in the subepithelial layers in all the specimens in the current study corresponded with the findings in the available literature [11,25,26], where this has been described as a striking feature in pterygium specimens. Contrary to the earlier belief of origin of the subepithelial elastotic material to be degeneration of collagen fibers as a result of sun exposure and subsequent insensitivity of elastosedigestion[27].

The presence of stromal vascularity that overwhelmed fibrosis in 83.82% samples in the present study corresponded with the findings in the study done by Reda AM et al [7]. Cliova[28]reported abundant vascularization in the body of the progressive pterygium as compared to the body of stationary pterygium. Also, a greater number of blood vessels positive to von Wilebrand factor (vWF) and vascular endothelial growth factor (VEGF) have been reported in pterygium samples. Overexpression of VEGF in pterygium tissue, along with abundance of vWF stained blood vessels suggests an important role of angiogenesis in the formation of pterygium. These findings have suggested that pterygium vascularity can be used as a possible target for treatment, especially for patients with cosmetic complaints.

Present study also found hemorrhages in 85.29% of the specimens which was similar to the findings of Reda AM et al [7]. The presence of recurrent hemorrhages in a pterygium was proposed to elicit a chronic inflammatory response, which was correlated with the dominance of chronic=c inflammatory response in most of the samples. The presence of conjunctival hemorrhages in pterygia has also been associated with the fragility of the endothelial cells and basement membrane in the capillaries, which easily induces hemorrhage when the eyes are irritated by rubbing or by conjunctival foreign bodies.

V. CONCLUSION

1. The presence of chronic inflammatory infiltrates in majority of the samples suggests a role of inflammation in the etiopathogenesis of pterygium.
2. The presence of vascularity has been advocated as a target for conservative treatment, especially for the patients with cosmetic complaints, but the presence of dysplasia, with no significance to the grade of pterygium advocates that we desist the use of conservative treatment modalities in the treatment of pterygium
3. The presence of dysplasia suggests that all the excised specimens of pterygia should be subjected to histopathological examination and should be followed up to look for recurrence of the lesion.

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