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A study on the association of ocular surface squamous neoplasia with pterygium

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Abstract
Background & Objectives: Pterygium is a fibrovascular degeneration of the conjunctiva. Ocular surface squamous neoplasia encompasses a wide spectrum of dysplastic changes including corneal and conjunctival intraepithelial neoplasia and squamous cell carcinoma. They both share common risk factors and can coexist concomitantly. This study aims to determine the association between OSSN and pterygium which will help to improve the management of pterygia cases with or without OSSN.
Methods: This interventional prospective study has evaluated histopathological changes of excised pterygia of 51 patients (52 eyes) over a period of 14 months attending the outpatient department of Vydehi Institute of Medical Sciences and Research Centre, Bangalore.
Results: The prevalence of OSSN coexistent with pterygium was found to be 1.92% and that of dysplasia was 9.61%. Also, these patients were found to have risk factors for malignancy like old age, smoking, recurrent pterygium, actinic keratosis.
Interpretation and Conclusion: All cases of pterygium, especially those with risk factors need histopathological examination after surgical excision without fail. These pterygia need to be screened for dysplasia, metaplasia, anaplasia, ocular surface squamous neoplasia and to be managed accordingly. Chemotherapy with MMC, 5 FU if dysplastic cells are present. Immunotherapy with Interferon alpha 2b, excision with no touch technique and 4-5mm free margins excision around lesion and alcohol epitheliectomy and application of cryotherapy to surgical margins for OSSN is ideal treatment of cases with risk factor.

Keywords: Pterygium, ocular surface squamous neoplasia, dysplasia, risk factors, chemotherapy, immunotherapy, surgery

Introduction

The word pterygium means wings (Greek). Pterygium is a triangular fibrovascular subepithelial growth of degenerative bulbar conjunctival tissue encroaching over the limbus onto the cornea. It is located commonly horizontally in the inter palpebral fissure on either nasal or temporal side of cornea or sometimes on both sides [1]. It is a common clinical entity encountered in ophthalmic practice and is considered as a degenerative condition of the subconjunctival tissues which proliferate as vascularised granulation tissue to invade the come a destroying the superficial stroma and Bowman's Membrane, the whole being covered by conjunctival epithelium. In early stages it is thick and vascular, becomes thin and pale when it ceases to progress but never disappears. Literature reveals 2 conflicting views for aetiopathogenesis of pterygium degenerative process and chronic inflammation of the conjunctiva due to irritation from the elements like wind, dust and sun.
Ocular surface squamous neoplasia was a term given by Lee and Hirst [2]. The first case was observed by Von Graefe [3] in 1860 and the disease has been subsequently extensively described. Corneal and conjunctival squamous lesions are uncommon but important because of their potential for causing ocular and even systemic morbidity and mortality. The clinical presentation of these lesions have a wide spectrum and can range from mild to severe dysplasia to full thickness epithelial dysplasia (carcinoma *in situ*) and invasive squamous cell carcinoma. Squamous lesions can involve the conjunctiva or the cornea but more commonly start in the conjunctiva and extend across the limbus to the adjacent cornea.
Ocular surface squamous neoplasia like pterygium has common risk factors like exposure to ultraviolet light, chronic ocular surface irritation resulting from a dusty, dry industrial environment. Other risk factors for ocular surface squamous neoplasia are older age, human papilloma virus, human immunodeficiency virus, xeroderma pigmentosa, light skin pigmentation.

Pterygium and ocular surface squamous neoplasia can coexist concomitantly [4]. The prevalence of OSSN with pterygia was reported to be 9.8% in Brisbane [5], 5% in Sidney [6] and 0% in Canada [7].

The presence of ocular surface squamous neoplasia with pterygium poses a therapeutic dilemma to ophthalmic surgeons as the surgical management varies. Simple excision with conjunctival/amniotic membrane graft is the preferred treatment for pterygia [4]. OSSN is managed by excision with no touch technique and 4-5mm free margins excision around lesion and alcohol epitheliectomy and application of cryotherapy to surgical margins [4]. It is also managed medically by topical 5 fluro uracil 1% and Mitomycin c 0.03%. This study aims to determine the association between OSSN and pterygium which will help to improve the management of Pterygia cases with or without OSSN.

Aim and objectives of the study

- To estimate the prevalence of ocular surface squamous neoplasia among patients undergoing excision for pterygium.
- To assess the factors associated with pterygium and ocular surface squamous neoplasia

Materials and Methods

Source of data and study population are patients attending the outpatient department of Ophthalmology at Vydehi Institute of Medical Sciences and Research Centre, Whitefield, Bangalore diagnosed as Pterygium undergoing excision surgery were studied.

It is a Cross sectional study done from 1.1.2019 to 31.11.2022. The Sample size was 52 eyes of 51 patients. Sample size is calculated based on the study by Oellers P *et al*. and using the following formula

$n=Z^2 (1-\alpha/2) P (1-P) / d^2$

Where p: expected proportion, d: absolute precision
Z (1-α/2): CI, Expected proportion =0.08,

Precision = 6%, CI=95%
Hence required sample size =52

Inclusion criteria: Patients aged above 18 years of either sex with ocular Pterygium, primary or recurrent

Exclusion criteria: Patients with pseudo pterygium ocular chemical injuries**,** corneal scarring due to trachoma membranous conjunctivitis, pseudomembranous conjunctivitis, peripheral corneal ulcer.

Methods of collection of data Informed written consent was taken prior to enrolling the patients in this study. A detailed medical history, history regarding other comorbidities, drug history, personal history were taken. General examination and Vital data recording including Pulse rate, Respiratory rate, Blood pressure was done. Ocular examination of patients was done which included visual assessment (Distant vision, near vision, colour vision), keratometry, Slit lamp examination of anterior segment, Fundus examination (90D), assessment of dry eye by doing TBUT, Schirmer's test. Routine blood investigation like CBC, BT, CT, RBS, HIV rapid test, HbsAg rapid test, blood urea, serum creatinine, urine routine microscopy and chemistry were done. Patients underwent surgical intervention under peribulbar anaesthesia with 5 ml mixture consisting of 3 ml of 2% Xylocaine and Adrenaline, with addition of Hyaluronidase- 5 IU/ml and 3 ml of 0.75% Bupivacaine. Complete excision of Pterygium with CAG or AMG placement was done for each patient with or without sutures. The excised sample was sent for Histopathological examination in Formaldehyde solution. In the lab evaluation of excised pterygia were done for any associated dysplastic changes. Depending upon the involvement of depth of epithelium and basement membrane invasion, result is graded as mild /moderate/severe dysplasia, conjunctival intraepithelial neoplasia, carcinoma *in situ*, squamous cell carcinoma.

Results

A total of 51 patients (52 eyes) were included in this study. HPE of excised Pterygium were done in all these 52 eyes.

Demographically, the mean age of the patients in this study was 45.82 with a standard deviation (SD) of 12.80.The youngest patient in this study was 20 years old and the eldest patient was 77 years of age. Most of the patients were in the age group of 41-60 years age group (50.98%)

Table 1: Age Distribution

Age group	Number of cases	Percentage
20-40	19	37.25%
41-60	26	50.98%
>60	6	11.76%
Total	51	

In this study, 37 patients were male (73%) and 14 patients were female (27%). The duration of Pterygium among the patients in this study ranged from 6 months to 10 years with the range of 1-4 years (29 patients; 56.86%).

Table 2: Duration of Pterygium

	Number of cases	Percentage
<1 year	14	27.45%
1-4 years	29	56.86%
>4 years	8	15.68%
Total	51	

Nasal pterygium was found to be more common (49 cases; 94%) compared to the temporal side (3 cases; 6%) in the population under study.

Table 3: Location of Pterygium

Location of pterygium	Number of cases	Percentage
Nasal	49	94%
Temporal	3	6%
Total	52	

With respect to laterality, 26 in Right eye, 21 in Left eye and 5 in both eyes among the study group.

Table 4: Pterygium Laterality

Eye involved	Number of eyes
Right eye	26
Left eye	21
Both eyes	5
Total	52

In the study group, a higher rate of incidence of Pterygium cases was seen in male patients in almost all age groups.

Table 5: Gender distribution by age group

Age group	Male	Female
20-40	14	5
41-60	18	8
>60	5	1
Total	37	14

Prevalence of OSSN among Pterygium Patients
Total no. of eyes diagnosed with OSSN 1
= ÷ = 0.0192 =1.92%
Total no. of eyes of Pterygium 52

Prevalence of dysplasia among pterygium patients
Total no. of eyes diagnosed with Dysplasia 5
= ÷ = 0.0961 =9.61%
Total no. of eyes of Pterygium 52

Table 6: Prevalence of OSSN and dysplasia in Pterygium patients

	Number of cases	Percentage
OSSN	1	1.92%
Dysplasia	5	9.61%

Among 51 patients under this study about 10 patients (19.6%) had associated comorbidities like HTN, DM, Asthma, Epilepsy, IHD S/P CABG, CKD, Actinic keratosis and 12 patients (23.5%) had habit of smoking, alcohol, tobacco chewing, betel nut consumption.

Mean TBUT-13.7500
SD-3.4521

Table 7: Dry eye assessment based on results of TBUT test

TBUT	<10 Seconds	>10 Seconds
Number of eyes	6	46
Percentage	11.53%	88.46%

Among the total number of 52 eyes under study, TBUT was found to be positive in 6 eyes (11.53%) that is TBUT< 10 seconds and negative in 46 eyes (88.46%) that is TBUT >10 seconds.

Mean value of schirmer's 2 test-18.84
SD-4.65

Table 8: Dry eye assessment based on results of Schirmer's test

Schirmer's test	<15mm	>15mm
Number of eyes	11	41
Percentage	21.15%	78.84%

Among the total number of 52 eyes under study Schirmer's test 2 was found to be positive in 11 eyes (21.15%) value < 15 mm. Schirmer's test 2 was found to be negative in 41 eyes (78.84%) value >15 mm

Discussion

Lee and Hirst proposed the term ocular surface squamous neoplasia, which would be the clinical continuum of mild, moderate and severe dysplasia, carcinoma *in situ* and invasive squamous cell carcinoma (SCC) [2]. Dysplasia and carcinoma *in situ* are together premalignant and termed conjunctival intraepithelial neoplasia (CIN) [8]. Clinicohistopathological correlation is vital for the type of management, recurrence and metastasis. An accurate interpretation will aid in planning the treatment and follow-up carefully and precisely as earlier treatment options could lead to suboptimal management [8]. A Clinician's understanding that a tumor of <5 mm with corneal or scleral invasion as T1 is inaccurate as it could lead to improper specific treatment. So, it is vital to understand the classification which has been given in the AJCC Cancer Staging Manual [8].

Table 9: AJCC-Cancer Staging Manual-8th Edition [9]

Tumor category	Tumor criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor (< 5mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures.
T2	Tumor (>5mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures.
T3	Tumor invades adjacent structures(excluding the orbit)
T4	Tumor invades adjacent structures
T4a	Tumor invades orbital soft tissues without bone invasion
T4b	Tumor invades bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades brain
Node (N) category	Node criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Metastasis(M) category	Metastasis criteria
M0	No distant metastasis
M1	Distant metastasis

Using a generic diagnosis of OSSN could cause a misunderstanding of treatment and prognosis. The main aim is to lay emphasis on careful clinical evaluation, management which includes topical chemotherapy /immunotherapy, alcohol-assisted kerato epitheliectomy, lamellar keratectomy/sclerectomy and excision edge double-freeze thaw cryotherapy [8].
Study done by Shrestha *et al*. [10] showed that benign lesions of conjunctiva are more common than dysplasia or malignant transformation of lesions. It also reported increased prevalence of OSSN among females. In contrast, Dandala *et al*. [11] reported that OSSN was more among males and people with outdoor occupation considering sun exposure to be an important risk factor.Studies done by Gichuhi *et al*. [12] and Wolffsohn *et al*. [13] revealed that the nasal limbus receiving the highest intensity of sunlight is the reason for it to be the most common site for OSSN. Honavar *et al*. [14] reported the recurrence rate of OSSN to be ranging from 15% to 52% and also that it can be reduced to <5% with the use of topical mitomycin C.
In the present study, 52 eyes of 51 patients were studied. The mean age at presentation of pterygium was 45.82 years. The age range of the patients in this study was from 20-77 years. Pterygium was more commonly seen in males compared to females and occurrence was found to be higher on nasal side compared to temporal side of the eye. Pterygium was found to be more common in the age group of 41- 60 years. There was no difference in the laterality of eye involved.

The occurrence of Ocular surface squamous neoplasia was found to be (1.92%) among pterygium patients under study. However dysplasia was found to be more common (9.61%) in these patients. The age of the patient who was diagnosed to have CIN with grade 1 OSSN was 71 years. Post Pterygium excision with CLA he was put on treatment with 0.02% mitomycin eye drops. Four patients were diagnosed to have mild dysplastic changes in excised pterygium after histopathological examination. All four patients were males. Two of them were in the age group of more than 45 years. One found to have risk factor like Actinic Keratosis [pre cancerous cutaneous lesion], another found to have recurrent dense pterygium. These patients have been asked for follow up every 2 months. If they develop any clinical symptoms like [pain, redness or watering of eyes] and signs of OSSN [like gelatinous or plaque like interpalpebral conjunctival gray or white lesion, irregular thickened limbal, corneal & conjunctival epithelium, neovascularisation] excision biopsy and histopathological examination to be done. The progression of normal conjunctival or limbal epithelium to limbal dysplasia is monitored closely, for OSSN transformation. An appropriate triage of the patient and care full planning of treatment option is essential as this is a common and easily curable premalignant condition.

Conclusion

In view of the high rate of dysplasia detected in this study and knowing that dysplastic epithelium can change to metaplasia, anaplasia to OSSN, application of cryotherapy to the cut margins of the conjunctiva in every case may be a suitable method to treat the patient. It is of utmost importance that every case of excised pterygium especially recurrent pterygium, Long standing, inflamed pterygium, Pterygium in patients with age more than 45 yrs, Pterygium in patients with risk factors like HIV has to be sent for histological examination so that the cases can be followed up subsequently for any malignant transformation. An alternative for cryotherapy is application of 0.02% mitomycin to cut margins of conjunctiva intraoperatively if OSSN or dysplasia is suspected. We would also like to emphasize that a close long-term follow up of patients is recommended. It is important for doctor to appraise the patient of the seriousness of the condition and emphasize the need for long term follow up (6-7 years).

Conflict of Interest

Not available

Financial Support

Not available

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