Original Article

Conjunctival Lesions: When Should We Perform Biopsy ?

Lubna Khan[1], Kamal Malukani[2] , Ankur Saxena[3]
[1,3]Department of Ophthalmology
[2]Department of Pathology
Sri Aurobindo Institute Of Medical Sciences, Indore,M.P., India

Abstract

Introduction: The conjunctiva is a thin and flexible mucus membrane that provides a protective barrier for the eye. Very few histopathologic studies have been conducted on biopsies from conjunctival lesions (CL) in central India. **Objective:** To study the spectrum of CL and define those lesions that need attention with regard to need of biopsy in order to prevent grave sequelae and ocular morbidity. **Results:** Degenerative conditions such as pterygium followed by pinguicula were the commonest lesions seen in conjunctiva. Out of 129 subjects, youngest in the series was 3 years old while oldest patient was 72 years of age. Commonest age interval for involvement was 35 to 50 years. In children below 8 years, cystic lesions (infective or inclusion), limbal dermoid and choristoma were seen. Vascular lesions were noticed by patients for the first time between mid-teens to 25 years age. Premalignant lesions were dysplasia, actinic keratosis and PAM with or without XP. Malignant lesions in this series were squamous cell carcinoma, basal cell carcinoma and sebaceous carcinoma; which were observed in the age interval 25 to 75 years. In none of the malignant conditions there was deeper penetration into the globe or orbit. Though diagnosed within two weeks duration (by incisional biopsy) from appearance of nodule, unfavourable outcome was seen only in one malignant CL; a case having sebaceous carcinoma. In all pediatric cases outcome was good, except in child having choristoma, where amblyopia ensued before a diagnosis was made. Response to sclerotherapy was excellent as all the epibulbar vascular malformations regressed. All degenerative lesions regressed except one recurrence in a recurred pterygium. Case diagnosed as large B cell lymphoma recurred after one year. Dysplastic changes were seen to occur at limbus on followup in one XP, but in all cases of naevi, neither cellular atypia was seen nor melanoma developed. **Conclusion:** An overview of various CL disclosed that clinician has to differentiate benign from premalignant and malignant lesions. Early diagnosis, proper histological study and patient education, all are equally important for achieving good outcome.

Key Words: Conjunctival Lesions (CL), Ocular surface squamous neoplasia (OSSN), squamous cell carcinoma (SCC)

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Corresponding author
Dr. Lubna Khan (Professor)
Sri Aurobindo Institute of Medical Sciences, ED - 45, Scheme No - 94 D, Near Sahil Regency, Ring Road, Indore, (M.P.), India
Additional Professor
Department of Ophtalmology
All India Institute of Medical Sciences (AIIMS), Rajpur, India
Email: lubnakhan65@yahoo.co.in

Introduction

The conjunctiva is readily visible and partially exposed to sunlight; therefore, conjunctival tumors and related lesions are recognizable

early in their course (Shields CL *et al.*, 2004). Conjunctival lesions (CL), based on their origin, are categorized into melanocytic and non-melanocytic types, both arising from epithelial and stromal components (Shields CL *et al.* 2004). Melanocytic and non-melanocytic tumors have been reported to comprise 53% and 47% of all excised CL, respectively (Shields CL *et al.*, 2004).

Various CL are recognized by their behavior and clinical appearance, although there are very few diagnostic challenging cases which need histopathological assessment (Alves LF *et al.*, 2011). The accuracy of clinical diagnosis ranged from 50.87% to 96% (Shields CL *et al.,* 2004). The importance of prompt diagnosis of CL is emphasized for two basic reasons. First and foremost, it is in order to save the eye functionally (prevent amblyopia); secondly, to curtail the intraocular progression of ocular surface squamous neoplasia (OSSN).

OSSN consist of epithelial lesions such as dysplasia, carcinoma *in situ* and squamous cell carcinoma (SCC), which involve the conjunctiva and cornea (Grossniklaus HE *et al*., 1987). Main factors associated with conjunctival epithelial lesions include sunlight exposure, human papilloma virus (HPV) subtypes and human immunodeficiency (HIV) infection (Alves LF *et al.* 2011). Other factors associated with OSSN are old age, male sex and fair skin (Lee GA *et al.*1995; Sun EC *et al.*1997). The incidence of ocular SCC increases 49% with every 10-degree decline in latitude (Newton R *et al.*, 1996) and the higher exposure of male subjects to sunlight while working outdoors may explain the higher prevalence of OSSN in males (Alves LF *et al.,* 2011; Lee GA *et al.,* 1997). Pola EC (2003) in a study conducted on population of Zimbabwe showed that 70% of patients having OSSN were females, as they were exposed to ultraviolet light during cultivation.

Ophthalmic biopsies are one of the rare biopsies we collect in the department of pathology. However, we should never forget that ophthalmic pathology is unique in many respects as it encompasses wide range of tissues and shows wide range of diseases. The objectives of this study were to determine the prevalence of various CL at a tertiary health care center and establish a diagnosis based on histopathology in all conditions where biopsy was performed. Also, histopathological information provided could be correlated with patient's history and other clinical data giving greatest benefit to ongoing patient care.

Material and methods

All patients having any lesion in conjunctiva of one or both the eyes were included. In conditions requiring surgical excision, an excision biopsy under local anesthesia (in two pediatric cases under general anesthesia) was performed after counseling. In all excised pterygia, conjunctival autografting was done as a routine; in recurred cases or deeper corneal involvement (seen in four cases) an amniotic membrane transplant was done over the defect. The excised tissue was processed in the department of pathology and paraffin wax moulds were prepared. Sections were cut and staining was done routinely with hematoxylin and eosin stain. If needed, Gram's stain or special stains like reticulin were done. Only in one patient FNAC was done as an aid for diagnosing the nature of recurrence, based on which the patient was managed surgically. On obtaining a report of premalignant or malignant lesion, further management was explained to all the patients including the importance of follow-up.

Subjects with vascular malformation were counseled for sclerotherapy. Intralesional injection bleomycin (sclerosing agent) was given in a dose of 1µg/kg body weight which, if needed, was repeated after six weeks.

Results

A total of 129 patients were evaluated clinically. Numbers of patients in age intervals were: upto 15years (3 subjects), 16 to 30 (n=32), 31 to 45 (n=66), 46 to 60 (n=22) and 61 to 75 years (n=6). Commonest age interval for CL to occur was thirty to fifty years. Degenerative lesions such as pterygium followed by pinguicula were the commonest lesions seen in conjunctiva. In children below eight years, cystic lesions (infective or inclusion), limbal dermoid and choristoma were seen. Vascular lesions were noticed by patients for the first time between mid teens to thirty years age. Malignant conditions such as squamous cell, basal cell and sebaceous carcinomas fell in the age interval of 25 to 75 years.

On the basis of histology various lesions were categorized as follows :

- Degenerative diseases (55.03%, n=71): Pterygium and Pinguecula.
- Vascular lesions (3.875%,n=5) lymphangioma (fig 1a & 1b), epibulbar varix and capillary hemangioma.
- Benign epithelial lesions and cysts (9.30%, n=12): Papilloma, choristoma (fig 1c & 1d), dermoid cyst, epithelial inclusion cyst.
- Premalignant and malignant epithelial lesions (6.98%, n=9): Dysplasia, actinic keratosis (fig 3c & 3d), squamous cell carcinoma in-situ, invasive squamous cell carcinoma (fig 2b), sebaceous carcinoma (fig 2a) and basal cell carcinoma.
- Melanotic lesions (12.40%, n=16): Naevus, PAM, PAM with XP and melanosis oculi.
- Lymphoid (0.78%, n=1): Large B-cell lymphoma.
- Miscellaneous (15.50%, n=15): Conjunctivochalasis, pyogenic granuloma, dermolipoma, schwannoma (fig. 3a), foreign body granuloma and molluscum (fig. 3b).

Table 1 show various CL based on histology in the present study. On the basis of anatomical location these lesions are enumerated and detailed in Table 2. The lesions were classified anatomically as; bulbar conjunctival, palpebral conjunctival, limbal and perilimbal, forniceal, marginal, caruncular, and canthal.

The prevalence of conjunctival neoplasia assessed from a total of 129 lesions, collective of malignant and premalignant epithelial lesions, was 6.97% of which malignant lesions were 4.65% and premalignant lesions were 2.32% seen in this study. One case each of dysplasia, actinic keratosis and PAM with XP (who developed dysplastic changes in both eyes) were the pre-malignant lesions. Two cases each of newly diagnosed SCC and sebaceous carcinoma and one case of basal cell carcinoma were the malignant lesions. Recurrence with orbital invasion due to invasive squamous cell carcinoma was seen in one case after enucleation done elsewhere in a mid aged female, which was confirmed by FNAC.

In cases of dermolipoma and conjunctivochalasis, reassurance was the mainstay. In cases of molluscum, shave excision with histopathological confirmation was done in all cases in adults. In the sole case of molluscum in paediatric age, carbolic cautery was done under sedation. In the series, 3 cases with varices (1 forniceal, 2 bulbar conjunctival and adjoining fornix) were treated with Injection bleomycin given subconjunctivally. Sequential observation was done for premalignant lesions. In none of the malignant conditions there was deeper penetration in eye or orbit or recurrence, except in one case of sebaceous carcinoma in which metastasis occurred.

Table 1: Various Conjunctival Lesions Diagnosed In The Present Study (n=129)

Degenerative Lesions (n=71)	Benign epithelial lesions & Cysts (n=12)	Premalignant & Malignant epithelial lesions (n=9)	Melanotic lesions (n=16)	Lymphoid Malignancies (n=1)	Miscellaneous lesions (n=20)
Pterygium, n=48; with Inflammatory changes, n=2	Papilloma, n=3	Dysplasia n=3	PAM n=1, PAM with XP n=2	Non Hodgkin's lymphoma, n=1	Conjunctivochalasis n=1, Molluscum Contagiosum, n=5
Pinguecula, n=21	Dermoid, n=2; Choristoma n=1	Squamous cell carcinoma , n=2	Melanosis oculi, n=5		Pyogenic granuloma, n=3 & Foreign body granuloma, n=2
	Epithelial Inclusion cyst, n=6	Invasive squamous cell carcinoma, n=1	Naevus, n=8		Dermolipoma, n=3
		Sebaceous carcinoma, n=1			Epibulbarvarices, n=3
		Actinic keratosis, n=1			Capillary haemangioma, n=1
		Basal Cell Carcinoma, n=1			Schwannoma, n=1
					Lymphangioma, n=1

Table 2: Conjunctival Lesions Based On Specific Anatomical Location.(n=128)

Caruncular (n=3)	Lateral canthal (n=4)	Forniceal (n=7)	Limbal & Perilimbal (n=91)	Palpebral conjunctival (n=7)	Marginal (Lid) (n=13)	Bulbar conjunctival (n=4
Capillary Hemangioma-n=1,	Dermolipoma- n=3,	Papilloma-n=1,	Schwannoma-n=1,	Pyogenic granuloma n=2+1 (in upper and lower lid)	Sebaceous carcinoma n=1,	Inclusion cyst n=2,
Papilloma- n=1,	Conjunctivochalasis =1	Cyst- n=3, 2 in upper fornix and 1 in lower fornix	Foreign body granuloma- n=2,	Lymphangioma n=1,	Basal cell carcinoma n=1	Pigmented naevus n=1,
Pigmented Naevus n=1.		Varix- n=2,	Complex choristoma- n=1,	Non Hodgkins lymphoma n=1,	Naevus, pigmented-n=4,	Varix n=1
			Actinic keratosis- n=1,	Cyst n=1	Non pigmented n=2.	
			Dysplastic lesion-n=3,	PAM n=1	Molluscum n=3(ul)+n=1(ll)+ n=1 in both ul& ll.	
			SCC*- n=2,			
			Pterygia n=50, including 2 in-flammedpterygia, pinguicula n=21			

*One case of squamous cell carcinoma was diagnosed on FNAC as invasive type, occurred as recurrence in socket after enucleation, hence not shown in the table.

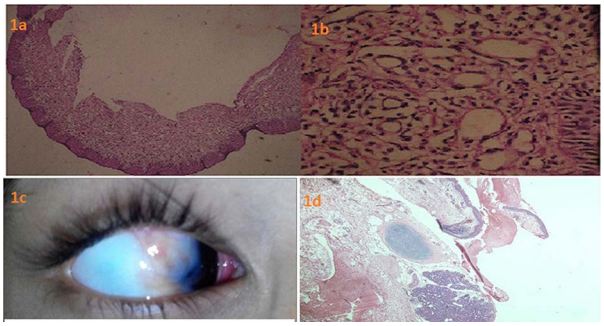

Figure 1a- Photomicrograph of lymphangioma showing subconjunctival tumor composed of conglomerated vascular channels (40X, H&E). **Fig 1b** Photomicrograph showing subconjunctival tumor composed of dilated and conglomerated vascular channels lined by endothelial cells with scanty interstitium (400X , H&E). **Fig 1c.**Choristoma involving lateral part of cornea in right eye. **Fig 1d.** Photomicrograph of choristoma showing normal epidermoid, chondroid, fibrous and glandular elements (40X, H & E).

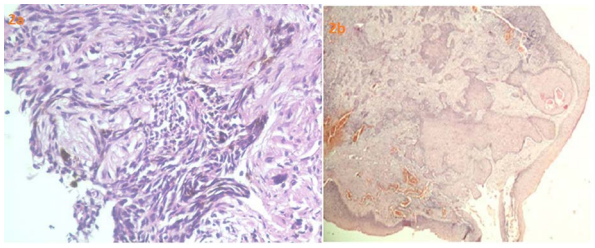

Figure2a- : Photomicrograph of sebaceous carcinoma showing sheets of atypical cells with high nucleo-cytoplasmic ratio and eosinophilic cytoplasm infiltrating the stroma (100X,H&E). **Fig2b.** Photomicrograph of squamous cell carcinoma showing groups and sheets of atypical polygonal cells infiltrating in the subconjunctival tissue (40X, H&E).

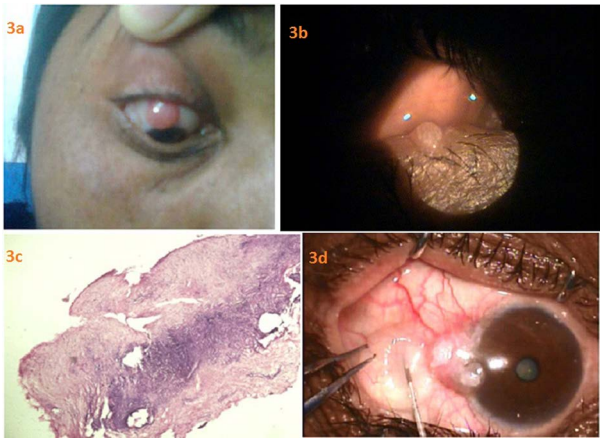

Figure3a- Preoperative photograph of the patient showing mass (Schwannoma) at perilimbal location. **Fig 3b.** Umbilicated lesion of Moluscum in intermarginal strip of conjunctiva. **Fig 3c.**

Photomicrograph of actinic keratosis showing marked surface keratinization of conjunctiva with inflammatory band in subconjunctival area (40X, H&E), **Fig 3d.** Gelatinous heaped up lesion on temporal limbus with prominent feeder vessel.

Discussion

Various studies have been done to determine the prevalence of CL in different parts of the world. A wide variety of neoplasms can arise from different ocular structures. OSSN is considered to be a broader term (Hirst LW *et al*, 1995), used nowadays to encompass various intraepithelial and invasive lesions of the conjunctiva and cornea, including dysplasia/conjunctival intraepithelial neoplasm, carcinoma *in situ* and invasive squamous cell carcinoma while Radhakrishnan A. (2011) extended inclusion of papilloma, pseudoepitheliomatous hyperplasia, benign hereditary intraepithelial dyskeratosis and mucoepidermoid carcinoma as well.

The observation and results of the present study were compared with various other similar studies & findings. An overview of frequency (%) of common benign/non-malignant lesions in the study carried out by Yoon YD *et al.* (1997)

showed pterygium 18%, inflammatory lesions 7%, and epithelial inclusion cyst 6%. The results of present study were comparable with the study carried out by Mondal SK *et al.* (2012). They reported pterygium (22.5%), pingueculum (9.16%), squamous papilloma (9.16%) and granulation tissue (8.33%) as common benign lesions in their study. In the present study, benign lesions included pterygium (38.76%), pinguicula (16.28%), epithelial inclusion cyst (4.65%), venolymphatic malformation (3.87%) and benign papillomas (2.32%).

The prevalence of conjunctival malignant lesions in the study by Yoon YD *et al.* (1997) was approximately 8%, which is comparable to overall malignant CL of 6.97 % in our study. They reported 7% dysplasia, <1% sebaceous carcinoma, 4% SCC, and 3% melanoma, whereas in our series 2.325% dysplasia, 0.775% sebaceous carcinoma and 2.32% SCC were seen. In a review done by Singapore Cancer Registry reported by Lee SB *et al.* (2000), out of 125 patients 12.8% were found to have conjunctival malignancies.

Mondal SK et al. (2012) have reported a total of 13.3% malignancies including 7.5% SCC, 1.66% lymphomas, 1.6% malignant melanoma and 0.83% each of muco-epidermoid carcinoma, sebaceous carcinoma and leukemic infiltration of acute myeloid leukemia (AML). They noted two out of nine SCC cases HIV positive whereas in our study none of the case of SCC was HIV positive. Lee SB et al. (2000) and Saronil MA et al. (2009) have stated infection by HIV virus to be amongst a known predisposing factor for SCC.

Viewing the incidence of melanoma of conjunctiva, it is reported from western world by Lee SB (2000) to be as high as 31.25%. We did not come across any conjunctival melanoma. In a study from eastern India, Mondal SK *et al.* in 2012 have reported 0.8% cases of conjunctival melanoma.

In the present study, of all the excised pterygia (38.75% of all conjunctival lesions), two were having a heaped up fleshy head (cystic pterygia) and on histology showed inflammatory changes. One case of pterygium (encroaching obliquely on temporal side of cornea, unilaterally) having flat broad head was a recurrent one, with deep encroachment into cornea. On previous excision done elsewhere, a biopsy was not done. It was only this case in our series where recurrence occurred. Hirst LW (2009) reported 52 (9.8%) OSSN amongst the 553 pterygia. Therefore, even in recurrences of pterygia biopsy must be done.

In a female child (8 years), conjunctival growth encroaching on cornea (fig1c) was excised, the tissue thus obtained, on its conjunctival aspect showed normal epidermoid, chondroid, fibrous and glandular elements on histology (figure1d). At the corneal end there was presence of only fibrous tissue. Excision had been done elsewhere previously, but histopathological examination of tissue was not carried out then. Krause FE (1998) have reported case of complex choristoma, which was shown to have been associated with nevus sebaceous of Jadassohn in previous case reports. We did not find such association in our patient, although genetic basis cannot be ignored, since first cousin of this female child, a four years old male, also had similar lesion in one eye. Surgical excision with amniotic membrane transplant was done in the female child. After two weeks, best corrected visual acuity (BCVA) amounted to 6/36 with refractive aid. Later, after occlusion therapy and use of glasses vision was 6/24. At final follow up, when contact lens was dispensed, her acuity was 6/18.

The patient having actinic keratosis (Fig 3c & 3d) had a gelatinous heaped up lesion over limbus temporally and was 63 years of age. Mondal SK *et al* (2012) reported such changes in pre-existing pterygium. We noticed a gelatinous, well-circumscribed heaped up

limbal growth with nothing resembling a pterygium; instead of a leash of conjunctival vessels having horizontal course as in pterygia, there was one larger calibre vessel appearing as a feeder. There was no history of any growth or biopsy done in the past. Incidence of actinic keratosis in our study was 0.77%. Mondal SK (2012) found changes of actinic keratosis in preexisting pterygium.

All three epibulbar vascular malformations in this series completely regressed with sclerotherapy. In accordance with Smit DP (2012), as for cutaneous capillary angiomas, 1-1.5 microgram /kilogram body weight Bleomycin was injected intralesionally. Of these, one patient was having similar lesions in skin overlying inferior orbital rim and buccal mucosa of same side. Histology showed large dilated vascular channels lined by single layered endothelium.

Prevalence of epithelial inclusion cysts of conjunctiva in our study was 4.65%, while Mondal SK *et al* (2012) reported 6% prevalence. Dermoid cyst straddling the limbus and developmental anomaly such as choristomas are not uncommon in pediatric age group. Prompt surgical intervention followed by occlusion of fellow eye and macular stimulation of affected eye is suggested in such cases in order to prevent amblyopia.

Umbilicated lesions of lid margin were seen in five cases of molluscum, three at upper lid, one at lower lid (Fig 3b) and in one case at both upper and lower lid in same eye, of which one was in pediatric age group. In one adult male it was symptomatic, situated adjacent to six O'clock limbus where it had caused superficial vascularization of cornea with infiltration. Ingraham HJ (1998) has stated molluscum to be uncommon in bulbar conjunctiva.

A middle aged female presented with well-circumscribed smooth lesion at twelve O'clock limbus. During excision, it was found to be well encapsulated. Histology showed it to be perilimbal conjunctival schwannoma (Fig. 3a). Andreoli CM *et al.* (2004), have shown in their study that perilimbal schwannoma can present as pingueculum. In a study done by Lawrenson JG *et al.* (1991) on conjunctival innervation by special staining method, it was found that limbus is exuberantly innervated. In our case, end bulb of Krause present in cornea could have been a source of origin of the perilimbal schwannoma, which is unlikely, as the lesion was not involving any part of cornea. It can occur as a part of MEN (multiple endocrinal neoplasia), for which our patient was examined systemically and relevant investigations were done. She had conjunctival schwannoma as an isolated occurrence.

Benign conditions like naevi and primary acquired melanosis of conjunctiva can be precursors of conjunctival malignant melanoma. Pigmented lesions of conjunctiva should be seen for presence of cellular atypia. Shields JA *et al.* (2007) reported that PAM with severe atypia shows progression to melanoma in up to 13% to as high as up to 50% cases. We came across 8 naevi in present study, histology did not reveal atypia in any case. Approximately 75% cases of conjunctival melanoma arise in association with PAM. Oellers P *et al.* (2012) concluded that complexion associated melanosis is seen in darkly pigmented individuals and does not progress to melanoma.

Though conjunctival malignant tumors are more prevalent with older age, Hertle RW *et al* (1991) found such cases associated with Xeroderma pigmentosum to be commonly seen in children. From the study reported by Pola EC *et al.* (2003), median age of OSSN was found to be 35 years. Two of the three patients in our series diagnosed as SCC were males (27 years and 34 years), whereas third was a 39 year old female who presented with recurred mass in enucleated socket. Histology showed squamous cell carcinoma in-situ in the 34 years

old male while well differentiated SCC with cell nests in the 27 years old male. In the latter, (the 39 years old female) there was presence of well differentiated invasive SCC (Fig 2b).

Two out of the three cases of SCC diagnosed on excision biopsy underwent a second surgical procedure within a week after histopathology disclosed well differentiated squamous cell carcinoma. Superficial sclerectomy was done and cryo applied at the edges and base of involved sclera and conjunctiva. Mitomycin C was given as recommended by Wilson MW et al. (1997); in a dose of 0.02mg/ml after complete healing of keratectomy, given in two pulses of one week each, two weeks apart. Both patients have been on follow up (ten and seven years) with favorable outcome. The only case where we chose to perform FNAC was recurred squamous cell carcinoma in a middle aged female, enucleation having been done elsewhere, we had to perform a lid sparing exenteration since FNAC revealed it to be invasive type. The fact that conjunctival lesions should be attended carefully with proper histological study is best exemplified by this subject requiring exenteration, where timely intervention and post excision palliation would have possibly curtailed enucleation and recurrence after it. One case of sebaceous carcinoma (Fig 2a) was non compliant to chemotherapy and radiotherapy after excision, developed metastasis and dropped out of follow up.

The prevalence of lymphoma in the present study was 0.775%. A young male having upper lid ptosis with palpebral conjunctival chemosis on biopsy showed large population of lymphocytes and was diagnosed as large B cell Lymphoma. White WL et al. (1995) studied orbital lymphomas extensively for more than a decade, and found that lymphomas usually present as a soft tissue mass either involving the conjunctiva, or elsewhere in the orbit.

Conclusion

From this study we derived inference that ophthalmic clinicians shoulder the responsibility of attending various CL in all age groups; in children with limbal involvement to prevent amblyopia and in adults to prevent complications arising from ocular surface neoplasias. Merely differentiating benign from malignant lesions does not suffice, an ophthalmic clinicians' acumen must be promptly directed towards premalignant entity. Also, premalignant and malignant conjuctival epithelial lesions can be managed efficiently by teamwork of ophthalmic surgeon and pathologist. Subjecting all degenerative lesions to biopsy should be our practice, so that patients having lesions with adverse prognosis do not go unattended, thus minimizing ocular morbidity.

A definitive diagnosis is made only by histology, following which there can be proper counselling, which will not only improve patient education, but also compliance, thus minimizing dropout rate, loss to follow ups and recurrence.

Though this series is small, yet such pilot studies as this done at different centers may be compiled to form the basis of a research review. Alternatively, in institutions where larger volume of patients attend ophthalmic outdoor, researchers can validate more reliable results.

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