

CLINICAL AND HISTOPATHOLOGICAL ANALYSIS OF CONJUNCTIVAL TUMOURS AT A TERTIARY CARE CENTRE IN INDIAN POPULATION

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ABSTRACT: The broad spectrum of conjunctival tumors ranges from non-neoplastic benign tumors to very aggressive malignancies, such as melanoma or Kaposi's sarcoma which threat visual function and life of the patient. There is a relative paucity of large published studies documenting conjunctival lesions. In the Indian population, reported 46% of epithelial origin (benign, premalignant, and malignant neoplasm), degenerative lesions (14%), chronic non-specific inflammation (12%), melanocytic tumors (12%), lymphoid tumors (6%). Squamous cell carcinoma (20%), miscellaneous (22%), pterygium (10%), squamous papilloma (8%), and OSSN (8%). A review of a large series of conjunctival biopsy specimens from an adult US population documented the following distribution: inflammatory/degenerative lesions (12%), benign epithelial (2%), pigmented (53%), premalignant and malignant epithelial (11%), lymphoid (8%), miscellaneous (12%) and congenital lesions (2%).

AIM: To study the clinical and histopathological features of conjunctival tumors at a tertiary care hospital in south Indian population. **MATERIAL AND METHODS:** In our study, 134 patients with conjunctival tumors followed between January 2009 and September 2010 were retrospectively reviewed. Clinical data were collected from medical records and analyzed. Of the 134 patients with conjunctival tumor, 80 were male (59.70%) and 54 were female (40.29%). The mean age of the 134 patients was 35 years (range 1 to 95 years). In our series, the most common diagnosis of 134 lesions were, nevus 18.66% (n=25), carcinoma in situ 10.44% (n=14), dysplasia 5.97% (n=8), squamous cell carcinoma (SCC) 5.22% (n=7), haemangioma 3.73% (n=5), squamous papilloma 3.73% (n=5), limbal dermoid 2.98% (n=4), malignant melanoma 1.49% (n=2) and lymphoma 0.74 % (n=1). **CONCLUSION:** Nevus was found to be the most common conjunctival benign tumor. Even though squamous cell carcinoma is a rare conjunctival malignant tumor, it may be encountered in younger male population.

KEYWORDS: Conjunctiva, Melanoma, Nevus, Squamous cell carcinoma.

INTRODUCTION: Tumours of the conjunctiva and cornea include a varied and large spectrum of conditions. These tumours are broadly categorized into two major categories of congenital and acquired lesions. The acquired tumours are further subdivided based on origin of the mass into surface epithelial, melanocytic, vascular, neural, fibrous, histiocytic, myogenic, myxoid, lipomatous, lymphoid, leukemic, metastatic and secondary tumours.⁽¹⁾

The broad spectrum of conjunctival tumours ranges from non-neoplastic benign tumours to aggressive malignancies, such as melanoma or Kaposi's sarcoma which may threat visual function and life of the patient.⁽²⁾ Ocular surface tumours include a wide variety of neoplasms originating from squamous epithelium, melanocytes, and lymphocytic resident cells of the conjunctival stroma.⁽¹⁾

Ocular surface squamous neoplasia (OSSN) denotes neoplastic lesions of epithelial origin on the cornea and conjunctiva and includes both squamous epithelial dysplasia and squamous cell

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carcinoma.⁽³⁾ Melanocytic lesions include naevus, melanoma racial melanosis, primary acquired melanosis and other ocular surface conditions like ocular melanocytosis and secondary pigmentary deposition. The most frequent non-melanocytic neoplastic lesions include squamous cell carcinoma and lymphoma, both of which have typical features appreciated on clinical examination.⁽¹⁾

In addition to evaluation of the conjunctival lesion, meticulous slit lamp examination of the cornea is essential in all patients with suspected conjunctival tumours. Invasion of melanoma and squamous cell carcinoma into the peripheral cornea may appear as a subtle gray surface opacity.⁽⁴⁾ Lymphoid tumours of the conjunctiva include a variety of monoclonal and polyclonal lymphoid tumours.⁽⁵⁾ The aim of this study was to analyse the clinic pathologic features of conjunctival tumours followed at a tertiary care hospital in Karnataka, South India.

MATERIAL AND METHODS: This retrospective study included 134 patients with conjunctival surface lesions who were treated conservatively or surgically for the same between January 2009 and September 2014. Patient's details including age, gender, clinical examination (visual acuity, slit lamp biomicroscopy, application tonometry, fundus evaluation) and histopathologic findings were retrieved from medical records and reviewed retrospectively.

Clinical diagnosis of conjunctival tumours was based on the patient's history, clinical findings on biomicroscopic evaluation of the lesion. The therapeutic options included periodic observation, surgical excision and administration of antitumour agent. The most common indication for tumour resection was suspected growth of the tumour on observation on recurrent visits or according to the patient's history, all such cases were subjected for surgical excision and biopsy. For confirmation of diagnosis, biopsy specimen was sent for histopathological examination. The study was approved by the Ethical Committee of the Institute.

RESULTS: Of the 134 patients, who had reported for conjunctival tumours, 80 (59.70%) patients were male and 54(40.29%) patients were female. The mean age of the 134 patients was 35 years (range 1 to 95 years). In our study 102(76.12%) were benign, 8(5.97%) were premalignant and 24(17.91%) were malignant cases.

In our series, the most common diagnosis of 134 conjunctival lesions were, nevus 18.66% (n=25), chronic inflammation 15%(n=20), followed by foreign body granuloma 13.4% (n=18), carcinoma in situ 10.44% (n=14), Squamous cell dysplasia 5.97%(n=8), tenons cyst 5.97% (n=8), squamous cell carcinoma (SCC) 5.22% (n=7), epithelial cysts 5.22%(n=7), dermolipoma in 4.48%(n=6), haemangioma 3.73% (n=5), squamous papilloma 3.73%(n=5), dermoid 2.98%(n=4), pyogenic granuloma 2.98% (n=4), malignant melanoma 1.49% (n=2) and lymphoma 0.74 % (n=1) respectively (Table 1).

The most common indication for resection of tumour was suspected growth of the tumour. In all cases of suspected growth, the tumour was excised surgically, 2 (1.49%) SCC was treated with topical mitomycin C after tumour resection. Malignant lesions had no systemic metastasis and local recurrence.

DISCUSSION: Tumours of the conjunctiva have a large spectrum which range from benign tumours to aggressive life and vision threatening malignancies.⁽²⁾ The conjunctiva can spawn neoplastic lesions from both its epithelial and stromal structures. Conjunctiva being visible, tumours and related lesions that occur are easily recognized at a relatively early stage. Tumours have typical clinical features,

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thus an accurate diagnosis can often be made by external ocular examination by slit lamp biomicroscopy.

A diagnostic biopsy is not usually necessary in cases of smaller tumours that appear benign. If a smaller tumour does require a biopsy, it is often better to completely remove the lesion, by excisional biopsy. In cases of larger lesions, however, it may be appropriate to remove a portion of the tumour (incisional biopsy) to obtain a histopathologic diagnosis before embarking on more extensive therapeutic approach.⁽⁴⁾

Depending on the presumptive diagnosis, the size and extent of the lesion, management of conjunctival tumours may consist of serial observation, incisional biopsy, excisional biopsy, cryotherapy, chemotherapy, radiotherapy, modified enucleation, orbital exenteration and other modalities if large areas of conjunctiva are removed, mucous membrane grafts from the conjunctiva of the opposite eye, buccal mucosa, or amniotic membrane may be necessary.^(2,4) Chi and Baek reported that most common conjunctival tumours were melanocytic nevi in 54.2%, and 29.2% of these tumours was compound nevus.⁽⁶⁾

Amoli and Heidari reported that the most common benign primary conjunctival tumour was nevus 38.7% (mean age of the patients 22.27) and the most common malignant tumour (25.1%) was SCC (mean age of the patients 58.63) in their series.⁽⁷⁾ In the present study, the most common tumour was conjunctival nevus in 25 of the patients (18.66%). Conjunctival nevus is a benign tumour most often located at the nasal or temporal limbus and rarely in the fornix, tarsus or cornea. The interpalpebral location of nevus near the limbus is typically classic and remains relatively stationary throughout life, with risk for transformation into malignant melanoma in less than 1%.⁽⁴⁾

Over time, Shield et al reported a change in tumour color detected in 13% (20/149) and a change in tumour size detected in 8% (12/149) from his study.⁽⁸⁾ Regarding the symptoms and clinical appearance of the conjunctival nevus, most patients reported noticing a spot on the eye (65%), 5% noted inflammation, and 30% of patients were unaware of the lesion. The symptoms were present for a mean of 12 years. Enlargement or color change in the lesion over the years prior to our examination was reported by 54% of patients, but support for such enlargement was rarely photographed.

The tumour was most commonly found in the bulbar conjunctiva (79%), caruncle (18%), or plica semilunaris (3%). Shield et al reports conjunctival nevus found most commonly in the bulbar conjunctiva (72%), caruncle (15%), or plica semilunaris (11%). Rarely was the tumour found in the fornix (1%), tarsal conjunctiva (1%), or within the cornea (1%). It has been suggested that the presence of a nevus in the palpebral and forniceal region should raise the suspicion of malignancy and early biopsy.⁽⁸⁾

In a Danish study by Gerner et al provided a clinicopathologic study on 343 conjunctival nevi. They described the following tumour locations: the bulbar conjunctiva in 33% caruncle in 29%, limbal conjunctiva in 27%, and at the eyelid margin in 1%.⁽⁹⁾ Fig 1 depicts the common benign conjunctival lesions.

Nevi of Conjunctiva generally stop abruptly at the limbus and typically do not involve the corneal epithelium or stroma. Overhang of the cornea from a large conjunctival nevus is possible, but invasion of the cornea by a nevus is unusual. On the other hand, melanoma of conjunctiva often grows beyond the limbus into the cornea.⁽⁴⁾ The tumour was most commonly brown. Cysts, feeder vessels and intrinsic vessels were recognised in some of the conjunctival nevus on biomicroscopic evaluation.

In contrast, conjunctival melanoma rarely, displays intralesional cysts. Feeder vessels are prominent with conjunctival melanoma. Thus, the importance of recognition of tumour cysts is a key point in differentiating conjunctival nevus from malignant melanoma as many other features overlap.⁽⁴⁾ Fig 2 shows the histopathological picture of conjunctival nevus.

Tumour treatment for conjunctival nevus included observation (68%) or excisional biopsy alone or with cryotherapy (32%). The most common reasons for excisional biopsy included our concern for malignant change based on recent growth (19%), clinical features (2%), color change (1%), or recurrence of previously excised lesion (1%). The other reasons for excision included cosmetic appearance (6%) and patient's concern for melanoma (3%).

Six cases (4.48%) of dermolipoma were described as pinkish yellow subconjunctival mass involving the outer canthus with no palpable posterior margin. Dermolipomas were partially excised in most cases for cosmetic reasons due to posterior orbital extension. Histopathologically, there was excessive fat tissue with associated retention ductal cysts. Solid limbal dermoids were excised in 4 cases (2.99%) due to encroachment over the cornea and for cosmetic reasons.

They were clinically described as solid globular elevated masses embedded in the superficial sclera and/or cornea on the temporal limbus or on inferior temporal globe, with occasional fine protruding hairs. Histologic composition was fibrous tissue and occasional few hairs with sebaceous glands below the conjunctival epithelium.

Papilloma represents 7-10% of conjunctival tumours in childhood and young ages. squamous cell papilloma caused by infection with HPV (type 6, 11, 16, 33) has a low risk of malignant transformation and can be treated either by surgical excision or cryotherapy, but the recurrence rate is unfortunately high.⁽²⁾ Our study reports 3.73%(n=5) of squamous papilloma cases.

Conjunctival intraepithelial neoplasia (CIN, conjunctival dysplasia): This includes a disease spectrum characterized by a replacement of the conjunctival epithelium by atypical squamous cells.⁽⁵⁾ In our series dysplasia was reported in 8(5.97%) cases. Clinically, CIN is an ill-defined gelatinous lesion that blends with surrounding normal conjunctiva. The surface mostly shows keratinization (leukoplakia) and the lesion is usually sessile (papilliform).

The lesion shows abrupt transition between normal and acanthotic dysplastic epithelium, which may involve less than 50% of epithelial layer in mild dysplasia and more than 50% of thickness in severe dysplasia. The lesion may show a recurrence rate of up to 50% at 10 years with positive surgical margins.^(10,11,12.) Carcinoma in situ(CIS)- It is a full thickness replacement of epithelium by frankly malignant cells. Epithelial basement membrane is intact, with no invasion into substantia propria.

Clinically, it presents as an opalescent papillary masses at limbus with minimal leukoplakia. Cells show loss of polarity and anaplasia. Spindle and epidermoid variants are detected on histopathology.^(10,11,12) In our case series we report 14 (10.45%) cases of Carcinoma in situ. Conjunctival SCC is generally seen in elderly male patients.⁽²⁾

There is an increased incidence of SCC of the conjunctiva in patients with HIV infection, Africans and especially in young individuals. Presumed causative factors for conjunctival SCC include ultraviolet light, human papillomavirus, HIV infection, and other unknown factors. Metastases to the conjunctiva are a poor prognostic sign for survival and. appear at an advanced stage of the disease, and.⁽¹³⁾

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Studies of large populations in Congo, Uganda, and United States have shown that AIDS is an increased risk factor for the development of conjunctival SCC.^(2,13) In our study, SCCs were 7 (5.22%) cases, mean age of patients 42 years, all 7 were males and 4 patients had a history of long time sunlight exposure, and none of the patients were affected by HIV or xeroderma pigmentosum. Fig 3 (A) and 3 (B) shows histopathological picture of SCC.

Conjunctival defects more than 3 clock hours due to excision of large SCCs have been used to repair with tissue replacement techniques. The disadvantages of conjunctival tissue replacement techniques such as tissue foreshortening, symblepharon, pseudopterygium, and recurrence of tumour have encouraged clinicians to investigate alternative or adjuvant treatment options such as topical mitomycin C and 5-fluorouracil.^(2,14) In our study, SCC was treated with topical mitomycin C in 2(1.21%) cases and mean age of the patients was younger than that of the previously reported cases in the literature.

It is important to recognize the precursor lesions of malignant melanoma including PAM with atypia, an enlarging or atypical nevus.⁽²⁾ The limbal epithelium, being rich in stem cells, was considered a common site for limbal tumours. UV-B or HPV could induce stem cell gene p53 (tumour suppressor gene) mutations and transformation into malignancy.^(15,16,17) Hence a lesion that increases in size on the bulbar conjunctival should be considered for biopsy because of a have high incidence of malignant melanoma.^(1,15)

Racial melanosis, which is especially bilateral in more heavily pigmented races is a benign proliferation of melanocytes, but rarely is unilateral, acquired and can be a precursor of melanoma.^(2,18,19) Primary acquired melanosis (PAM) presents as a unilateral patchy area of conjunctival pigmentation, mostly found in middle-aged or elderly white patients. The presence or absence of atypia is helpful in determining the potential for malignancy, because PAM without atypia is usually benign.^(2,20) In our study, malignant melanoma was reported in 2 cases (1.49%) and mean age was 61years.

In the new classification system, the idea is to use the term 'primary acquired melanosis' only as a clinical description, highlighting the fact that the biologic behavior of acquired melanotic lesions cannot be predicted solely based upon clinical grounds without histopathologic examination. Conjunctival melanoma represents only 5% of all melanomas arising in the ocular region and is associated with a high mortality rate.⁽²¹⁾ Conjunctival melanoma shows considerable clinical variability.

One of the case was an extensive pigmented elevated lesion involving limbus, spreading on to bulbar conjunctiva and in another case the lesion was a small pigmented elevated lesion at limbus. Malignant melanoma of the conjunctiva most commonly arises from PAM, but it can also arise from a pre-existing nevus or de novo.⁽⁸⁾ Ocular adnexal lymphoma may commonly be seen in the sixth to seventh decade with slightly female preponderance. Non-Hodgkin lymphoma may involve the eyelids, conjunctiva, lacrimal gland or orbital connective tissue.^(2,22)

The present study showed 1 (0.74%) elderly male patient aged 75 years presented with diffuse slightly elevated pink mass over medial aspect of bulbar conjunctiva of acute onset over 2 months and on incisional biopsy it proved to be Conjunctival lymphoma. Conjunctival lymphoma often appear to masquerade as conjunctivitis and a misdiagnoses is possible.^(2,23) Lymphoid tumours can manifest in the conjunctiva as isolated lesions, or they can be a presentation of systemic lymphoma.

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It is not usually possible to differentiate clinically between a benign and malignant lymphoid tumour.⁽⁴⁾ Therefore, biopsy was necessary to establish the diagnosis, and a systemic evaluation done in the affected patient excluded the presence of systemic lymphoma. Histo-pathologically, sheets of lymphocytes are found and reported as malignant lymphoma and are B cell lymphoma (non-Hodgkin's type). For further treatment of the localized conjunctival lymphoma the patient was referred to higher center for further management.

CONCLUSION: In conclusion, the present study reported nevus as the most common benign conjunctival tumour and SCC as the most common malignant tumours of conjunctiva. SCC can be seen in young patients and is a rare malignant conjunctival tumour. In the differential diagnosis of conjunctivitis especially in elderly adults malignant lymphoid tumours of the conjunctiva should be considered and may be a rare presentation of systemic metastasis of NHL.

Melanoma of conjunctiva is a potentially lethal neoplasm, and early recognition of precursor lesions have markedly reduced the late diagnosis. The characterization of precancerous lesions in this study emphasizes their potential to transform into malignant lesions and the need for sufficient early management and follow up.

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TUMOUR	Number=n	%
Nevus	25	18.66
Chronic Inflammatory	20	14.93
Foreign body granuloma	18	13.43
Carcinoma in situ	14	10.45
Squamous cell dysplasia	8	5.97
Tenon's cyst	8	5.97
Squamous cell carcinoma	7	5.22
Epithelial cyst	7	5.22
dermolipoma	6	4.48
Haemangioma	5	3.73
Squamous papilloma	5	3.73
Dermoid	4	2.99
Pyogenic granuloma	4	2.99
Malignant melanoma	2	1.49
Lymphoma	1	0.74

Table 1: Histopathological classification of conjunctival tumors (n=134) n %

Fig. 1: Clinical Figures of Benign Conjunctival Lesions



Fig. 1A

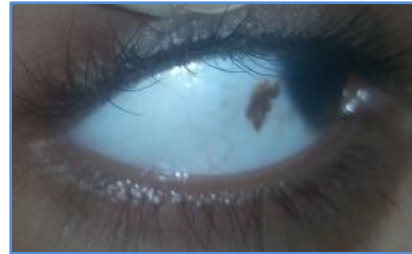


Fig. 1B



Fig. 1C

Fig. 1(A): Conjunctival limbal dermoid –well-circumscribed pinkish-white solid mass at the corneoscleral limbus inferotemporally extending to the cornea and has two fine black hairs and associated with Goldenhar's syndrome(ipsilateral preauricular skin appendages).

Fig. 1(B): discrete, pigmented, lesion It is typically located in the interpalpebral bulbar conjunctiva near the limbus temporally.

Fig. 1(C): Dermolipoma in the supertemporal conjunctival fornix.

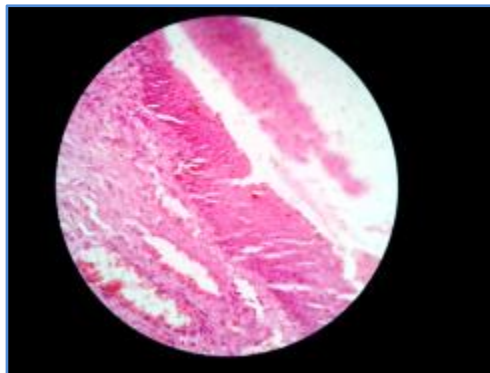


Fig. 2

Fig 2: Conjunctival nevus-Microphotograph shows brown pigment (melanin) laden cells in the conjunctival epithelium and overlying the conjunctival epithelium.{H & E x400}

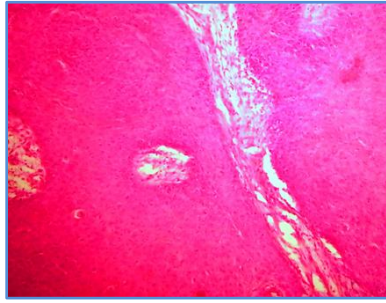


Fig. 3A

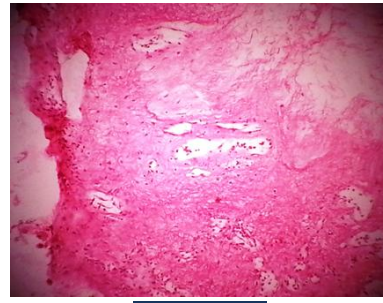


Fig. 3B

Fig. 3(A): Squamous cell carcinoma-Microphotograph shows malignant squamous cells violated the basement membrane, grown in sheets into the stromal tissue. {H & E x200}

Fig. 3(B): Squamous cell carcinoma with focal mucoepidermoid differentiation. The mucoepidermoid variant contains mucus-secreting cells that often produce mucus-containing cysts within the lesion. {H & E x200}

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