Histopathological Results of Conjunctival Masses with Suspected Malignancy Based on Slit-lamp Biomicroscopy

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ABSTRACT

Objective: To evaluate the histopathological results of conjunctival masses suspected to be malignant based on biomicroscopic examination.

Study Design: Observational study.

Place and Duration of the Study: Department of Ophthalmology, Celal Bayar University, Hafsa Sultan Hospital, Manisa, Turkiye, from November 2013 to February 2021.

Methodology: Patients who underwent excision for the diagnosis and treatment of conjunctival surface masses with clinical suspicion of malignancy were evaluated retrospectively. The masses were categorised as benign, premalignant, and malignant lesions according to the histopathological results. The distribution of conjunctival masses was analysed according to patients' gender and age groups.

Results: The study included 98 conjunctival masses in 98 patients (57.1% men, mean age 48.6±21.85 years). On pathological examination, 63 of the masses were found to be benign (64.3%), 22 were premalignant (22.4%), and 13 were malignant (13.3%). The most common benign lesion was nevus (n=21, 21.4%). All detected premalignant lesions were conjunctival intraepithelial neoplasms (CIN), detected in 22 patients (22.4%). Of these, 13 patients (13.3%) had carcinoma *in situ* (CIN III). Thirteen (13.3%) of the masses were malignant, the most common being squamous cell carcinoma (n=10, 10.2%). The frequency of premalignant and malignant lesions increased with age (p<0.001). There was no statistical relationship between malignancy and gender (p=0.619).

Conclusion: Most conjunctival masses in this series were benign, with nevi being the most common. The most common premalignant and malignant lesions were intraepithelial neoplasia and squamous cell carcinoma, respectively. Malignant conjunctival lesions were more common in older patients.

Key Words: *Conjunctival nevus, Conjunctival intraepithelial neoplasia, Squamous cell carcinoma.*

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INTRODUCTION

The conjunctiva is a thin, flexible membrane extending from the palpebral region to the fornix and the anterior surface of the globe to the sclerocorneal limbus. It produces the mucus layer, the innermost layer of the precorneal tear film, and forms a protective barrier against infectious agents and foreign bodies.

Because the squamous epithelium of the cornea and conjunctiva is continuous, similar epithelial tumours also occur in the cornea, but corneal stromal tumours are rare.[1] Factors involved in the development of conjunctival squamous cell neoplasia include ultraviolet light exposure, chronic inflammation, microtrauma, industrial chemicals, smoking, genetic predisposition, Human Papilloma Virus types 6, 11, 16, and 18, and tumour suppressor gene inactivation.[2,3]

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While primary acquired melanosis and conjunctival nevi predispose to conjunctival melanomas, immune deficiency, autoimmune diseases, genetic mutations and immunomodulatory drugs predispose to conjunctival lymphoid tumours.[4]

Conjunctival tumours have a wide spectrum ranging from non neoplastic benign tumours to melanoma or aggressive malignancies. Unlike other mucous membrane tumours, most of these lesions are visible externally. Early diagnosis and treatment are important in preserving patients' visual and adnexal functions and preventing cosmetic deformity and the systemic spread of malignant disease.

The management of conjunctival masses may involve serial ophthalmologic examinations, incisional biopsy, excisional biopsy, cryotherapy, chemotherapy, enucleation, exenteration, or combinations of these methods based on the suspected diagnosis, size, and extent of the mass on slit-lamp examination.[1]

The aim of this study was to investigate the histopathological results and demographic distribution of patients having conjunctival mass with suspicion of malignancy based on slit-lamp biomicroscopy.

METHODOLOGY

The study was approved by Celal Bayar University Ethics Committee. Ninety-eight eyes of 98 patients who were followed in Celal Bayar University Eye Clinic, between November 2013 and February 2021 were included in the study. Informed consent was obtained from all patients. Age, gender, histopathological diagnosis, preoperative and postoperative anterior segment photographs of the patients, and clinical data of the patients were obtained from the hospital archive and patient cards. These data were analysed retrospectively.

In order to evaluate the distribution of the masses by age, the patients included in the study were divided into 4 age groups. These age groups were group as under 19 years old (n=12), 19-39 years (n=19), 40-60 years (n=29), and over 60 years (n=38).

Benign masses such as pterygium and pinguecula with atypical biomicroscopic appearance, atypical localizations, or those who needed clinical pathological confirmation were included in the study (Figure 1-a). The pyogenic granuloma patients included had no history of recent ocular surgery or trauma. In the biomicroscopic examinations of the nevi during follow-up, those who showed growth in the anterior segment photographs taken consecutively or those who did so according to the anamnesis were considered suspicious. Pigmented lesions involving the cornea or located in the palpebral conjunctiva, plica or caruncle were suspected to be conjunctival melanoma.[5]

Conjunctival masses that could not be definitively diagnosed biomicroscopically or occurred in non-typical age groups, were accepted as suspicious for malignancy (Figure 1-b).

Surgery was performed under general anaesthesia in patients younger than 15 years of age and under local anaesthesia in older patients. The mass was excised with a surgical safety margin of 2 mm of normal tissue. The excised tissues were sent for histopathological examination.

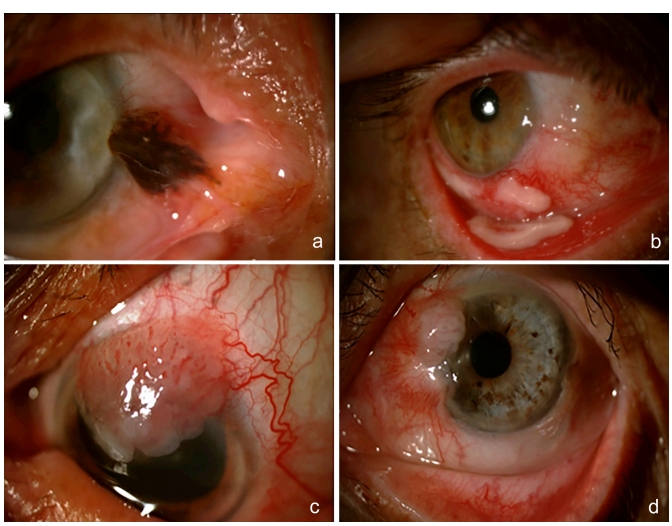


Figure 1: (a) Pigmented pterygium. (b) Ligneous conjunctivitis. (c) Conjuctival squamous cell carcinoma. (d) Conjuctival basal cell carcinoma.

IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY) software package was used for statistical analysis. Categorical variables were expressed as numbers and percentages (%), and numerical variables as mean ± std. Relationships between patient age groups and gender and the numbers of benign, premalignant, and malignant masses were analysed. Groups were compared using Chi-square or Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

RESULTS

The mean age of the 98 patients included in the study was 48.6 (±21.85) years. Fifty-six patients (57.1%) were male and 42 (42.9%) were female.

Of the 98 surgically excised conjunctival masses, pathology reports indicated benign disease in 63 (64.3%), premalignant disease in 22 (22.4%), and malignancy in 13 (13.3%) of the cases. The most common benign conjunctival lesion was nevus (n = 21). This was followed by pterygium in 13 patients (13.3%) and pyogenic granuloma in 6 patients (6.1%). The only premalignant lesion in this series was conjunctival intraepithelial neoplasia (CIN), detected in 22 (22.4%) samples. No other premalignant conjunctival lesions such as actinic keratosis or primary acquired melanosis were observed. CIN III, also known as carcinoma *in situ*, was detected in 9 of the patients with CIN (9/22, 40.9%). Of 13 patients diagnosed as having malignant disease, the most common type was SCC (76.9%) (Figure 1-c). Conjunctival basal cell carcinoma (BCC), a rare condition, was detected in one patient (Figure 1-d). The distribution of conjunctival masses is shown in detail in Table I.

There was no gender-based difference in the numbers of malignant, premalignant, and benign masses (p=0.619). When compared among the age groups, the frequency of malignant and premalignant masses increased significantly with age (p<0.001; Figure 2).

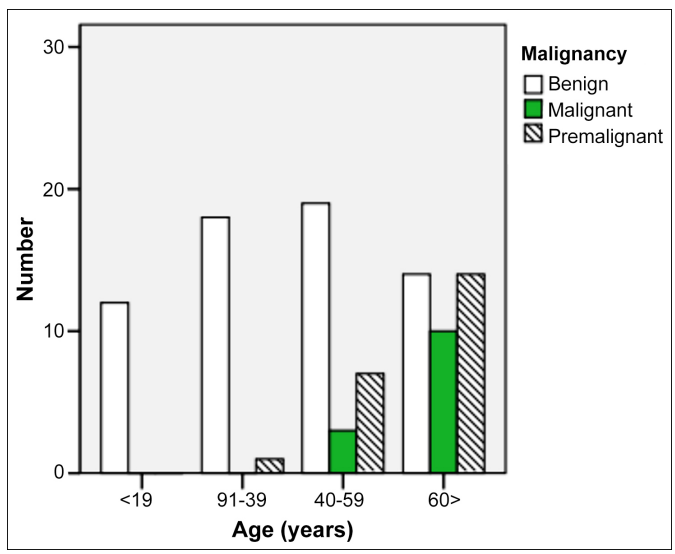


Figure 2: Distribution of malignant, premalignant, and benign masses by age group.

Table I: Classification and frequency of conjunctival lesions.

Lesions	Frequency	Percent	Mean age ± SD (years)
Benign	63	64.3	40.1 ± 21.61
Nevus	21	21.4	
Pterygium	13	13.3	
Pyogenic granuloma	6	6.1	
Conjunctival cyst	5	5.1	
Papilloma	4	4.1	
Pinguecula	4	4.1	
Seborrheic keratosis	2	2.0	
Lipoma	2	2.0	
Dermoid cyst	1	1.0	
Hemangioma	1	1.0	
Lymphangioma	1	1.0	
Ligneous conjunctivitis	1	1.0	
Conjunctival lithiasis	1	1.0	
Fibrous tumours	1	1.0	
Premalignant	22	22.4	62.2 ± 10.97
CIN I-II	9	9.2	
Carcinoma in situ (CIN III)	13	13.3	
Malignant	13	13.3	67.1 ± 11.96
SCC	10	10.2	
BCC	1	1.0	
Malignant melanoma	1	1.0	
Lymphoma	1	1.0	
Total	98	100	48.6 ± 21.85

CIN, Conjunctival intraepithelial neoplasia; SCC, Squamous cell carcinoma; BCC, Basal cell carcinoma.

DISCUSSION

Benign tumours of the eyelid and conjunctiva are slow-growing lesions. Due to a lack of pronounced symptoms, they are rarely surgically removed and histopathological examination cannot be performed in most cases. Therefore, the actual frequency of these lesions is believed to be higher than those reported in the literature. Melanocytic nevus, hemangioma, and papilloma are among the most common benign conjunctival lesions.[6]

In a prevalence study of 613 conjunctival lesions conducted by Navahi *et al*., the most common benign lesion was pterygium (n = 357, 56.6%) and melanocytic lesion was the second most common (n = 79, 12.5%).[2] Chi and Baek reported that the most common conjunctival tumour was melanocytic *et al*. nevus (54.2%).[7] Nevus was also the most common benign primary conjunctival tumour (38.7%) in the studies by Amoli *et al.* and Cevik *et al*.[8,9] In the present study, the most common benign conjunctival lesion was nevus (25%), followed by pterygium (20%). This difference among studies may be related to regional and climatic factors as well as differences in inclusion criteria. In prevalence studies examining all conjunctival masses regardless of malignancy suspicion, the most common benign lesion was pterygium, whereas conjunctival nevus was observed more frequently in retrospective analyses of patients who underwent excisional biopsy for suspected malignancy, as in this study.

The frequency of malignant conjunctival tumours varies in incidence studies.[10,11] These rates are influenced by environmental factors as well as age and gender distribution.[9] Sunlight exposure and xerodermal pigmentosis were shown to increase the risk.[8] Studies in Asian countries have shown that sebaceous carcinomas are more common there than in other regions.[12] Basal and squamous cell carcinomas are more common in regions that receive intense sunlight.[13] Similar to other studies, the prevalence of malignant and premalignant lesions increased with age in this study.

An analysis of 1595 conjunctival tumours in the Eye Clinic of Erlangen Nuremberg University indicated that the most common malignant conjunctival tumours were malignant melanoma, squamous cell carcinoma, non-Hodgkin lymphoma, sebaceous carcinoma, and Kaposi's sarcoma.[14] Amoli *et al*. reported that SCC was the most common malignant conjunctival tumour in their study, detected at a rate of 25.1% (mean patient age, 53.68 years).[8] Similar to their study, SCC was also the most common malignant tumour in this study (76%).

Ocular surface squamous neoplasm is the general term for a group of diseases ranging from dysplasia to invasive SCC. Premalignant pathologies in this category are called squamous dysplasia or CIN. CIN is classified as I, II, and III according to epithelial layer involvement.[15] CIN III corresponds to squamous carcinoma *in situ*, in which there is involvement of the entire epithelium by neoplastic cells.[15] Patients with CIN should be evaluated as malignancy, and their follow-up and treatment should be planned in this way. As with other malignant conjunctival masses, the most important risk factor for the recurrence of masses in patients with CIN is the lack of adequate surgical resection.[16] Cryotherapy to the conjunctiva after resection reduces the recurrence rate.[16] In this study, conjunctival squamous neoplasia was detected in 32 patients (32.6%). Of the conjunctival squamous neoplasms, 13 (40.6%) were squamous carcinoma *in situ*, 8 (25%) were squamous dysplasia, and 10 (28%) were invasive SCC.

The management of conjunctival tumours depends on the size and dimensions of the lesion. Each patient should be considered individually. Treatment options include observation, biopsy, cryotherapy, chemotherapy, radiotherapy, enucleation, and orbital exenteration.[17] However, the primary treatment is surgery.[18] The standard treatment approach used in this study was primary surgical excision and cryotherapy. Although there was no additional benefit of cryotherapy especially in benign conjunctival lesions, the masses in this study could not be definitively diagnosed biomicroscopically before surgery, so conjunctival cryotherapy was applied to the masses for safety purposes. Atypical cells are more affected by cryotherapy than normal cells.[17] After total excision, cryotherapy applied to the conjunctiva at the excision margins and the lesion base ensures cell destruction and ischemic infarction. Many studies suggest that cryotherapy reduces recurrence.[17]

This study had several limitations. Although the approach to suspected malignancy is standardised in the clinic, it is subject to

the clinician performing the biomicroscopic examination. In addition, the retrospective nature of the study and the sample size can be considered as limitations.

CONCLUSION

Most conjunctival masses in this series were benign, with nevi being the most common. The most common premalignant and malignant lesions were intraepithelial neoplasia and squamous cell carcinoma, respectively. Malignant conjunctival lesions were more common in older patients. The diagnosis of a conjunctival mass should be confirmed by histological evaluation and biopsy. Therefore, clinicopathological correlation is essential and requires good communication between the clinician (ophthalmologist) and the pathologist.

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ETHICAL APPROVAL:
Ethical approval for the study was granted by the Celal Bayar University, Hafsa Sultan Hospital, Manisa, Turkey (IRB No. 20.478.486).

PATIENTS' CONSENT:
Since it was designed as a retrospective study, the data were collected from the hospital archive following the approval of the Ethics Committee. Informed consent was obtained from all the patients before the procedure.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
HM, ME, SM: Study conception and design.
SM, HM, MA, ME: Data collection.
HM, MA, ME, SSI: Analysis and interpretation of results.
ME, SM, MA: Manuscript preparation.
All authors reviewed the results and approved the final version of the manuscript.

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