

A Clinico-Pathological Study of Peri-Ocular Tumors and Tumor-Like Lesions at Prince Rashid Bin Al-Hassan Military Hospital in the North of Jordan

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ABSTRACT

Objectives: This study was conducted to analyze the histologically-proven peri-ocular tumors and tumor-like lesions at Prince Rashid Bin Al-Hassan military hospital in the North of Jordan.

Methods: This was a hospital based, non-comparative, retrospective review, conducted at Prince Rashid Bin Al-Hassan Military Hospital in the North of Jordan over a period of 4 years between January 2008 and January 2012. Medical records of patients who underwent excisional biopsy of a tumor or tumor-like lesion, or incisional biopsy when complete resection was impossible and proven by histopathology during that period, were reviewed and included in the study. Descriptive statistics like mean, average, frequency, and percentages were used.

Results: A total of 105 patients were enrolled in this study. The affected cases were 55.2% male and 44.8% female with a male to female ratio of 1.2: 1. The median age of the patients was 27 years with a range of 10 months to 94 years. The 10-20 years age group was most frequently affected. Histopathological examination revealed that 87 (82.9%) cases were benign, six (5.7%) premalignant, and 12 (11.4%) malignant. The eyelids were the most common site for the lesions and accounted for more than half of the cases. The most frequent benign lesion was nevus and the most common malignant tumor was basal cell carcinoma. The commonest indication for tumor excision was cosmetic followed by suspicion of malignancy.

Conclusion: Peri-ocular tumors appear to be frequent although the true prevalence in the North of Jordan is not detected. Males were more frequently affected. The frequency of malignant and pre-malignant tumors was significant (11.4% and 5.7% respectively), for this reason any suspicious lesion should be biopsied particularly after the fifth decade of life.

Key words: Clinico- pathological, Peri-ocular, Tumor, Tumor- like

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Introduction

A benign tumor or neoplasm is a non-cancerous (non-malignant) abnormal mass of tissue that forms when cells in a localized area reproduce at

an increased rate. Peri-ocular area is a common site for benign and malignant lesions in all age groups.⁽¹⁾ Peri-ocular structures that include the eyelids, eyebrows, lacrimal sac, conjunctiva, and

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cornea epithelium are derived from the surface ectoderm and congenital anomalies can present as tumor or tumor-like lesion at birth or soon after birth. For example, choristomas, which are normal tissues in abnormal location, such as dermoid are usually found at birth,⁽²⁾ while capillary hemangiomas, which are hamartomas *i.e.* benign tumor-like growth with abnormal, localized proliferation of vascular endothelial cells, usually appear soon after birth.⁽³⁾ Other tumors appear during adolescence such as conjunctival nevi that are usually amelanotic during childhood and present cosmetic and sometimes functional problems when they start to grow and gain melanin pigments during adolescence. These tumors are benign and it is extremely rare to undergo malignant transformation at an early age,⁽⁴⁾ although they might become inflamed thus urging excision to rule out malignant transformation.⁽⁵⁾ The primary malignant lesions are usually due to prolonged sun exposure⁽⁶⁾ and seen more frequently in elderly patients⁽⁷⁾ or patients with chromosomal abnormalities that lead to formation of skin cancers such as Gorlin- Goltz syndrome.⁽⁸⁾ However; metastasis from distant sites or invasion from adjacent structures may occur.⁽¹⁾

In clinical practice, eye tumors and tumor-like lesions can be classified into extra- and intra-ocular.⁽⁹⁾ In this study, only extra- ocular tumors that are located outside the eye were investigated. In most of the cases the clinical diagnosis is obvious and does not need histopathological investigations such as, chalazion, pterygium and nevus unless there are suspicious signs of malignancy.^(1,4-5) For example, recurrent chalazion after excision in an elderly patient, abnormal vessels, bleeding, or elevated mass from a pterygium or a nevus, all necessitate a diagnostic biopsy.⁽¹⁰⁾

Prince Rashid Bin Al-Hassan is a general district hospital with a bed capacity of about 300 beds. The ophthalmology clinics cover all aspects of ophthalmology including oculoplastic and pediatric specialities. Benign lesions and malignant tumors that do not need major reconstruction after excision are usually treated locally without referral to King Hussein Medical Center. After tumor excision, all specimens, even if the diagnosis is obvious clinically, are sent to

pathology laboratory for histopathological examination fixed in 10% buffered formalin solution where it takes two weeks to collect the results. Review of literature revealed some data available from Jordan Cancer Registry about the eye malignant lesions in Jordan but not peri-ocular malignant lesions.⁽¹¹⁾

The aim of this study was to analyze the histologically proven peri-ocular tumors at Prince Rashid Bin Al- Hassan military hospital in the North of Jordan.

Methods

This was a hospital-based, non-comparative, retrospective study, conducted at Prince Rashid Bin Al-Hassan military hospital in the North of Jordan over a period of 4 years between January 2008 and January 2012. Medical records of patients who underwent excisional biopsy of a tumor or tumor-like lesion, or incisional biopsy when complete resection was impossible and proven by histopathology during that period, were reviewed and included in the study.

Exclusion criteria include patients who were not Jordanian, patients with intra-ocular tumor, eviscerated or enucleated globe, and patients with incomplete medical records. Descriptive statistics like mean, average, frequency, and percentages were used.

The ethical committee of the Royal Medical Services approved the study.

Results

A total of 105 medical records were reviewed. There were 58 males (55.2%) and 47 females (44.8%) with a male to female ratio of 1.2: 1. The distribution of the lesions with regards to gender and age are shown in Table I with the age group of 11 - 20 years being most frequently affected. The median age of the patients was 27 years with a range of 10 months to 94 years. Histopathological examination revealed that 87 (82.9%) cases were benign, six (5.7%) premalignant, and 12 (11.4%) malignant. The eyelids were the most common site for the lesions and accounted for more than half of the cases. Table II demonstrates the distribution of the tumors and tumor-like lesions in the peri-ocular structures and its malignant potential and it shows that the eyelid was the commonest site for benign, premalignant, and malignant tumors

Table I: Gender and age distribution of patients with tumor and tumor-like lesions of the peri-ocular area.

	Male	Female	Total
Up to 10	12	10	22
11 – 20	11	15	26
21-30	7	5	12
31-40	5	5	10
41-50	1	2	3
51-60	5	2	7
61-70	10	4	14
71-80	5	3	8
81-90	2	0	2
91-100	0	1	1
Total	58	47	105

Table II: The distribution of the tumors and tumor-like lesions and its malignant potency in the peri-ocular structures.

Location	Benign	Premalignant	Malignant	Total
Eyelids	51(48.6%)	2(1.9%)	10(9.5%)	63(60%)
Conjunctiva	27(25.7%)	3(2.9%)	2(1.9%)	32(30.5%)
Eyebrows	6(5.7%)	0	0	6(5.7%)
Limbal	2(1.9%)	0	0	2(1.9%)
Lacrimal gland	1(0.95%)	0	0	1(0.95%)
Cornea	0	1(0.95%)	0	1(0.95%)
Total	87(82.9%)	6(5.7%)	12(11.4%)	105(100%)

Table III: The histological results of the lesions and their distribution in the peri-ocular area

Histological type		Eyelid	Conjunctiva	Eyebrows	Limbal	Lacrimal gland	Cornea
Malignant	Basal cell carcinoma	7					
	Squamous cell carcinoma	2	1				
	Malignant melanoma		1				
	Sebaceous gland carcinoma	1					
Pre-malignant	Actinic keratosis	1					
	Kerato-acanthoma	1					
	Conjunctiva and corneal intra epithelial neoplasia		3				1
Benign tumors (89 patients)	Squamous Papilloma	4					
	Capillary hemangioma	3					
	Seborrheic keratosis	4					
	Pleomorphic adenoma					1	
	Epibulbar dermoid				2		
	Dermoid	8		3			
	Chalazion	3					
	Nevus	8	14				
	pilomatrixoma	2		3			
	Pterygium		3				
	Pyogenic granuloma	2	2				
	Lipodermoid		3				
	Nonspecific inflammation and benign lymphocytic hyperplasia		1				
	Retention Cyst		4				
	Sebaceous cyst	10					
	Apocrine hydrocystoma	3					
Xanthelasma	3						
Sebaceous hyperplasia	1						

and cornea was the least site for benign lesions. Table III summarizes the histological results of the lesions and their distribution in the peri-ocular area. Of the benign lesions the most

frequent was nevus and the most common malignant tumor was basal cell carcinoma (BCC), however the least common benign tumors were lacrimal gland pleomorphic adenoma,

Table IV: Indications for excision of periocular tumors and tumor-like lesions according to age group.

Age group	Cosmetic	Astigmatism	Ptosis	Suspicion of malignancy	Total
Up to 10	19(18.1%)	1(0.95%)	2(1.9%)	0	22(21%)
11 – 20	23(21.9%)	2(1.9%)	1(0.95%)	0	26(24.8%)
21-30	12(11.4%)	0	0	0	12(11.4%)
31-40	10(9.5%)	0	0	0	10(9.5%)
41-50	0	0	0	3(2.9%)	3(2.9%)
51-60	0	0	0	7(6.7%)	7(6.7%)
61-70	0	0	0	14(13.3%)	14(13.3%)
71-80	0	0	0	8(7.6%)	8(7.6%)
81-90	0	0	0	2(1.9%)	2(1.9%)
91-100	0	0	0	1(0.95%)	1(0.95%)
Total	64(61%)	3(2.9%)	3(2.9%)	35(33.3%)	105(100%)

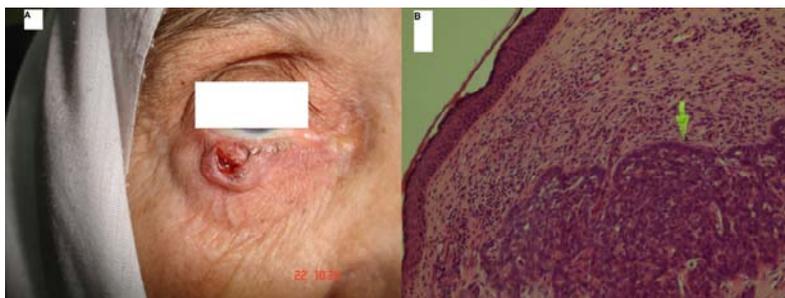


Fig. 1: A, nodulo-ulcerative basal cell carcinoma of the right lower eyelid. B, histopathology slide showing nuclear palisading at the periphery (arrow) (X200).

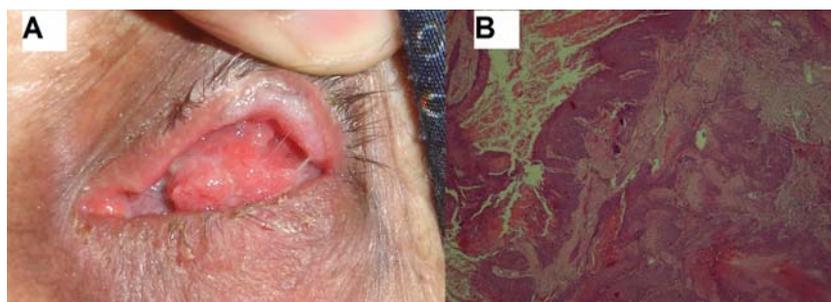


Fig. 2: A, Recurrent conjunctival squamous cell carcinoma overriding the globe with deep orbital invasion. B, The malignant squamous epithelial cells are infiltrating from the palpebral conjunctiva, through the basement membrane down into the sub-epithelium (X40).

nonspecific inflammation and benign lymphocytic hyperplasia, and sebaceous hyperplasia, and the least common malignant tumors were eyelid sebaceous gland carcinoma and conjunctival malignant melanoma.

Keratoacantoma of the eyelid was seen in the lower eyelid of a female patient that developed over few weeks. Histologically it showed a central crater filled with keratin surrounded by buttress of epidermis and it is considered as a low grade of squamous cell carcinoma. All basal cell carcinomas were nodulo-ulcerative type and histopathologic examination showed nests of atypical cells resembling basal cell showing peripheral palisading that contain mitotic figures, and all of them were completely excised (Fig. 1).

Eyelid squamous cell carcinoma (SCC) originates from the epidermis and conjunctival

SCC originates from squamous mucosa. The atypical cells are pleomorphic with central nucleus and abundant cytoplasm. They destroy the basement membrane and invade the dermis and had cell nests, which are keratinized squamous cells with concentric layers. In contrast to well differentiated tumor poorly differentiated tumors have no keratinization but more pleomorphic cells (Fig. 2).

One case with right upper eyelid nodular sebaceous gland carcinoma in a 70-year old male patient was completely excised and histopathology report showed irregular lobular masses of cells showing abundant cytoplasm and many of these cells are lipid positive with fat stains. Table IV shows the indications for tumors excision according to age group and revealed that cosmetic reason was the commonest indication

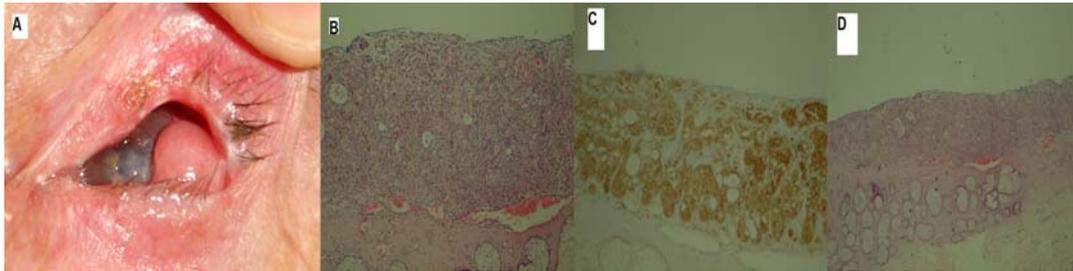


Fig. 3: A, Recurrent malignant melanoma of the conjunctiva. B, Malignant melanocytes proliferating in the epithelium and infiltrating down into the subepithelium(H&EX40). C, The tumor cells are immune-reactive for Melan-A immunohistochemical stain (X200). D, Pagetoid spread in the epithelium is characteristic (H&EX100).

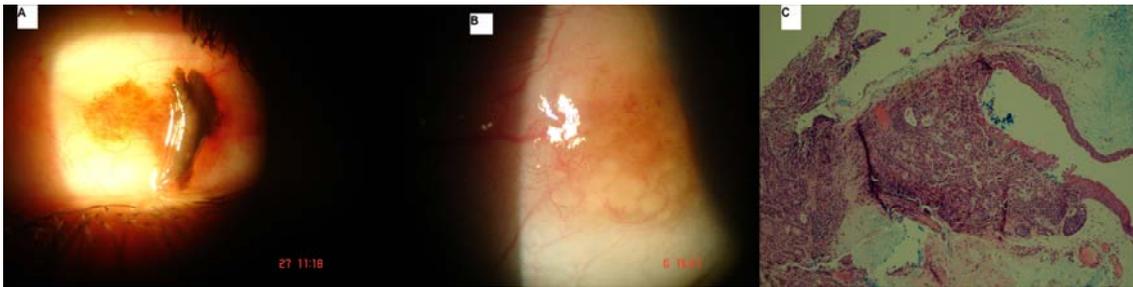


Fig. 4: A, Conjunctival nevus involving the bulbar conjunctiva and the plica semilunaris. B, Bulbar conjunctival nevus with microcysts. C, Small round cells represent nevus cells surrounding associated cystic epithelial inclusions (H&EX100).



Fig. 5: A, Dermoid cyst above the tail of the eyebrow at the zygomatico- frontal suture. B, surgical excision showing bony fossa formation at the location of the dermoid. C, The dermoid cyst is lined by stratified squamous epithelium and its wall contains cutaneous appendages, such as sweat glands and hair follicles (H&EX!!).

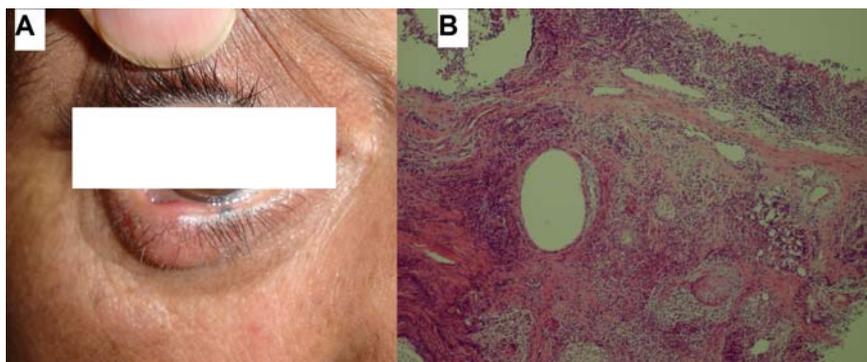


Fig. 6: A, Chalazion of the right lower eyelid. B, The lipo-granulomatous inflammation in the eye lid is characteristic, (H&EX100).

overall while suspicion of malignancy was the main indication in the middle age and elderly patients.

Discussion

Jordan cancer registry (JCR) showed that eye cancer incidence in Jordan in 2009 was 0.3%, with females being slightly more affected than

males. The incidence of cancer in the governorate of Irbid was 13.2%, but the incidence of eye cancer in this governorate was not determined.⁽¹¹⁾ None of the eye cancers occupied the top ten cancers in Jordan though, and the peri-ocular tumors are under diagnosed in Jordan.⁽¹¹⁾

In comparison with JCR,⁽¹¹⁾ our cohort showed that males were affected more frequently than females and this can be explained by the following: first, this study included benign and malignant tumors, and tumor-like lesions, second, intra-ocular tumors were excluded, and third, some of these tumors are related to prolonged exposure to sunlight⁽⁶⁾ which is more frequent in male military personnel.

In contrast to Reddy *et al.*⁽⁹⁾ who found males in the first decade to be more frequently affected, the commonest age group to be affected in our study was 11-20 years with female preponderance (24.8%) probably related to the cosmetic worries of female patients and their parents, especially at this age. This is followed by those below the age of 10 years where peri-ocular congenital anomalies and acquired lesions might lead to amblyopia due to visual obscuration or astigmatism and parents' anxiety and these findings are comparable with previous studies presented in literature.⁽¹²⁾ In general, the main indication for excision was cosmetic below the age of 40 years and suspicion of malignancy after that age. In our study, none of the malignant lesions were discovered in the younger age groups. These cases are usually referred to King Hussein Medical Center where they can receive further more complicated management after excision in collaboration with other specialties.

Malignant lesions formed 11.4% of the lesions with basal cell carcinoma affecting the eyelids (83%) being the commonest tumor which is slightly less than previously reported studies.⁽¹⁾ Malignant tumors affecting the conjunctiva were encountered in 16.7% and the conjunctiva was the commonest site to encompass benign lesion such as nevus and this was comparable to Amoli *et al.*⁽¹³⁾ study but different from Luiz *et al.*⁽¹⁴⁾ study who found conjunctival intraepithelial neoplasia to be the most frequent lesion. The chronic exposure to sunlight was blamed to be the main risk factor for peri-ocular malignant lesion and the risk is usually decreased by protective measures such as using sunglasses and

sunscreen⁽¹⁵⁾ and this may explain why two thirds of malignant lesions in men (8/12) who usually had more outdoor activities.⁽⁶⁾

Sebaceous gland carcinoma of the eyelid is a very rare tumor that frequently involves the upper eyelid. It originates from either the meibomian glands or glands of Zeis. The upper eyelid contains more meibomian glands than the lower eyelid which explains the higher frequency of the upper eyelid involvement.^(7,16-17) It is more common in middle aged women.⁽¹⁶⁾ Sebaceous gland carcinoma may spread intraepithelially to invade the conjunctiva and the cornea (pagetoid spread).⁽¹⁷⁾ Conjunctival malignant melanoma is a rare tumor that accounts for 2% of all ocular malignancies, that is frequently seen in elderly patients.^(4,13-16,18,19) It is treated by excision and cryotherapy or Mitomycin.⁽¹⁸⁻¹⁹⁾ If orbital recurrence occurs then exenteration is an option if cannot be controlled with other methods, although it does not improve the survival rate.⁽¹⁹⁾ Our case was 73- year old male patients with recurrent conjunctival malignant melanoma and orbital invasion with no metastasis (Fig. 3). Peri-ocular malignant tumors need long-term follow to rule out early recurrence or new primary tumors. A study conducted in UK showed the recurrence rate after complete excision of BCC tumors with five years follow up to be 0.26%.⁽²⁰⁾

Premalignant tumors were seen in 5.7% of patients. Recently some premalignant lesions, such as kerato-acanthoma, were considered histologically as a low grade malignancy.^(13,21) Conjunctiva and corneal intra-epithelial neoplasia is an uncommon conjunctival and/or corneal disease that has a low malignant potential.⁽¹³⁾ Characterized by mild to severe epithelial dysplasia with dysplastic cells (carcinoma in situ).⁽¹⁸⁾ These tumors are usually seen in patients above the age of 50 years who had outdoor activity, history of human papilloma virus, and patients with low immunity disorders.⁽²²⁾ Our four patients were between 30 and 50 years and all of them were males, treated with surgical excision with or without cryotherapy. Solar keratosis is by far the most common benign tumor of the eyelids that usually seen in fair- skin elderly patients with excessive exposure to ultraviolet light and the immune system is important in its development and pathogenesis.^(1,23) Histologically characterized by

focal to confluent parakeratosis overlying an epidermis and atypia in the keratinocytes. Treatment of kerato-acantoma of the eyelid is with excision because spontaneous involution may lead to an ugly residual scar.^(1,21)

Benign lesions were encountered in about 83% of the tumors and tumor-like lesions and 45% of them were found in the eyelids and followed by the conjunctiva (27.6%). The frequency was slightly higher than Reddy *et al.*⁽⁹⁾ but lower than Sanjay *et al.*⁽²⁴⁾ studies. This might be due to inclusion of extra-ocular tumors only. All these lesions were seen in young patient below the age of 40 years. On contrary to previous studies where dermoid cyst was the most frequent benign tumor,^(9,24) in our study the most frequently encountered benign growth was the nevus (22/87) (Table III), eight nevi were seen in the eyelids and 14 in the conjunctiva. All conjunctival nevi were compound type while eyelid nevi, five of them were compound, two intradermal and one junctional. Most of the conjunctival nevi were encountered in the second and third decade of life and the main indication for excision was cosmetic and this was less than that encountered in Saudi population with regard to age and indication.⁽²⁵⁾ The conjunctival nevus is usually melanotic, amelanotic (30%), or mixed with various shapes and sizes. It usually contains micro-cysts that can easily be seen with slitlamp biomicroscopy, (Fig. 4) malignant transformation is usually seen in less than 1% of conjunctival nevi.⁽⁴⁾ Dermoid cyst, which is a choristoma,⁽²⁾ was encountered in 13 (12.4%) cases; the majority (8/13) was seen in the eyelids (above the lateral canthus at the zygomatico-frontal suture, (Fig. 5), and above the medial canthus at the fronto-ethmoidal suture), three cases above the tail of the eyebrow, and two cases epibulbar. In the other similar studies dermoid cysts were the commonest tumors and of all them were located above the outer canthus.^(9,24) These lesion were found in pediatric age group and presented since birth. All peri-ocular demoid cysts were completely excised and found to be lined with stratified squamous epithelium containing cutaneous appendages. Ruptured dermoid cyst may lead to severe inflammation that may mimic rhabdomyosarcoma at pediatric age group,⁽²⁾ that is why we always try to excise the tumor before the child starts to walk that might lead to rupture

of the dermoid cyst if the child falls down or receive a trauma to the cyst. Ten patients between 30 and 50 years had peri-ocular sebaceous cysts. All were completely excised and most of them were found in the medial canthal area. These lesions are very common and usually result from minor trauma or surgery and contain pasty contents.⁽¹⁾ The cyst is lined by keratinized squamous epithelium and filled with keratin material. Pilomatrixoma is a benign tumor of the hair follicle that is usually seen in the young age group with the upper eyelid and eyebrow as favorable sites.⁽²⁶⁾

Seborrheic keratosis was diagnosed in four elderly patients and this was almost the same as Sanjay *et al.*⁽²⁴⁾ They are light to dark, well demarcated plaques, with granular cobblestone surface. Histologically, proliferation of bland epidermal cell and formation of horn cysts are seen. There are few variants of these lesions and the treatment is usually with curettage.⁽¹⁾ Conjunctival retention cyst, which is a cystic dilatation of a mucin gland secondary to obstruction of its duct,⁽¹⁴⁾ was present in 4(3.8%) patients and this was less than Reddy *et al.* (5.6%) findings;⁽⁹⁾ one of them was in the vicinity of a pterygium. Pyogenic granuloma contains endothelial proliferation of blood vessels with associated stromal eosinophilic infiltrates, ulceration and granulation. While Reddy *et al.*⁽⁹⁾ cases were seen after chalazion and pterygium excision our cases were associated with chalazion in patients below the age of 30 years, two in the eyelids and two in the conjunctiva.

Capillary hemangioma is a hamartoma, a benign tumor-like growth lesion, which is usually congenital or appears after birth as in our three cases. The early lesions are lobulated masses of small tight capillaries with plump endothelial lining cells.⁽³⁾ These lesions should be allowed to regress unless there is a risk of amblyopia then surgical excision can be done if tumor is small and localized.⁽¹²⁾ Nowadays treatment with beta blockers is a promising modality and should be tried as long as there are no contraindications.^(3,27)

A chalazion is a localized, chronic, sterile, lipo-granulomatous inflammatory lesion of sebaceous (meibomian) gland secondary to its duct blockage.⁽¹⁰⁾ Diagnosis of chalazion is obvious clinically in young patients but

recurrent or suspicious chalazion in elderly patients should be biopsied to rule out sebaceous gland carcinoma. In our study three chalazia in elderly female patients (all above the age of 65 years) were biopsied and proved histologically to be none malignant (Fig. 6).

Apocrine hydrocystomas are benign cystic lesions that are seen along the eyelid margin with white precipitates at the bottom secondary to blockage of glands of Moll ducts.⁽¹⁾ They were seen in three middle aged women and in contrast to Sanjay *et al.*⁽²⁴⁾ study none of them were eccrine hydrocystoma. Lacrimal gland pleomorphic adenoma is the most common benign tumor of the lacrimal gland that needs complete surgical resection to decrease the risk of malignant transformation or recurrence after incisional biopsy.⁽²⁸⁾ It was encountered in a 16-year female patient.

Limitations of the Study

Our study suffers from few limitations. First, not all histopathologic reports of patients with peri-ocular tumor could be found in the medical files. Second, this was a hospital-based review and it does not represent the true prevalence of peri-ocular tumor in the North of Jordan, so there should be a cooperation between all the hospitals in the North of Jordan (governmental, military, university, and private sector) to detect the true incidence and prevalence. Third, because this hospital is a general district hospital so advanced malignant tumors were not involved, and finally, only extra-ocular tumor was included, so our data cannot be compared with the JCR and other studies accurately.

Conclusion

Peri-ocular tumors appear to be frequent but the true prevalence in the North of Jordan cannot be determined by this study. Male to female ratio of peri-ocular tumors was different from that reported in literature. The frequency of malignant and pre-malignant tumor lesions was 17.1% and this percentage should be taken seriously. Any suspicious lesion should be biopsied particularly in elderly patients, after the fifth decade of life.

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