CONJUNCTIVAL TUMORS

TUMORES DE LA CONJUNTIVA

SAORNIL MA1, BECERRA E2, MÉNDEZ MC3, BLANCO G4

ABSTRACT

Conjunctival tumors are one of the most frequent of the eye and adnexa. They comprise a large variety of conditions, from benign lesions such as nevus or papiloma, to malignant lesions such as epidermoid carcinoma or melanoma which may threaten visual function and the life of the patient. They can arise from any cellular component, but the most frequent are of epithelial and melanocytic origin. Early diagnosis is essential for preventing ocular and systemic spread and to preserve visual function. In this paper we review the clinical characteristics of the most frequent conjunctival tumors, and we discuss tumor management (Arch Soc Esp Oftalmol 2009; 84: 7-22).

Key words: Conjunctival tumors, intraepithelial neoplasia, nevus, melanoma, lymphoma.

RESUMEN

Los tumores de la conjuntiva son unos de los más frecuentes del ojo y anejos. Abarcan un amplio espectro desde lesiones benignas como el papiloma a otras malignas que pueden poner en peligro la función visual y la vida del paciente, como el carcinoma epidermoide y el melanoma. Pueden surgir de cualquiera de las células que componen la conjuntiva aunque los más frecuentes son los de origen epitelial y melanocítico. El diagnóstico precoz es fundamental para prevenir la extensión ocular y sistémica y para preservar la función visual. En este artículo se revisan las características clínicas de los tumores conjuntivales más frecuentes y se discute su tratamiento.

Palabras clave: Tumores conjuntivales, neoplasia intraepitelial, nevus, melanoma, linfoma.

EPIDEMIOLOGY AND CLASSIFICATION

Conjunctival tumors are one of the most frequent of the eye and adnexa. They comprise a large variety of conditions, from benign lesions such as papiloma to malignant lesions such as epidermoid carcinoma or melanoma which may threaten visual function and the life of the patient if not diagnosed early (table I) (1,2). Conjunctival tumors may arise from any of the cells comprising the conjunctiva, although the most frequent ones are of epithelial and melanocytic origin (Table I). Epithelial tumors account for a third to half of all tumors, with prevalence being higher in countries with larger actinic exposure. As regards melanocytic tumors, most are
benign with variations according to the ethnic pigmentation and age of patients (1,2).

At the Ocular Oncology Unit of the Valladolid University Hospital 314 conjunctival tumors have been diagnosed, of which 149 (48%) were melanocytic (87% benign), 124 (39.6%) of epithelial origin (64.5% precancerous), 30 (9.6%) originated in soft tissue and 10 (3.2%) of the lymphoid type (3,4). In the majority of cases, the clinical differentiation between precancerous benign and malignant lesions is difficult, requiring a biopsy for a definitive diagnostic. On many occasions the biopsy is also therapeutic as it involves complete extraction in the case of circumscribed lesions (excisional biopsy).

### ANATOMICAL-HISTOLOGICAL UPDATE

The conjunctiva is a thin and flexible mucous membrane that extends from the internal surface of the eyelids (palpebral) to the fornix and the anterior surface of the ocular globe (bulbar) up to the sclerocorneal limbus (limbar). Its functions include contributing to the pre-corneal lachrymal film by means of producing the mucosal layer, as well as being an important barrier for foreign bodies and inspections, and limbar zone for maintaining the corneal epithelium. It received vascularization from branches of the margin on arches of the eyelids (tarsal) and the anterior ciliary arteries (bulbar). The lymphatic connections of the conjunctival run parallel to those of the eyelids, draining the pre-auricular and sub-mandible lymphatic nodes, and the sensory enervation is derived from the V cranial pair (1,2,5,6).

Histologically (5,6) the conjunctiva is similar to other mucous membranes and comprises a non-keratinized stratified epithelium having two or more layers over a stroma formed by fibrovascular connective tissue containing vessels, nervous and lymphatic tissue (fig. 1). The basal layer of the epithelium comprises melanocytes which produced melamine and inject it in the surrounding cells. Throughout the length of the epithelium we can observe cup-shaped cells in charge of producing the mucoid component of the lachrymal film. These cells are more numerous in the lower nasal portion of the bulbar conjunctiva. In the internal edge we find the half-moon fold and the carbuncle where we

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**Table I. Classification of conjunctival tumors based on origin**

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<thead>
<tr>
<th>Origin</th>
<th>Benign</th>
<th>Pre-cancerous</th>
<th>Malign</th>
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<tbody>
<tr>
<td>Epithelial</td>
<td>* Papillomas</td>
<td>* Actinic keratosis</td>
<td>* Squamous Ca.</td>
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<td></td>
<td>* Pseudoepitheliomatous hyperplasia</td>
<td>* ICN: Intraepithelial neoplasia</td>
<td>* Mucoepidermoid Ca.</td>
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<td>Melanocytic</td>
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<td>* Nevus with atypia</td>
<td>* Melanoma</td>
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<td>* Racial Pigmentation</td>
<td>* Acquired Melanosis 1st with atypia</td>
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<td>Secondary glands</td>
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<td>Soft tissue</td>
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<td>* Kaposi’s Sarcoma</td>
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<td>* Hemangioma</td>
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<td>* Fibrous Histiocytome</td>
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<td>Lymphoid</td>
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<td>* Leukemia</td>
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<td>* Plasmocitoma</td>
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**ARCH SOC ESP OFTALMOL 2009; 84: 7-22**
can find thin pilous follicles and sebaceous glands, and even secondary lachrymal glands.

Throughout the bulbar conjunctiva and up to the sub-tarsal folds of the eyelids there is a lymphoid layer which, in some areas, forms specialized aggregates known as Conjunctival-associated Lymphoid Tissue -CALT- corresponding to the Mucosa-associated Lymphoid Tissue -MALT-) from other regions of the body, formed by aggregates of T- and B- lymphocytes related to the anti-genic information process (5-7).

**EPITHELIAL TUMORS**

**Benign**

**Squamous Papilloma.** Expresses as exophytic lesions, pink color, soft to the touch and irregular surface. It can be of viral origin (human papillomavirus) in which case it can recur. It tends to be pedunculated in children (more frequent in lower fornix) and short in adults (more frequent in bulbar conjunctiva). It is generally non-symptomatic and free of associated inflammation signs. At the clinical level, it can be difficult to differentiate from precancerous and carcinomatous lesions. Histologically, it consists in connective-vascular axes covered by acanthotic conjunctival epithelium without signs of atypia (fig. 2) (1,2,8).

**Pseudo-epitheliomatous or pseudo-carcinomatous Hyperplasia.** This is an epithelium hyperplasia which is reactive to inflammation or chronic irritation processes. The source of the inflammation is usually a pre-existing pterygium with chronic inflammation wherein the epithelium begins to proliferate and keratinize. Clinically it consists in a raised, pinkish, rapidly growing mass similar to a carcinomatous lesion which may appear leukoplakic. Histologically, the epithelium proliferates forming lobules and exhibits an increased mitotic activity secondary to the inflammation. It can be differentiated from the squamous carcinoma by the absence of nuclear atypia and the marked underlying stromal inflammation. A variant of this lesion with rounded morphology, abrupt and raised edges is the keratoacanthoma (1,2).

**Precancerous**

**Actinic keratosis.** This a leukoplakic lesion which is well circumscribed, raised and limbic and grows slowly on the epithelium of the inter-palpebral area, generally over a pre-existing pterygium. It may simulate a carcinoma. Histologically it is characterized by acanthotic and hyper-kerathotic epithelium with abrupt edges and different degrees of cellular atypia which rarely comprises the entire epithelium (slight or moderate displasia) and elasthotic degeneration in the stroma. It can evolve to become a conjunctiva squamous carcinoma, although this is highly infrequent (fig. 3) (1,9).

**Intraepithelial neoplasia: In situ displasia/carcinoma.** This is one of the most frequent tumors of the ocular surface, with an approximate prevalence of 2 cases /100,000 per year. Clinically it appears in 60-70 year-old patients with pale skin. It can also appear in young people with immune depression and can be bilateral. It is a gel-like lesion, short or papillomatous with a tendency to superficial diffuse extension, generally in the...
inter-palpebral groove, affecting the limbus with poorly defined edges. It usually extends over the corneal epithelium. Pathogenically, it is akin to displasia which appears in non-exposed mucous. The human papillomavirus is involved in its development (even more so in immune-suppressed patients or with bilateral disease). Also involved is the acquired immunodeficiency virus, solar exposure and environmental factors such as exposure to petroleum derivatives, industrial oil, tobacco, etc. (fig. 4) (2,10.11).

The clinical appearance is a consequence of the histological changes consisting in the appearance of an epithelial hyperplasia in varying degrees where the corneal epithelium (full or partial thickness) is substituted by a proliferation of atypical cells (displasia) which begins in the basal layers of the epithelium and may involve the epithelium partially (slight, moderate and severe displasia) or fully (in situ carcinoma). The term ICN (conjunctival intraepithelial neoplasia) includes the various degrees of displasia (slight, moderate or severe) (fig. 5) and the in situ carcinoma (fig. 6), meaning that these entities are different levels of the development range of an intraepithelial neoplasia, considered as a pre-cancerous lesion, because if the atypical cells break the basal membrane and invade the sub-conjunctival tissue, the result is the conjunctiva invasive squamous carcinoma (1,9,10). The risk of developing squamous carcinoma is low but probably greater than the risk of developing actinic keratosis.
Due to the lack of precise limits and the tendency towards diffuse growth, incomplete resection is easier than in actinic keratosis, giving rise to frequent relapses. Compared with similar lesions in other locations, its development is relatively benign as it usually is restricted to the epithelium and rarely becomes invasive. For the most part, these lesions do not follow the course of a truly malignant tumor which is invasive and metastasizing, with the surface extension and recurrences creating a bigger problem than the risk of systemic extension. Early diagnostic is important because the excisional biopsy with resection margin, with or without supporting treatment, is usually definitive. However, advanced lesions can extend throughout the cornea and a large part of the conjunctiva, obstructing complete removal and jeopardizing the visual function and requiring complex surgery and coadjuvant therapies such as topical chemotherapy (Mitomycin C, 5-Fluorouracyl, Interferon alfa-2b) (12-17) (fig. 7).

Malign

**Squamous carcinoma.** This growth originates from actinic keratosis and intra-epithelial neoplasia. It appears when an in situ carcinoma breaks the basal membrane and invades the subconjunctival tissue, accessing lymphatic vessels and
becoming potentially metastasic. Clinically, it expresses as an exophytic lesion, short or pedun-culated in the inter-palpebral exposure area, with variable appearance, frequently close to the limbus, with slow growth. In its natural evolution it can occupy the entire conjunctival bulbar area and from there extend through the orbitary septum, invading the orbit (fig. 8). Alternatively it can invade the sclero-corneal lamella penetrating in the ocular globe (18,19). However, in most cases it tends to be only superficially invasive and to have a relatively benign course. Even though it accesses lymphatic vessels metastatic disease is rare: percentages found in literature are around 1%. Immuno-suppressed patients (organ transplant, AIDS) are at greater risk of developing this carcinoma, and in these cases it is more aggressive and with higher potential for metastasis (1,2,20).

Histologically, most carcinomas are well differ-entiated, with exophytic growth of epithelial cells. In more advanced tumors the matter usually exhibits inflammation containing niches of atypical cells with hyperplastic hyper-chromatic nuclei, diskerosis, cornea pearls (collections of keratinized cells) and atypical mitosis (1,2,5).

**Fusiform squamous carcinoma.** This carcinoma is rare and much more aggressive, expressing as highly aggressive flat lesions with a tendency towards intra-ocular penetration, sometimes simulating peripheral corneal ulcers. Histologically, the cells are fusiform and pleomorphic, with a hyper-chromatic nucleus, sometimes difficult to differentiate from fibroblasts leading to the possibility of an erroneous diagnostic as fibrous histiocytes or fibrosarcoma. Positive immune-histochemical studies for cytokeratines confirm the epithelial nature of this tumor (21).

**Mucous-epidermoid carcinoma.** This carcinoma is rare and generally appears in elderly peo-ple, being more aggressive than squamous carcinoma and with a tendency to invade the ocular globe and the orbit. It usually appears in the conjunctival sac fundus, exhibiting a yellowish globular component due to the mucous-secreting cells component. Its histological characteristics are those of an epithelial neoplasia containing a variable proportion of mucus-secreting cells and on some occasions areas of differentiation to adenocarcinoma (1).

**Treatment of epithelial tumors**

The objectives in treating conjunctival tumors are:

- To completely destroy or extirpate the tumor by means of surgery and adjuvating treatments if prescribed and necessary (cryotherapy, topical chemotheraphy, radiotherapy).
- Carry out a precise histopathological diagnostic because at the clinical level it is very difficult to distinguish benign, pre-cancerous and malign lesions. Diagnostic confirmation will allow for the right therapeutic approach, as well as prognosis and follow-up.
- Minimizing recurrences

To achieve the above, a complete pre-op assess-ment must be made, including a highly precise clinical approach to the diagnostic: whether the lesion is circumscribed or diffuse, bilateral or unilateral, suspected to be pre-cancerous or malign. The exten-sion of the tumor must also be assessed, determining the existence of intra-ocular and/or orbitary invasion, carrying out a palpation of regional lymphatics and, when considered appropriate, a systemic extension study for detecting metastasis (which are rare) (22).

In general, for tumors which are circumscribed, limbar or conjunctival bulbar, complete extirpation (excisional biopsy) with the smallest possible amount of manipulation and a resection margin of 3-5 mm could be sufficient treatment. Bowman’s layer should be respected because its removal would facilitate the intraocular penetration of any recurrence. Cryotherapy and controlling the resec-tion edges by means of intra-op biopsies have proved to diminish recurrences in pre-cancerous and malign lesion cases (20,22-24).

In diffuse and extended lesions where com-plete resection is difficult, the largest possible
extirpation must be made which must also allow for a precise histopathological diagnostic. If the resection is too large, autologous conjunctival or buccal mucosa grafts can be implanted. For the residual tumor adjuvating therapies can be employed such as topical chemotherapy (Mitomycin C, 5-Fluorouracil, interferon) and also radiotherapy (25,15-17).

In the case of intra-ocular invasion, enucleation is prescribed. If there also is anterior orbitary invasion, anterior exenteration must be performed, preserving the eyelids provided the palpebral conjunctiva is not affected.

MELANOCYTIC TUMORS

Pigmented conjunctival tumors account for about half of conjunctival tumor lesions (1,2) and mainly affect white patients. These tumors are derived from melanocytes which migrate from the neural crest during embryological development to the epithelium and sub-conjunctival tissue. Epithelial melanocytes are located at the basal layer and account form most of pigmented conjunctival lesions, causing a range of alterations from benign lesions such as conjunctiva nevus to malign and potentially mortal conditions such as the conjunctival melanoma. The clinical and histopathological identification of these lesions is important for their correct treatment (26-27) as benign lesions treated as malign will mean unnecessary treatments, while undervalued melanomae or melanosis which are not treated early lead to a reduction in the patient’s vital prognosis as they evolve towards melanomas having a mortality rate of 25% after 5 years (26).

Benign

Congenital/acquired Nevus. This is the most common melanocytic lesion of the conjunctiva. It is congenital and expresses clinically during childhood as a circumscribed, flat, scarcely pigmented, slightly elevated lesion in the inter-palpebral bulbar conjunctiva (fig. 9). It usually increases in pigmentation and form cysts in the second decade of life, at which time the patient generally visits the ophthalmologists practice (fig. 9B). As of this stage, the nevus remain stable during adult life and any change in size, color, edges or appearance must lead us to suspect its malign transformation into melanoma, but this occurs in under 1% of cases (fig. 9C). Its characteristic location is the bulbar conjunctiva, but it also can appear in the juxta-limbar area and in the caruncle. It moves freely over the sclera but does not extend over the cornea. Exceptionally it is found in the sac fundus and tarsal conjunctiva, so any lesion in these locations must be considered as a melanoma or precursor thereof and biopsied. As regards pigmentation, it varies broadly from light brown to dark chocolate, and 30% are not pigmented (1,26-28).

Histologically, this nevus undergoes evolutionary changes as those in the skin, evidenced in the clinical changes described above. In the initial stage, the niches of nevus cells are in the basal layer (epithelial nevus) to appear later on in the interface between the epithelium and the stroma (junctional nevus). In its evolution, the niche of nevus cells penetrate the stroma (composite nevus), dragging epithelial cells which can form pseudo-cysts to end up locating only in the sub-conjunctival tissue (subepithelial or stromal nevus) (1,22,24) (fig. 10).
Racial pigmentation. In African and dark-skinned subjects it is frequent to find more pigmentation in the conjunctival epithelium. This pigment is more prominent in the inter-palpebral fissure, is usually bilateral, it moves over the ocular globe surface and it can be marked in the limbus and extend to the peripheral cornea. Microscopically, it is characterized by a uniform hyper-pigmentation of the conjunctiva epithelium basal layer.

Ocular melanocytosis. This condition is the result of the incomplete migration of melanocytes from the neural crest, which do not reach the conjunctiva and may appear in the uvea, sclera, episclera, optic nerve, meninges and the eyelid skin. If only the ocular globe is involved, it is called Congenital ocular melanosis or Melanosis Oculi. When the pigmentation reaches the skin of the eyelid, it is called Oculodermic melanocytosis or Nevus of Ota.

Clinically, it is unilateral and appears as a diffuse episcleral bluish-gray pigmentation. The edges of the pigmentation do not move with the conjunctiva (fig. 11), it is spiculated and the melanocytes surround and limit the lymphatics and blood vessels. The ipsilateral uvea and iris usually have a darker color, producing heterochromia of the iris and the eye fundus (fig. 11B). Histologically, the melanocytes are uniformly but not intensely pigmented and are located in the sclera and episclera more than in the conjunctiva. Although this entity exhibits greater risk for the development of orbit and uvea glaucoma and melanoma (1/400), it does not pose a risk for conjunctival melanoma as there is not a single case described in the literature (29,30).

Secondary acquired melanosis. This is the increase of conjunctival pigmentation due to different causes such as metabolic diseases (for ex., Addison’s disease), deposits due to topically instilled drugs, irradiation, inflammation, hormonal changes or chronic conjunctival disorders. This melanosis does not predispose to the development of melanoma. Histologically, the normal epithelium melanocytes become excited, proliferate and produce melanine.

Pre-cancerous

Nevus with atypia. As described above, nevus are benign lesions with cells which may undergo a malignant transformation, generally in adult life over 40, associated to changes in clinical morphology that, without treatment, usually evolves to melanoma (fig. 9C) (28).

Primary acquired melanosis (PAM). This is a multicentric, acquired, unilateral, epithelial melanocytic proliferation which appears in adults and affects predominantly white and light-skinned people. In literature it is referred to in a number of ways, including Reese precancerous
melanosis, benign or idiopathic acquired melanosis and atypical intraepithelial melanocytic hyperplasia.

Clinically, it begins insidiously in the middle age as a subtle, multicentric and unilateral pigmentation extended throughout the conjunctiva, including sac fundus and tarsal conjunctiva (fig. 12). When the conjunctiva of the palpebral edge is involved, it frequently extends to the adjacent skin. In contrast to nevus, it usually is flat, with increased volume being a sign of malignization. Its color is irregular, ranging from no pigmentation at all to dark brown. Its evolution is unpredictable: pigmentation can disappear in one area and appear or increase in another. The rate of development is variable, but generally it is measured in years (26,31).

Histopathologically, primary acquired melanosis is classified as PAM with or without atypia (26). The Latter group involves melanocytic hyper-pigmentation or hyperplasia limited to the epithelial basal layer. Any type of atypical cell growth different to a basilar hyperplasia is considered a PAM with atypia. This differentiation is relevant for prognosis because atypical PAM has a 70-90% risk of evolving to melanoma, whereas PAM without atypia has a low risk of malignization (20%).

Melanoma

Conjunctival melanoma is an extremely rare and potentially deadly neoplasia, with an estimated prevalence of 0.2 to 0.5 cases per million inhabitants/year in Caucasian populations. It accounts for 1-2% of ocular malign tumors. Even though ultraviolet radiation has been signaled as causal agent, its etiology remains unknown. In about 75% of cases, it originates at the clinical level in a PAM with atypia (fig. 5), but it also can originate in a previous nevus (20-30%) or appear de novo (5-10%) without pre-existing lesions (fig. 5B) (32-34).
It affects adult or elderly Caucasian populations and has no gender preference. The most common clinical presentation is an elevated mass with variable pigmentation and associated signs of PAM or history of nevus, localized in the limbus, bulbar conjunctiva, fornix or palpebral conjunctiva. It can extend locally to the orbit and ocular globe, and systemically through the lymphs. Accordingly, prior to treatment it is important to determine the degree of tumor extension, with a complete ocular and orbital assessment, palpation of neck ganglions and systemic extension study.

At the histopathological level, the conjunctiva melanoma comprises atypical melanocytic cells with diverse morphology which invade the conjunctival substance (fig. 16). Morphology is highly variable, ranging from large pleomorphic cells with prominent nucleoles to small polyhedral or fusiform cells without identifiable pigmentation. Immune histochemistry for protein S-100 and HMB-45 can assist in the diagnostic of non-differentiated and amelanocytic cases (1,29-34).

Even with adequate treatment, about half of patients exhibit local recurrences, and one third metastases within 10 years (32,33). Accordingly, ongoing follow-up is important for these patients. The most frequent localization of initial metastases are regional lymphatic nodes (preauricular, under the jaw and cervical), although there also is remote dissemination through the hematogenous route. When the disease appears disseminated there is no efficient treatment and patients have a relatively short survival time. The most important prognostic factors are the tumor thickness, the palpebral or caruncle localization, lymphatic invasion, elevated proliferation rate and the pagetoid histological pattern and recurrences (1,26,32-34). At present, different aspects are under research such as the importance of the sentinel lymphatic ganglion biopsy in early detection of

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**Fig. 14:** Primary acquired melanosis with atypia. A: Atypical melanocytic cell niches occupying virtually the entire epithelium with sub-epithelial inflammatory infiltration (HE10x). B: Melanocytic cells leave a positive mark with HMB45 demonstrating that the basal membrane is respected (HMB4510x).

**Fig. 15:** Multicentric conjunctiva melanoma originated in a PAM (A), and advanced de novo melanoma (B).

**Fig. 16:** Conjunctival melanoma. A: Cell proliferation in sub-conjunctival tissue with irregular pigmentation (HE4x). B: with a larger zoom (HE40x) atypical pleomorphic cells can be observed, of epithelioid nature and variable pigmentation with multiple mitosis.
regional metastases (35,37), the identification of risk factors for tumoral development and the assessment of prognostic markers for morbidity and mortality (5,34,37,38).

**Treatment of melanocytic tumors**

The general objectives in melanocytic tumor treatment are similar to those described for epithelial tumors: excision or complete destruction of the tumor, precise histopathological diagnostic and minimization of recurrences. This is a particularly important objective in pigmented tumors as they worsen the patient prognosis.

Generally, benign lesions do not require much more than a correct clinical diagnostic and regular observations. Most nevus occurring in patients under 40 do not require treatment except for esthetic purposes. The same occurs with repetition inflammatory processes because melanoma is extremely rare in young people, even in elderly people. Only in the case of growth or color or morphology changes should the lesion be removed to discard malign transformation.

The management of PAM depends on the extension of the lesion. If small, occupying under one fourth of the conjunctiva, its full removal should be considered. If the lesion is large, the thickened areas should be removed (due to suspected melanoma) and perform map biopsies of the non-removed PAM areas to determine the risk of evolving to conjunctival melanoma. In addition, biopsies should be taken in apparently uninvolved areas due to the presence of PAM without pigmentation. If the complete removal of atypia areas cannot be done or recurrences emerge, supporting therapies should be utilized such as intra-op cryotherapy or post-surgery topical chemotherapy, of which Mitomycin C is the most tested and tried (fig. 17) (32,39-41).

In the de novo melanoma or one arising from a nevus, the primary treatment for the tumor is complete surgical removal with 3-5 mm of free margins, with or without intra-op supporting cryotherapy. Regardless of the origin of the melanoma, the objective is its removal combining necessary therapies in the first approach to prevent recurrences because these deteriorate the vital prognosis of the patient.

In follow-up, patients must carefully checked, exploring the full conjunctiva surface with palpation of pre-auricular and cervical ganglions. If pre-auricular ipsilateral, sub-mandibular and/or cervical invasion is detected, a non-radical regional ganglionic cleaning is recommended.

If orbitary and/or intraocular invasion is detected, the usual primary treatment consists in exenteration. Enucleation is not usually performed because it leaves the conjunctiva (the origin of the tumor, which can give rise to new recurrences).

**TUMORS IN SOFT TISSUE, GLANDS AND THEIR APPENDICES**

Non-epithelial conjunctival tissue comprises vascular and lymphatic structures, peripheral...
nerves, connective elements, glands and their skin appendices in the caruncle, which may give rise to any soft tissue tumor with the same histopathological characteristics, although most of them are rare. Sarcomas, fibromas, neurofibromas, schwannomas, neurotekiomas and other soft tissue tumors may appear in the conjunctiva but more frequently the conjunctiva is a secondary area of involvement in the orbit (1,2,42,43). The most frequent and/or relevant tumors are described below.

Benign tumors

Caruncle: Oncocytoma or eosinophilic cystadenoma. Most tumors originating in secondary eyelid structures, eyebrows and orbit, can start in the caruncle (e.g., pleomorphic adenoma, oncocytopoma, sweat glands carcinoma, sebaceous carcinoma). This is not surprising because the caruncle contains accessory lachrymal teas, sebaceous glands and hair follicles. The most frequent malign tumor in the caruncle is the sebaceous carcinoma, while the most frequent benign tumor is oncotyoma which also appears in the lachrymal sac and gland. It appears as a slow-growing raised pink-colored mass in elderly patients (1,42).

Microscopically, oncotyomas have a variable pattern and the cells can arrange themselves in flat planes, strings or nests and can form cystic or glandular structures. Their cells typically have the broad eosinophilic cytoplasm full of substance which, in electronic microscopy, are mytochondriae. This oncocytic transformation is not specific and takes place in other glands and mucous of the body and can represent a change of ageing.

Pyogenic granuloma. Clinically, this expresses as a pedunculated lesion, of papillomatous appearance which develops after a surgical or accidental trauma or a local inflammatory process (reaction against a foreign body). The differential diagnostic must be made mainly with a pediculated papilloma, as the main differentiating factor is the progression rate and the history of traumatism. Histopathologically, it consists in granulated tissue comprised by a lax stroma containing numerous capillaries extending radially outward and a combination of acute and chronic inflammatory cells (fig. 18) (1). Its treatment consists in excisional biopsy (4).

Hemangioma. These are tumors which consist in a benign vascular proliferation which can be located in the conjunctiva itself or as part of hemangiomas affecting other structures. The conjunctiva is an unusual place for hemangiomas but it is involved in capillary orbit and eyelid hemangiomas which appear early but regress spontaneously in the first years of life, and also in the Sturge-Weber syndromes which frequently exhibit ipsilateral conjunctival diffuse hemangiomas (1).

Lymphangiectasia/Lymphangioma. This tumor consists in the dilatation of conjunctival lymphatic vessels, which can appear in the bulbar or tarsal conjunctiva. They appear as an irregular reddish mass made up of numerous dilated lymphatic vessels which can contain blood. Their development is slow and becomes exacerbated with catarrh. These are lymphangiomas which are frequently part of a lesion involving the orbit and eyelids (fig. 19) (1).

Fig. 18: Pyogenic granuloma after surgical trauma. A: Exophytic pinkish formation, richly vascularized. B: granulation tissue with numerous capillaries extending radially (HE4x).
Malign tumors

**Caruncle: Sebaceous cell carcinoma.** A rare tumor but, according to the Washington Armed Forces Institute, it is the most frequent caruncle malign tumor (1). It originates in the sebaceous glands and its pagetoid dissemination substituting the conjunctival epithelium can simulate a unilateral conjunctivitis. The conjunctiva is also frequently invaded by this superficial dissemination of a sebaceous gland originated in the eyelids.

**Kaposi sarcoma.** Until a few years ago, this was a rare disease affecting elderly patients, associated to Jewish-Mediterranean types. At present it appears in young individuals affected by AIDS and could be taken as one of the early expressions of said disease. Clinically it consists in the appearance of nodules or reddish-bluish spots on the skin of the legs in patients with the typical expression of the disease, but in AIDS patients the lesions appear in the upper part of the body (face, eyelids) and the conjunctival involvement can be the first clinical sign of AIDS. It also appears as sub-epithelial nodules in the fornix or palpebral conjunctiva. Histologically it comprises fusiform cells with oval nucleus and numerous capillaries (fig. 20) (1).

**LYMPHOID TUMORS**

The eye and surrounding area lymphomas account for 2-10% of extra-nodal lymphomas. These are rare and comprise a range from lymphoid reactive hyperplasia to malignant lymphoma, always based on microscopic characteristics. Conjunctiva lymphomas account for 20-30% of lymphoid tumors of the eye and surrounding areas, and only 20-30% of cases are associated to systemic disease (which may appear years later), and are bilateral in nearly 40% of cases (44,45).

The majority of eye area lymphomas are of low degree non-Hodking type B cells and the greater part of the MALT type conjunctiva (low degree B lymphoma of the lymphoid tissue associated to mucosa) and are located at the most favorable end of malignant lymphomas and on many occasions on difficult ground for differential diagnostic in which there is no clear dividing line between the low degree malignant lymphoma and lymphoid reactive hyperplasia.

Clinically, both benign and malignant lesions tend to have a salmon-like color and are generally sub-
conjunctival lesions with flat surface and soft to the touch, located close to the fornixes. Clinically it is impossible to differentiate between benign lesions (lymphoid reactive hyperplasia) and malign ones. Therefore it is essential to carry out a biopsy and, if the malign lesion diagnostic is confirmed, a systemic exploration of the patient must be performed to exclude the presence of a systemic disease (fig. 21).

In systemic lymphoma cases, the adequate treatment is systemic chemotherapy. The conjunctival involvement will respond to chemotherapy in the same way as the other affected cells of the body. If there is no systemic involvement and the lesion is localized in the conjunctiva, surgical removal may be made followed by external radiotherapy if the lesion is extended or orbitary involvement is suspected (20-40Gy). Alternatively, local interferon injections may be made and also observation (44-47).

**SUMMARY**

A large variety of tumors may appear in the bulbar or tarsal conjunctiva, sac fundus, semicircular fold or caruncle, affecting the epithelium or subepithelial tissue. Most are easy to detect in a routine ophthalmological assessment and their benign nature allows for a conservative or hardly invasive treatment. However, more aggressive, pre-malign or openly malign tumors such as carcinoma, melanoma or lymphoma, which jeopardize the visual function and/or the patient’s life are not an exception. Therefore a vigilant attitude must be maintained to detect their presence at an early stage. In these cases, their existence must be confirmed with a biopsy and surgery combined with different supporting therapies (chemotherapy, cryotherapy or others) for achieving local control of the disease, preserving as much as possible the anatomical and functional integrity of the ocular surface. New imaging techniques and methods such as the study of the sentinel ganglion are important for identifying the local or remote extension of the disease. In spite of all the diagnostic and therapeutic developments, the core of a good approach for treating conjunctival tumors continues to hinge on a good histopathological study and diagnostic. For this, the clinical-pathological correlation is crucial, requiring good communication between the ophthalmologist and pathologist.

**REFERENCES**


