Tumors of the ocular surface have a wide clinical spectrum and include several forms of epithelial, stromal, caruncular, and secondary tumors [Table 1]. As a group, these tumors are seen commonly in the clinical practice of a comprehensive ophthalmologist, cornea specialist, and an ocular oncologist. This review is aimed to discuss the common tumors of the ocular surface and emphasize on their clinical diagnosis and appropriate management.

**Epithelial Tumors of the Ocular Surface**

**Nonmelanocytic epithelial tumors**

**Squamous papilloma**
Squamous papilloma occurs in both children and adults with variable presentation. In children, it results from infection of the conjunctival epithelium with human papilloma virus (HPV) 6, 11 or 16. Sometimes, it is solitary or multiple, and sessile or pedunculated. It becomes confluent in extreme cases. It is reported to have low malignant potential. Occasionally, it can assume an inverted growth pattern, which has a greater tendency towards malignant transformation into transitional cell carcinoma, SCC, or mucoepidermoid carcinoma. Histopathologically, the lesion shows numerous vascularized papillary fronds lined by acanthotic epithelium [Fig. 1]. Surgical excision by the “no-touch technique” followed by cryotherapy is the treatment of choice. Other reported treatment modalities include laser, dinitrochlorobenzene immunotherapy, interferon alpha 2b (IFN-α-2b), and topical mitomycin C (MMC) drops. Recent reports show significant role of oral cimetidine in treating recalcitrant and recurrent conjunctival papillomatosis. It enhances the immune system by inhibiting certain T-cell functions.

**Inverted papilloma**
The papilloma may invaginate inward into the underlying conjunctiva and substantia propria to present as a mixed inverted exophytic papilloma. It occurs as a conjunctival lesion secondary to irritation by concurrent or preexisting stromal inflammation such as pterygium, pinguecula, allergic conjunctivitis, and foreign body. It appears as an elevated leukoplakic pink lesion in the limbal area [Fig. 2]. Histopathologically, it is characterized by massive acanthosis, hyperkeratosis, and parakeratosis of the conjunctival epithelium. Complete excision and additional cryotherapy would constitute optimal management, as difficulty prevails in clinically and histologically differentiating the lesion from low-grade SCC.

**Conjunctival pseudoepitheliomatous hyperplasia**
It is a benign reactive inflammatory proliferation of the epithelial cells, which simulates carcinoma clinically and histopathologically. It occurs as a conjunctival lesion secondary to irritation by concurrent or preexisting stromal inflammation such as pterygium, pinguecula, allergic conjunctivitis, and foreign body. It appears as an elevated leukoplakic pink lesion in the limbal area [Fig. 2]. Histopathologically, it is characterized by massive acanthosis, hyperkeratosis, and parakeratosis of the conjunctival epithelium. Complete excision and additional cryotherapy would constitute optimal management, as difficulty prevails in clinically and histologically differentiating the lesion from low-grade SCC.

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**Key words:** Conjunctiva, cornea, lymphoma, melanoma, ocular surface, ocular surface squamous neoplasia, tumor
Keratoacanthoma
It is a variant of conjunctival pseudoepitheliomatous hyperplasia. Though it is a benign lesion, some believe that it may represent an abortive malignancy that rarely progresses to SCC. An elevated mass with hyperkeratosis or leukoplakia is the usual presentation. Onset as well as the progression is rapid. Treatment is by complete excision and cryotherapy.

Table 1: Classification of tumors of the ocular surface

| Epithelial tumors          | Nonmelanocytic | Melanocytic | Stromal tumors | Vascular | Fibrous | Neural | Histioytic | Myogenic | Lipomatous | Lymphoproliferative | Choristoma | Caruncular tumors | Metastasis and secondary tumors |
|----------------------------|----------------|-------------|----------------|----------|---------|--------|------------|----------|------------|---------------------|------------|-------------------|-------------------------------|

Dacryoadenoma
Dacryoadenoma is a rare condition affecting children and young adults. It appears as a translucent and fleshy pink lesion in the bulbar, fornixal or palpebral conjunctiva. It arises from the surface epithelium and proliferates inward into the stroma and develops glandular lobules similar to those seen in normal lacrimal glands but with abundant goblet cells. Complete excision is the treatment of choice.

Conjunctival epithelial cyst
Conjunctival epithelial cyst can be congenital or acquired. There are two subtypes-inclusion cysts and ductal cysts. Inclusion cysts are further classified as spontaneous or posttraumatic. These cysts typically are smooth translucent lesions containing clear fluid. The contents may be turbid, containing epithelial debris seen layered like pseudohypopyon. Ductal cysts are lined by two layers of the epithelium and may contain secretory material. The cysts may remain stable and asymptomatic, and rarely undergo spontaneous resolution. Excision is the treatment of choice for a cyst that enlarges or becomes symptomatic.

Hereditary benign intraepithelial dyskeratosis
This is a rare autosomal dominant condition of the conjunctiva and other mucous membranes. It is specifically seen among the inbred Caucasians, African-Americans, and Native Americans known as Haliwa Indians but, is also seen in the population of other descent. The lesion generally presents in the first decade of life as an elevated hyperemic and fleshy V-shaped plaque on the nasal and temporal bulbar conjunctiva and limbus. It may be asymptomatic or, if severe, can cause redness and discomfort. Severe form can lead to corneal vascularization, opacification, and loss of vision. Smaller symptomatic lesions are treated conservatively with lubricants and topical steroids while larger lesions undergo local resection with ocular surface reconstruction. It carries no risk of malignancy, but recurrence is common. Hence, complete excision with clear margins is warranted. Histopathologically, there is marked acanthosis and hyperkeratosis of the conjunctival epithelium with prominent dyskeratosis.

Table 2: Epithelial tumors of the ocular surface

| Epithelial tumors of the ocular surface | Benign | Malignant |
|----------------------------------------|--------|----------|
| Squamous papilloma                     | CIN    | SCC      |
| Keratoacanthoma                        |        |          |
| Keratotic plaque                       |        |          |
| Reactive hyperplasia                   |        |          |
| Inverted follicular keratosis           |        |          |
| Hereditary intraepithelial dyskeratosis|        |          |
| Oncocytoma                             |        |          |
| Dacryoadenoma                          |        |          |

SCC: Squamous cell carcinoma, CIN: Conjunctival intraepithelial neoplasia

Figure 1: Microphotograph of squamous papilloma (OM x4). The lesion shows numerous vascularized papillary fronds lined by acanthotic epithelium

Figure 2: Conjunctival inclusion cyst, a smooth translucent lesion with turbid fluid
Conjunctival keratotic plaque
This leukoplakic lesion that may develop in the bulbar conjunctiva is usually in the interpalpebral region. There is thickening and keratinization of conjunctival epithelium characterized mainly by acanthosis, hyperkeratosis, and parakeratosis. Dyskeratosis is always absent. It has little or no malignant potential.

Actinic keratosis
Seen commonly as a focal leukoplakic lesion occurring at the interpalpebral area presenting as flat, white plaque sometimes with a frothy covering, actinic keratosis progresses very gradually and shows no tendency towards aggressive growth. Clinically, it may often be indistinguishable from conjunctival intraepithelial neoplasia (CIN) [Fig. 4]. Rose bengal staining of the surface of the lesion tips the clinical suspicion in favor of CIN. Actinic keratosis is a relative indication for surgical excision and supplemental cryotherapy. Close observation of the lesion until progression is documented is a reasonable option.

Ocular surface squamous neoplasia
Ocular surface squamous neoplasia (OSSN) is an encompassing term for precancerous and cancerous epithelial lesions of the conjunctiva and cornea. It includes the spectrum of dysplasia, CIN, and invasive SCC. Previously used terms for this condition include intraepithelial epithelioma, Bowens disease, and Bowenoid epithelioma. CIN accounts for 39% of all premalignant and malignant lesions of the conjunctiva and for 4% of all conjunctival lesions. Unlike CIN, incidence of invasive SCC is of much lesser frequency, varying from 0.02 to 3.5/100,000 population. About 75% occur in men, 75% are diagnosed in older patients and over 75% occur at the limbus. Factors associated with the development of OSSN are exposure to sunlight, HPV type 16 infections, and immunocompromised status. Studies have shown interaction of AIDS with ultraviolet-induced damage and HPV infection. Systemic associations of the development of OSSN include xeroderma pigmentosum and Papillon–Leferve syndrome.

Ocular surface squamous neoplasia is mostly unilateral and is seen in middle-aged and older patients. Rarely, it is bilateral in immunosuppressed patients. It often presents with redness and ocular irritation. Vision is usually unaffected unless it encroaches the center of the cornea. The tumor appears as fleshy or nodular, sessile minimally elevated lesion with surface keratin, feeder vessels, and secondary inflammation. Rose bengal staining is helpful in the diagnosis and delineation of the tumor extent [Fig. 5d]. The tumor may extend for a variable distance into the adjacent corneal epithelium and appear as a subtle wavy, advancing, gray, superficial opacity that may be relatively avascular or may have fine blood vessels. Whereas some lesions may present as diffuse gelatinous or papilliform form usually encroaching the cornea [Fig. 5]. Primary corneal dysplasia affects the corneal epithelium with minimal limbal involvement. Primary SCC of the cornea is rare.

There are no consistent clinical criteria for distinguishing CIN from invasive SCC. Leukoplakia is usually absent or minimal in CIN; extensive leukoplakia raises the suspicion of malignancy. The presence of feeder vessels and intrinsic vascularity favors SCC. Although greater thickness is believed to be a sign of malignant transformation, there are thick tumors that remain within the epithelium. The nodular lesion causes suspicion of invasive SCC. A diffuse lesion can masquerade as chronic conjunctivitis [31] [Table 3]. It is also important to examine the tarsal conjunctiva after everting the eyelid of patients with OSSN to detect contiguous or multifocal involvement of the tarsal conjunctiva.

Table 3: Morphological types of OSSN

| Morphological types of OSSN |
|-----------------------------|
| Placoid                     |
| Gelatinous                  |
| Papilliform                 |
| Velvety                     |
| Leukoplakic                 |
| Nodular                     |
| Diffuse                     |

OSSN: Ocular surface squamous neoplasia

Figure 3: Pseudoepitheliomatous hyperplasia. Elevated leukoplakic pink lesion in the temporal limbal area with apparent feeder vessels and pigmentation. Note that it closely mimics a nodular ocular surface squamous neoplasia

Figure 4: Actinic keratosis, a focal leukoplakic lesion seen in the interpalpebral area. It can easily be misdiagnosed as pinguecula
Advanced cases can infiltrate the cornea and sclera to have the intraocular extension.[28] Rarely, the tumor may extend into the orbit causing proptosis. The tumor can metastasize to the regional lymph nodes and rarely distant metastasis may occur. Aggressive variants include spindle cell squamous carcinoma, mucoepidermoid carcinoma, and adenoid SCC.[1,2,24,33,34]

According to the American Joint Committee on Cancer (AJCC)-tumor, node, and metastasis (TNM) classification, SCC is classified depending on the size, tumor location, and extent of involvement [Table 4].

Histopathologically, mild CIN (dysplasia) is characterized by partial thickness replacement of the epithelium by anaplastic cells that lack normal maturation. Severe CIN is characterized

| Table 4: AJCC-TNM classification of SCC of conjunctiva |
|-------------------------------------------------------|
| Clinical stage | Definition |
| Primary tumor (T) | |
| Tx | Primary tumor cannot be assessed |
| T0 | Tumor absent |
| T (is) | Tumor present as carcinoma in situ/CIN |
| T1 | Tumor present with largest basal diameter <5 mm |
| T2 | Tumor present with largest basal diameter >5 mm, without invasion of adjacent structures |
| T3 | Tumor invades adjacent structures excluding the orbit |
| T4 | Tumor invades orbit with or without further extension |
| T4a | Tumor invades orbital soft tissues, without bone invasion |
| T4b | Tumor invades bone |
| T4c | Tumor invades adjacent paranasal sinuses |
| T4d | Tumor invades brain |
| Regional lymph node (N) | |
| Nx | Regional lymph node cannot be assessed |
| N0a | No regional lymph node metastasis, biopsy done |
| N0b | No regional lymph node metastasis, no biopsy done |
| N1 | Regional lymph node metastasis |
| Distant metastasis (M) | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

Source: Edge SB, Byrd DR, Compton CC, et al., editors. Carcinoma of the conjunctiva. In: AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
AJCC: American Joint Committee on Cancer, TNM: Tumor, node, and metastasis, SCC: Squamous cell carcinoma, CIN: Conjunctival intraepithelial neoplasia

Figure 5: Ocular surface squamous neoplasia. (a) Elevated nasal limbal mass involving the cornea with abundant keratin and feeder vessels. (b) Pigmented variant seen as a nodular mass. (c) Diffuse, elevated, papilliform lesion involving the entire ocular surface with intrinsic vessels. (d) Gelatinous type with episcleral feeder vessels with speckled rose bengal staining
by full thickness replacement of the epithelium by similar cells. Both the variants show a characteristic abrupt demarcation between affected epithelium and normal epithelium. Invasive SCC shows a breach in the basement membrane of basal epithelium and is typically a fairly well-differentiated neoplasm composed of abnormal epithelial cells with mitotic activity and keratin. Occasionally, it can be poorly differentiated and shows bizarre, pleomorphic cells, numerous mitotic figures, acanthosis, and dyskeratosis

Complete but gentle surgical excision using a technique without touching the tumor called the “no-touch” technique [Table 5] is the treatment of choice.[1,23-35] The steps of surgical excision include:

- Conjunctival incision is made approximately 4 mm outside the clinically determined tumor margin. The incision incorporates full thickness conjunctiva and tenon’s fascia
- Dissection is carried out in the episcleral plane (if there is no episcleral adhesion) to reach the limbus
- Thin lamellae of the tumor-free sclera, 0.2 mm in depth including 2.0 mm outside the adherent conjunctival mass are removed if scleral fixity is noted
- Absolute alcohol is applied with cotton-tipped applicator to the involved cornea to allow for controlled corneal epitheliectomy 2 mm outside the corneal component
- The corneal epithelium is scrolled off to the limbus using a controlled sweeping motion with a beaver blade
- The entire tumor is removed in one piece without touching the tumor by excising it along the limbus
- Cryotherapy, double freeze-thaw cycle, is applied to the edge of the remaining bulbar conjunctiva and the scleral base if there was episcleral adhesion. Limbal cryotherapy should be limited to 6 clock hours

| Table 5: Tips to surgical excision of OSSN |
|---------------------------------------|
| Complete excision with 4 mm margin clearance |
| AKE with 2 mm margin |
| Lamellar sclerectomy (0.2-0.3 mm depth) |
| Double freeze-thaw edge cryotherapy |
| Base cryotherapy |
| Amniotic membrane grafting |

AKE: Alcohol keratoepitheliectomy, OSSN: Ocular surface squamous neoplasia

**Figure 6:** Histopathology of ocular surface squamous neoplasia (OSSN). (a) Microphotograph of OSSN showing abnormal epithelial cells with mitotic activity (OM ×10). (b) Seen at higher magnification (OM ×40)

**Figure 7:** Primary treatment of ocular surface squamous neoplasia. (a) Nodular lesion with abundant keratin at the limbus. (b) Immediate postoperative appearance following complete excision with margin clearance, double freeze cryotherapy and ocular surface reconstruction with amniotic membrane transplantation with tissue glue
Excision is followed by direct closure of the conjunctiva or with amniotic membrane graft [Fig. 7]. Reported recurrence rate of OSSN is 15–52%. Lee and Hirst reported a 17% recurrence after excision of conjunctival dysplasia, 40% after excision of CIN and 30% for SCC of the conjunctiva.[24] However, with the protocol-based technique as described above, the recurrence rate can be limited to <5%.

Plaque brachytherapy is used to control gross or microscopic residual tumors. More extensive orbital invasion requires orbital exenteration.[2,44]

Conjunctival intraepithelial neoplasia and mild forms of SCC can be treated with topical MMC 0.02–0.04% [Tables 6 and 7].[1,2,24,25,36‑38] There are several protocols [Table 6] but a dosage of 0.04%, qid, 4-days-a-week for 4 weeks works best in our experience. Associated local complications include conjunctival hyperemia, punctate corneal erosions, and inadvertent prolonged use may lead to scleral melt. Interferon alpha 2b is currently most accepted and favorable form of treatment for OSSN. It is less toxic with fewer complications compared to topical MMC. Their beneficial role includes immunomodulation, anti-proliferative, and anti-viral. The reported success rate is 83% with topical IFN 1 million IU administered 4 times daily for 6–12 months.[39,40] Intralesional injection of IFN α-2b of 3 million IU to 10 million IU combined with 1 million IU topical IFN is widely used as a primary modality (immunotherapy) for unresectable extensive tumors.[39‑41] It also helps in reducing the tumor size (immunoreduction), ideally followed by complete excision of the residual tumor. Similarly it plays a major role in immunosuppressed patients with OSSN, with a high rate of recurrence.[42] The long-term use of topical IFN helps to prevent recurrence by way of immunomodulation.[43] The most common complication is transient flu-like syndrome, whereas local complications are minimal.[36‑40] [Table 8]. Other available drugs are 5-fluorouracil and cidofovir.[43]

Ocular surface squamous neoplasia has a good prognosis. With the modern techniques, the local recurrence rate is about 5% and regional metastasis of 2%. Prognosis is worse in mucoepidermoid or spindle cell variants and in immunosuppressed patients.[1]

**Table 6: Protocol for topical MMC**

| Rule of four                                                                 |
|-----------------------------------------------------------------------------|
| 0.04% (0.4 mg/ml)                                                          |
| 4 times a day                                                                |
| 4 days a week                                                                |
| 4 weeks                                                                     |
| 2 weeks of treatment-free interval                                          |
| MMC: Mitomycin C                                                             |

**Table 7: Indications for topical chemotherapy in noninvasive OSSN**

| >2 quadrants of conjunctival involvement                                      |
| >180° of limbal involvement                                                  |
| Clear corneal extension encroaching the papillary axis                      |
| Positive margin after excision                                               |
| Patient not fit for surgery                                                  |
| OSSN: Ocular surface squamous neoplasia                                      |

**Table 8 Topical chemotherapeutic agents for OSSN**

| Drugs  | Type                  | Mechanism of action                                                                 | Dosage                  | Adverse effects                                        |
|--------|-----------------------|------------------------------------------------------------------------------------|-------------------------|-------------------------------------------------------|
| MMC    | Alkylating agent      | Under aerobic condition generates free radicals                                     | Topical 0.02-0.04%      | Conjunctival hyperemia, Blepharospasm, Corneal punctuation erosion, Punctal stenosis, Limbal stem cell deficiency |
| 5-FU   | Pyrimidine analog     | Inhibits thymidylate synthetase, Inhibits production and incorporation of thymidine into DNA, Inhibits RNA synthesis | Topical 1%              | Eyelid erythema, Conjunctival hyperemia, Corneal punctuation erosion |
| IFN α-2b | Type 1 IFN            | Immune-mediated suppression of IL-10, stimulates IL-2 and IFN-γ, m RNA, Anti-proliferative, Anti-viral | Topical or intralesional 1 million IU/ml, 3 million IU/ml, 10 million IU/ml | Superficial punctate keratopathy, Follicular conjunctivitis, Systemic, Flu-like syndrome, Fever/myalgia |

OSSN: Ocular surface squamous neoplasia, IFN α-2b: Interferon alpha 2b, 5-FU: 5-fluorouracil, IL: Interleukin, MMC: Mitomycin C
Conjunctival nevi are mostly located near the limbus in the interpalpebral area (72%). Other locations are the caruncle, semilunar folds, fornix, tarsus, and cornea. Characteristic clear cysts strongly support the diagnosis. They may also clinically demonstrate feeder vessels (64%) and intrinsic vascularity (77%) [Fig. 8a]. It can vary in size, color, and location. Conjunctival nevus can increase in size in growing young children, during puberty, pregnancy, and sun exposure. Malignant transformation was estimated to be <1%. Sudden increase in size, alteration in color, and increased thickness with prominent feeder vessels indicates malignant transformation. Irregular and diffuse growth pattern poses a diagnostic confusion with primary acquired melanosis (PAM), melanoma, lymphoma, and pigmented OSSN. Histopathologically, a conjunctival nevus is composed of nests of benign melanocytes in the stroma near the basal layers of the epithelium [Fig. 8b]. Positive immunostaining for HMB-45 and Ki-67 are useful adjuncts in differentiating benign melanocytic lesion from suspected malignant entities.

### Table 9: Melanocytic epithelial tumors

| Benign                        | Malignant                        |
|-------------------------------|----------------------------------|
| Conjunctival melanocytic nevi | Conjunctival melanoma            |
| Racial melanosis              |                                  |
| Congenital ocular melanosis   | PAM                              |
| PAM                           |                                  |

**Ocular melanocytosis**

Ocular melanocytosis is a congenital pigmentary condition of the periocular skin, sclera, orbit, meninges, and soft palate. It appears as irregular patches of scleral and episcleral pigmentation varying in color from brown to gray [Fig. 9]. Typically, there is no conjunctival pigment. It can involve the underlying uveal tract. Since it is episcleral involvement, it does not move with manipulation of the conjunctiva. This condition imparts a 1 in 400 risk for the development of uveal melanoma.

If associated with the dermal component, it is known as oculodermal melanocytosis or nevus of Ota [Fig. 7b and c]. It is mandatory that all patients with oculodermal melanocytosis undergo fundus examination to exclude uveal melanocytosis or melanoma. Associated hairline pigmentation predisposes them for meningeal melanoma and palate pigmentation to esophageal melanoma, therefore, these signs should be elicited with appropriate referrals when needed.

### Table 10: Indications for excision of a conjunctival nevus

- Distinct onset in middle age or later in life
- Location in the fornix or palpebral conjunctiva
- Lesions more than 10 mm in diameter
- Exuberant feeder blood vessels
- Exuberant intrinsic vascularity and hemorrhage
- Lesions with no cysts
- Lesions with dark uniform pigmentation
- Corneal epithelial invasion >3 clock hours and 3 mm from the limbus
- Episcleral fixity
- Cosmetic concern

**Figure 9:** Ocular melanocytosis showing episcleral pigmentation

**Figures 8:** (a) Conjunctival nevus with intralesional cysts and feeder vessels. (b) Microphotograph of a subepithelial nevus showing clumps of melanocytes with no cellular atypia (OM ×40)
Complexion-related conjunctival pigmentation
Complexion-related conjunctival pigmentation is a relatively common bilateral, flat, diffuse conjunctival pigmentation.\(^{[1,2]}\) It is more concentrated in the limbus, often for 360°, with variable pigmentation at the perilimbal bulbar conjunctiva and cornea [Fig. 8]. Uncommonly, it may also involve the fornix and rarely the palpebral conjunctiva. Periodic observation is recommended.

Primary acquired melanosis
Reese noted the tendency of a certain type of acquired conjunctival pigmentation to evolve into melanoma and named it precancerous melanosis. Zimmerman replaced the term with benign acquired melanosis, which was further modified by WHO as PAM in 1980.\(^{[50]}\)

Etiology
Sunlight exposure may play a role in the development of PAM. It has also been seen in patients with neurofibromatosis raising suspicion that it may have a developmental relationship to the neural crest.\(^{[52]}\)

Presentation
Primary acquired melanosis usually manifests in the middle age as unilateral, superficial, solitary, patchy, diffuse or multifocal pigmentation of the bulbar, fornical and palpebral conjunctiva, and cornea [Fig. 10a]. Occasionally PAM can be amelanotic.\(^{[1,47,54]}\) In PAM without atypia, there occurs

Table 11: Indications for biopsy of PAM\(^{[2]}\)

| Indications                          |
|-------------------------------------|
| Lesion diameter ≥5 mm               |
| Documented progression              |
| Thickening of the involved conjunctiva |
| Distant nodule arising within the lesion |
| Nutrient vessels                    |
| Involvement of the cornea           |
| Involvement of the palpebral conjunctiva |
| Dysplastic nevus syndrome in the patient or close relative |
| Personal history of cutaneous/uveal melanoma |

PAM: Primary acquired melanosis

![Figure 10: Primary acquired melanosis (PAM). (a) Diffuse flat pigmentation of the bulbar conjunctiva in an elderly male. (b) Microphotograph of PAM with cellular atypia (OM x10)](image1)

![Figure 11: Conjunctival melanoma. (a) Elevated, nodular, pigmented mass at the inferior limbus with extension into the peripheral cornea. Note the presence of feeder vessels and intrinsic vessels. (b) Microphotograph of conjunctival melanoma showing variably pigmented melanocytes with mitotic activity (OM x40)](image2)
Table 12: AJCC-TNM classification of conjunctival melanoma

| Stage | Clinical | Stage | Pathological |
|-------|----------|-------|--------------|
| Primary tumor (T) | | | |
| Tx | Primary tumor cannot be assessed | Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor | T0 | No evidence of primary tumor |
| T (is) | Malignant melanoma confined to conjunctival epithelium | T (is) | Malignant melanoma confined to conjunctival epithelium |
| T1 | Malignant melanoma of the bulbar conjunctiva | pT1 | Malignant melanoma of the bulbar conjunctiva |
| T1a | <1 quadrant | pT1a | <0.5 mm thick, with invasion of substantia propria |
| T1b | >1 but <2 quadrant | pT1b | >0.5-1.5 mm thick, with invasion of substantia propria |
| T1c | >2 but <3 quadrant | pT1c | >1.5 mm thick, with invasion of substantia propria |
| T1d | >3 quadrant | | |
| T2 | Malignant melanoma of palpebral conjunctiva, fornical conjunctiva, and/or caruncle | pT2 | Malignant melanoma of palpebral conjunctiva, fornical conjunctiva, and/or caruncle |
| T2a | <1 quadrant but not involving caruncle | pT2a | ≤0.5 mm thick, with invasion of substantia propria |
| T2b | >1 quadrant but not involving caruncle | pT2b | >0.5-1.5 mm thick, with invasion of substantia propria |
| T2c | <1 quadrant and involving caruncle | pT2c | >1.5 mm thick, with invasion of substantia propria |
| T2d | >1 quadrant and involving caruncle | | |
| T3 | Malignant melanoma with local invasion | pT3 | Malignant melanoma invading the eye, eyelid, nasolacrimal system, sinuses or orbit |
| T3a | Globe | | |
| T3b | Eyelid | | |
| T3c | Orbit | | |
| T3d | Paranasal sinus | | |
| T4 | Malignant melanoma with intracranial extension | pT4 | Malignant melanoma with intracranial extension |
| Regional lymph node (N) | | | |
| Nx | Regional lymph node cannot be assessed | | |
| N0a | No regional lymph node metastasis, biopsy done | | |
| N0b | No regional lymph node metastasis, no biopsy done | | |
| N1 | Regional lymph node metastasis | | |
| Distant metastasis (M) | | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis | | |

Source: Edge SB, Byrd DR, Compton CC, et al., editors. Carcinoma of the conjunctiva. In: AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010. AJCC: American Joint Committee on Cancer, TNM: Tumor, node, and metastasis.

Melanin pigmentation of the basal epithelium with or without hyperplasia of cytological benign melanocytes. This may progress to cytological atypical melanocytes to form PAM with atypia, where there is an increased risk of developing melanoma [Fig. 10b]. Studies show that among those with atypia, 13% develop melanoma.\(^{[1,47]}\)

Clinically, larger the extent of PAM, greater the risk of malignant transformation.

**Treatment**

Management strategies are [Table 11]:
- Observation for PAM without atypia
- Cryotherapy for PAM with atypia <3 clock hours
- Excision with excision edge cryotherapy for PAM >3 clock hours
- Topical MMC for diffuse PAM with atypia.

**Conjunctival melanoma**

Conjunctival melanoma is most common in light-skinned individuals. It usually presents in the middle-aged or elderly.\(^{[35]}\) It has no predilection for gender. It arises from PAM in about 75%, preexisting nevus in 20%, and de-novo in 5%.\(^{[12]}\) Other risk factors are dysplastic nevus syndrome, neurofibromatosis, and xeroderma pigmentosum.\(^{[35]}\) Sunlight exposure is also suggested as a cause, but that fails to explain the occurrence of melanoma in the fornices and palpebral conjunctiva.

**Presentation**

Conjunctival melanoma appears as a pigmented fleshy mass located in the bulbar, fornical or palpebral conjunctiva [Fig. 11a]. As a variant, it may appear as diffuse or multifocal with ill-defined margins particularly if arising from PAM. It occasionally originates in the fornical and palpebral conjunctiva.\(^{[54-58]}\) It may extend to cover the cornea or even arise as a primary corneal tumor. Conjunctival melanoma may rarely develop secondary to continuous touch from an eyelid margin melanoma (implantation melanoma).\(^{[59]}\) Melanoma can be sparsely pigmented or amelanotic. It is typically amelanotic, fleshy, and vascular when it recurs after prior excision.\(^{[2]}\) Conjunctival melanoma is classified according to the AJCC-TNM classification [Table 12].
Regional metastasis involves preauricular and submandibular lymph nodes. Sentinel lymphangiography makes it possible to accurately remove lymph nodes and is indicated in tumors more than 2 mm thickness. Distant metastasis occurs in the brain, liver, skin, and bone.

Histopathologically, conjunctival melanoma is composed of variably pigmented malignant melanocytes. These cells are positive for S-100 protein, tyrosinase, melan-A, HMB-45, HMB-50, and microphthalmia conscription factor. 

Treatment
Treatment of conjunctival melanoma is based on certain established principles:

- Complete excision in the episcleral plane with 4 mm clinically clear margins
- Alcohol keratoepitheliectomy of the corneal epithelial component
- Partial lamellar sclerokeratectomy if sclera or corneal stroma are involved
- Double freeze-thaw cryotherapy to the excision edge, excision base cryotherapy if sclera is involved and the extent of involvement is <3 clock hours
- Postoperative adjuvant plaque brachytherapy if excision base is clinically detected to have been involved >3 clock hours and if the excision base is positive for tumor cells on histopathology. Since conjunctival melanoma is not radiosensitive, brachytherapy is not used as a sole treatment
- Extended enucleation with en-bloc excision if the tumor has deep corneal or sclera invasion or intraocular extension
- Eyelid sparing exenteration if the tumor extends into the orbit. Proton beam radiotherapy may be used as an alternative and/or adjunct to exenteration
- Systemic chemotherapy is administered with combination of IFN and interleukin-2 in disseminated melanoma.

Prognosis
Local recurrence after therapy is as high as 50–70% at 10 years. Overall mortality rate is 25% in 10 years and more than 30% in 15 years. Critical thickness that may serve as a prognostic factor, according to various studies implies a value between 0.8 and 4 mm. Conjunctival melanoma AJCC-TNM staging predicts the prognosis and outcome [Table 12].

Stromal Tumors of the Ocular Surface

Vascular stromal tumors

Pyogenic granuloma

Pyogenic granuloma is a misnomer; it is neither pyogenic nor a granuloma, but exuberant granulation tissue. It is a fibrovascular response to a tissue insult such as surgical or nonsurgical trauma or inflammation. It has rapid onset and progression and presents as fleshy, elevated, red, richly vascular mass. It can be round to ovoid, typically pedunculated, rarely broad-based, and even mushroom shaped. It may be seen in any part of the conjunctiva, limbus, and the cornea. Histopathologically, it is composed of granulation tissue with lymphocytes, plasma cells, scattered neutrophils, and numerous small caliber vessels.

Treatment
- Often responds to topical steroids when diagnosed early
- Excision at the base followed by cautery or cryotherapy to the excision base is the treatment of choice for larger, unsightly, symptomatic or bleeding pyogenic granuloma
- Along with excision, it is optimal to take care of the inciting factor if found to minimize the risk of recurrence. It is usual to find a suture knot or a foreign body at the base if the cause is prior surgery or trauma
- Exuberant recurrence can be treated with low dose plaque brachytherapy.
Capillary hemangioma

Capillary hemangioma is common in the eyelids but is less common in the orbit and uncommon in the conjunctiva [Fig. 12b]. Seen as diffuse red elevated lesion, it may present as a small conjunctival component of a predominant eyelid lesion in a neonate. It may uncommonly develop as an acquired lesion in adults.

It presents at birth along with the lid lesion involving the conjunctiva, growing over the initial several months and then regresses spontaneously over several years. Spontaneous regression is often complete by 4–5 years of age. Histologically, it is composed of lobules of proliferating endothelial cells separated by thin fibrous septa.

Management generally is observation until spontaneous regression. Intervention is indicated if the concurrent eyelid component is amblyogenic-is large enough to induce mechanical ptosis or astigmatism. Intervention is also considered if the lesion is unsightly, ulcerates and bleeds and relentlessly progresses. Typical primary intervention is intralessional steroid injection. Triamcinolone is used in the maximum dose of 6 mg/kg body weight. In general, one injection results in significant involution of the lesion. Injection may be repeated at 6–8 weeks interval if there is a suboptimal response. Dermatologists favor using high-dose oral steroids over 4–6 weeks. Systemic propranolol 2 mg/kg body weight is being tried as an alternative therapy with encouraging results. If the tumor does not respond to these measures or if there is an indication for an emergent management (as in ulcerated and bleeding lesions), controlled surgical excision or debulking may help.

Cavernous hemangioma

Cavernous hemangioma is a common orbital tumor, but relatively uncommon in the conjunctiva. It appears as red blue lesion in the deep conjunctival stroma. Histology shows dilated congested veins separated by connective tissue with smooth muscles in the walls of the blood vessels. Treatment is by surgical excision.

Varix

Varix refers to venous malformation of the conjunctiva that may range from an isolated single channel to dilated complex venous channels [Fig. 12c]. Often, it is the anterior extension of an orbital varix. Management is generally conservative by observation and symptomatic treatment.

Racemose hemangioma

Racemose hemangioma involves loops of dilated arteries and veins communicating directly without the interface of a capillary bed. The lesion is clinically seen as loops of dilated vessels in the conjunctival stroma with no evidence of a stimulus for such vascularization or planned direction. It may be associated with Wyburn-Mason syndrome. It is generally observed unless symptomatic or a cosmetic blemish.

Hemangiopericytoma

Hemangiopericytoma is known to be derived from the vascular pericytes but is recently considered to be a vascular entity of the solitary fibrous tumor. It is a very rare conjunctival tumor that presents as an elevated or pedunculated red mass, which is slowly progressive. A wide surgical resection with tumor-free margins is advocated.

Kaposi sarcoma

Kaposi sarcoma was a rare tumor before the AIDS era. It is a malignant tumor seen more frequently in immunocompromised individuals, specifically with HIV infection. Sometimes the conjunctival Kaposi sarcoma is the first sign of immunocompromised status. It clinically appears as single or multifocal vascular red conjunctival lesion, which may become confluent and resemble hemorrhagic conjunctivitis.

Treatment

- It is moderately responsive to IFN α-2a and chemotherapy and markedly responsive to low dose radiotherapy (800–2000 cGy).
- The current thinking is in favor of the immediate institution of highly active antiretroviral therapy. The tumor is known to involute with improved immune status.

Lymphangiectasia

When lymphatic channels in the conjunctiva are dilated and prominent, the condition is called lymphangiectasia. There exists a communication with conjunctival veins, and hence these dilated channels may often be filled with blood, termed hemorrhagic lymphangiectasia. Surrounding conjunctiva appears edematous and is occasionally associated with sub-conjunctival hemorrhage. It can occur spontaneously or after trauma or inflammation. It is intermittent with a resolution between episodes. No treatment is required unless it is a cosmetic blemish, and the patient is keen on excision.

Lymphangioma

Lymphangioma is a benign tumor of the lymphatic vessels that usually manifests in the first decade of life. It can occur as an isolated conjunctival lesion, but often represents a superficial component of an orbital lymphangioma. These are multiloculated lesions with dilated cystic spaces. Those that contain blood are called chocolate cysts. Histopathologically appears as nonencapsulated, irregular mass composed of numerous cyst-like channels that contain clear fluid, blood, or a combination of the two. The ectatic channels are lined by somewhat attenuated endothelial cells. These channels are separated by loose connective tissue that contains aggregates of small lymphocytes, sometimes forming lymph follicle.

Treatment

- Surgical debulking
- CO₂ laser-assisted debulking
- β-irradiation using strontium-90 applicator
- Brachytherapy is used with partial success.

Lymphoproliferative Tumors

They are of three major types of conjunctival lymphoproliferative lesions, varying from benign to malignant and present as a spectrum, but may appear identical clinically:

- Reactive lymphoid hyperplasia
- Atypical lymphoid hyperplasia
- Conjunctival lymphoma.

There is increasing emphasis that many conjunctival lymphomas may be low-grade B-cell lymphomas of the mucosa-associated lymphoid tissue type. In a third of patients,
conjunctival lymphoma manifests with coexisting systemic lymphoma. Patients usually present with a conjunctival mass. They may also present with nonspecific irritation, ptosis, epiphora, blurred vision, proptosis, and diplopia.

Conjunctival lymphoproliferative lesions appear as diffuse, slightly elevated pink mass, resembling smoked salmon. Seen mostly in the bulbar conjunctiva and fornix. Some appear in the caruncle and plica, but very rarely in the palpebral conjunctiva. In the unilateral cases chance of systemic lymphoma is 17%, and if bilateral the chance is 47%. Systemic lymphoma occurs in 15% of patients at 5 years and 28% in 10 years.

Histopathologically, conjunctival lymphoproliferative tumors are composed of solid sheets of lymphocytes, with overlap between benign reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, and malignant lymphoma. Benign reactive lymphoid hyperplasia is generally polymorphic, with well-differentiated lymphocytes and plasma cells, while lymphoma tends to be more monomorphic and poorly differentiated. Most are non-Hodgkin’s B-cell lymphomas whereas Hodgkin’s and T-cell lymphoma affect the conjunctiva rarely. Immunohistochemistry may be helpful in determining the cell types.

Prognostic factors for developing systemic lymphoma are fornicial or mid-bulbar location, multifocality, and bilaterality. There are several treatment options.

**Fibrous Tumors**

Fibrous tumours manifest generally as slowly progressive acquired white stromal tumors in adults. These could be a well-circumscribed lesion or multi-nodular. Common fibrous tumors affecting the ocular surface are fibrous histiocytoma and nodular fasciitis.

**Fibrous Histiocytoma**

It can be benign, locally aggressive, and malignant, seen in adults. Presents commonly as well-circumscribed to diffuse amelanotic mass, often in the limbus and frequently extends to involve the cornea. Deep in the conjunctiva and attached to the sclera. It has yellow color owing to the presence of histiocytes. Malignant transformation is extremely rare. Benign fibrous histiocytoma is completely excised while malignant fibrous histiocytoma may need radical excision with clear margins.

**Nodular Fasciitis (Pseudosarcomatous Fasciitis)**

It is thought to arise from the tenon’s capsule. It presents in the varied age group ranging from 3 to 81 years as a solitary white episcleral enlarging nodule at the limbus or over the sclera anterior to the insertion of one of the rectus muscle. The nodule may grow quickly and show signs of inflammation. Treatment is by complete surgical excision.

**Neural Tumors**

**Simple Neuroma**

Simple neuroma is soft mucosal neural tumors that appear in the conjunctiva and other mucous membrane in patients with MEN-2b. All such patients have prominent corneal nerves. Clinically, these lesions appear as pink-yellow and grow over time. There is significant association with medullary carcinoma of the thyroid.

**Schwannoma**

Schwannoma of the ocular surface are rare and can occur in any part of the conjunctiva. These present as pink or yellow elevated slow-growing lesion and may have mildly dilated conjunctival or episcleral nutrient vessels. Treatment is by complete excision along with the tumor capsule.

**Granular Cell Tumor**

Granular cell tumor, also known as myoblastoma, is extremely rare. Originally thought of having a striated muscle origin, recent suggestions are that it is of neural derivative, Schwann cell origin. It is seen as a pink elevated smooth mass of the
conjunctival stroma. Pseudoepitheliomatous hyperplasia of the overlying conjunctival epithelium is a recognized feature of this tumor. Treatment is by complete excision.

**Histiocytic Tumors**

**Xanthoma**

Xanthoma presents as a yellow subepithelial mass on the epibulbar surface. In xanthoma disseminatum, multiple limbal lesions are found in both the eyes.

**Xanthogranuloma**

Xanthogranuloma occurs as a solitary orange-pink stromal mass usually near the limbus in adults. There are isolated case reports of juvenile xanthogranuloma of the conjunctiva in children. Histopathologically, histiocytes admixed with Touton’s giant cell confirms the diagnosis. It is managed by observation for spontaneous resolution, topical or systemic steroids for cases that do not resolve, and excision in recurrent cases.

**Reticulohistiocytoma**

Reticulohistiocytoma is a benign conjunctival lesion that is often a part of the systemic disorder known as multicentric reticulohistiocytosis. It appears as a single painless mass localized to the cornea and limbus with evidence of systemic disease. Treatment is by complete excision.

**Myxoid Tumors**

Myxoid tumors are rare benign stromal tumors, manifesting as slowly growing, asymptomatic freely movable unilateral, soft, pink white lesions usually seen in the temporal bulbar conjunctiva. These can be associated with Carney complex. The presence of these lesions should prompt the evaluation of cardiac myxoma—a life-threatening condition. Histologically, they are hypocellular and are composed of stellate and spindle-shaped cells interspersed in the loose stroma.

**Rhabdomyosarcoma**

The occurrence of rhabdomyosarcoma in the conjunctiva alone is rare—it generally has an orbital component. Most commonly the embryonal type manifests with a conjunctival component. Botryoid rhabdomyosarcoma may be seen in the conjunctival fornices. Rhabdomyosarcoma presents as a pink, rapidly growing vascular conjunctival mass. It may appear as a pedunculated soft tissue mass but occasionally swelling and erythema precede the visible tumor. Complete surgical excision with protocol-based adjuvant chemotherapy and radiotherapy is the treatment of choice for rhabdomyosarcoma localized to the conjunctiva.

**Lipomatous Tumors**

**Lipoma and liposarcoma**

Lipoma is usually seen in adults. It appears as yellow pink stromal mass. Liposarcoma is clinically similar to lipoma but histopathology reveals neoplastic stellate lipid cells and signet ring cells have been observed.

**Choristoma**

Choristoma is a congenital lesion representing the excess of normal tissue in an abnormal location. It is considered a complex choristoma when a combination of displaced tissue is involved. Epibulbar choristomas are generally found in children, dermoid and dermolipoma being most common. Usually locations are cornea, limbus, and episclera. Epibulbar choristomas can be associated with eyelid and uveal coloboma, Goldenhar syndrome or organoid nevus syndrome [Fig. 15a].

**Dermoid**

Epibulbar dermoid is a well-circumscribed yellow white solid lesion involving the corneoscleral limbus. It most commonly occurs at the inferotemporal limbus and has fine white hairs that are best seen with slit lamp biomicroscopy. It is not uncommon to see them associated with Goldenhar syndrome [Fig. 15a]. Rarely, it can extend to the central cornea or be located in the other quadrants. In addition to becoming a cosmetic blemish, can cause severe astigmatism and amblyopia in some cases. Histopathologically, epibulbar dermoid is a simple choristomatous malformation that consists of dense fibrous tissue lined by conjunctival epithelium with deeper dermal elements including hair follicles and sebaceous glands.

**Treatment**

Observation alone is preferred if the dermoid is small and does not cause visual symptoms. Larger demoids can be excised by lamellar keratosclerectomy with amniotic membrane grafting if the defect is superficial or closure using lamellar or full thickness corneal or sclerocorneal graft if the defect is deep or full thickness. While the cosmetic appearance does improve with surgery, the astigmatic error and visual acuity may not change significantly unless the child is treated early.

**Dermolipoma**

Although dermolipoma is congenital and present at birth, it typically remains asymptomatic for years and may not be detected until adulthood. The lesion presents as a pale yellow, soft, fluctuant, mass protruding from the orbit through the conjunctival fornix superotemporally. Unlike herniated orbital fat, dermolipoma may show the fine white hair on its surface. Histopathologically, it is lined by conjunctival epithelium on its surface, and sub-epithelial tissue has variable quantities of collagenous connective tissue and adipose elements. Pilosebaceous units and lacrimal gland tissue may occasionally be present.
Treatment
No treatment is required unless for cosmetic considerations or in symptomatic patients with exuberant hair growth over the lesion. Visible portion of the dermolipoma may be debulked, and the ocular surface reconstructed with amniotic membrane graft.

Caruncular Tumors and Cysts
The caruncle is a unique anatomic structure containing elements of both conjunctiva and skin. The lesions occurring in the caruncle are similar to those that occur in mucous membranes and cutaneous structures. By histopathological analysis, 95% of the caruncular lesions are benign, and 5% are malignant. The most common lesions in the caruncle include papilloma and nevus. Other lesions of caruncle include pyogenic granuloma, inclusion cysts, sebaceous hyperplasia, sebaceous adenoma, and oncocytoma. Oncocytoma is a benign tumor that occurs more commonly in the lacrimal or salivary glands. It probably arises from the accessory lacrimal gland tissue in the caruncle. Malignant tumors occurring rarely in the caruncle are SCC, melanoma, lymphoma, and sebaceous carcinoma. [Fig. 16a and b] Treatment includes either observation or local resection, depending upon the diagnosis.

Metastatic and Secondary Tumors
Metastatic tumors
Metastatic tumors are rare, but conjunctival metastasis can occur from breast carcinoma, cutaneous melanoma, or other primary tumors. They appear as one or more fleshy pink

Figure 16: Caruncular tumors. (a) Pigmented caruncular nevus. (b) Squamous cell carcinoma arising from the caruncle
vascularised conjunctival stromal tumors. Metastatic melanoma to the conjunctiva is usually pigmented.[1,2,9]

Leukemic infiltrate
Conjunctival leukemic infiltrate is associated with acute myeloid leukemia. It is often an early sign of relapse of previously treated disease. It may be unilateral or bilateral with focal or diffuse lesions in the bulbar or palpebral conjunctiva.[2]

It has a spectrum of presentation, ranging from subconjunctival hemorrhage to direct infiltration of the tissue with leukemic cells but often manifests as a firm, nontender, pink smooth mass associated with hemorrhage.[10] It has the tendency to appear in the perlimbal tissue near the cornea.

Secondary tumors
The conjunctiva can be secondarily involved by tumors of adjacent structures, particularly by direct extension from the tumor of the eyelid. Intraocular and orbital tumors may also extend into the conjunctiva. Most important is the sebaceous gland carcinoma of the eyelid which can exhibit pagetoid invasion and direct invasion into the conjunctival epithelium.[1,2] Uveal melanoma can extend extrasclerally into the subconjunctival tissues. Rhabdomyosarcoma of the orbit in children occasionally presents first with its conjunctival component.

Conclusion
Tumors of the ocular surface have a wide clinical spectrum. It is possible to make an accurate clinical diagnosis in most cases. Benign tumors and choristomas are excised only if there is a cosmetic or functional concern. Malignant tumors generally need complete excision with clear margins and excision edge cryotherapy. Prognosis for local tumor control is excellent with protocol-based management.

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