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CLINICAL APPROACH TO NEOPLASTIC DISORDERS OF THE CONJUNCTIVA AND CORNEA

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- Ocular surface tumors of the conjunctiva and cornea are considered together because the lesions can affect both tissues concurrently.
- Ocular surface tumors are associated with a spectrum of conditions, from benign to premalignant to malignant neoplasia, often with similar clinical appearance and presentation.

These lesions are classified by cell type:

1- Epithelium

2- Melanocyts and nevus cells

3- Vascular endothelium and mesenchymal cells

4- Lymphocytes

The most common ocular surface malignant tumors:

- **Malignant melanoma**
- **Squamous cell carcinoma**
- **Lymphoma**

Approach to the Patient With a Neoplastic Ocular Surface Lesion:

- **History**: sun exposure, prior skin cancer, immunosuppression, duration and changes in the lesion appearance, The racial or ethnic background of the patient.

Evaluation of the patient with a suspicious ocular surface lesion:

- complete eye examination(including a dilated fundus examination, entire ocular surface including the superior fornix)

- Palpation for lymphadenopathy in the neck and preauricular region especially when malignancy is suspected (eg, conjunctival melanoma)

CLINICAL CHARACTERISTICS OF THE LESION:

- Size and shape
- Involvement of the bulbar or palpebral conjunctiva, fornix, limbus or cornea
- Flat or elevated
- Pigmented or amelanotic
- Solid or cystic
- Fixed to underlying tissues or mobile
- Vascularity, presence of feeder vessels
- Single or multifocal

Note :

It is important to **document the appearance** and extent of the lesion, using either photographs or a detailed diagram

This aids in surgical planning if the lesion is to be removed or in following the lesion if observation is recommended

Management of Patients With Ocular Surface Tumors:

Observation:

- Many lesions are not suspicious for malignancy(eg, inclusion cysts).
- Others will be indeterminate: regular(annual or even more frequent) ophthalmic examinations are essential.
- If growth or suspicious changes in the lesion are observed, surgery or topical chemotherapy is usually indicated.

Findings that raise concern for malignancy in such lesions:

- enlargement
- elevation
- extensive pigmentation, even if lesion is flat
- fixation to underlying tissues
- large feeder vessel

Management of Patients With Ocular Surface Tumors:

Optical biopsy(noninvasive imaging technologies):

-optical coherence tomography(OCT)

-confocal microscopy

-ultrasound biomicroscopy (UBM)

May assist the clinician in deciding whether to continue observation or proceed with surgical excision, chemotherapy, or other treatment options

Management of Patients With Ocular Surface Tumors:

Surgical resection:

Advantages: Providing tissue for definitive histopathological diagnosis/ Confirmation of clear margins/Immediate results/Cost efficiency due to fewer medications and office visits.

Disadvantages: incomplete treatment of microscopic, subclinical disease/Scarring and symblepharon/If more than two-thirds of limbal epithelium is removed, stem cell deficiency and chronic epitheliopathy

Principles of surgical excision of ocular surface tumors:

- Performing a complete excision with 2 to 4 mm clear margins
- Using the “no-touch technique” to prevent tumor seeding
- Administering cryotherapy to surrounding conjunctival andlimbal margins and applying absolute alcohol or cryotherapy to involved and surrounding corneal epithelium for squamous cell or melanocytic tumors

Principles of surgical excision of ocular surface tumors:

Evaluation by an ophthalmic pathologist

The lesion edges labeled with suture to indicate the orientation Immunostaining can help in distinguishing benign from malignant lesions.

The clinical history is relevant to the pathologist's interpretation (the age and race or ethnicity of the patient, the duration of the lesion, and whether the lesion has changed clinically)

Management of Patients With Ocular Surface Tumors:

Topical Chemotherapy:

(alternative to surgical excision for primary treatment of ocular surface tumors or as adjunctive therapy preceding or following surgical excision)

-Advantage: treating beyond areas of clinically visible involvement.

-Disadvantage: it does not provide the opportunity for histologic diagnosis or the determination of clear margins.

Topical chemotherapeutic agents:

INF-α2b: 1 million IU/ml solution

Better tolerated than 5-FU and MMC, but may require longer treatment and greater expense

5-FU: 1%

MMC: 0.02% solution

Less likely to be tolerated than INF-α2b or 5-FU but more effective

Ocular surface toxicity: ocular pain, hyperemia, keratitis, corneal erosion, and limbal stem cell deficiency

Tumors of Epithelial Origin:

Benign Epithelial Tumors (conjunctival papilloma):

-Pedunculated papilloma

- Sessile papilloma

Ocular Surface Squamous Neoplasia (OSSN):

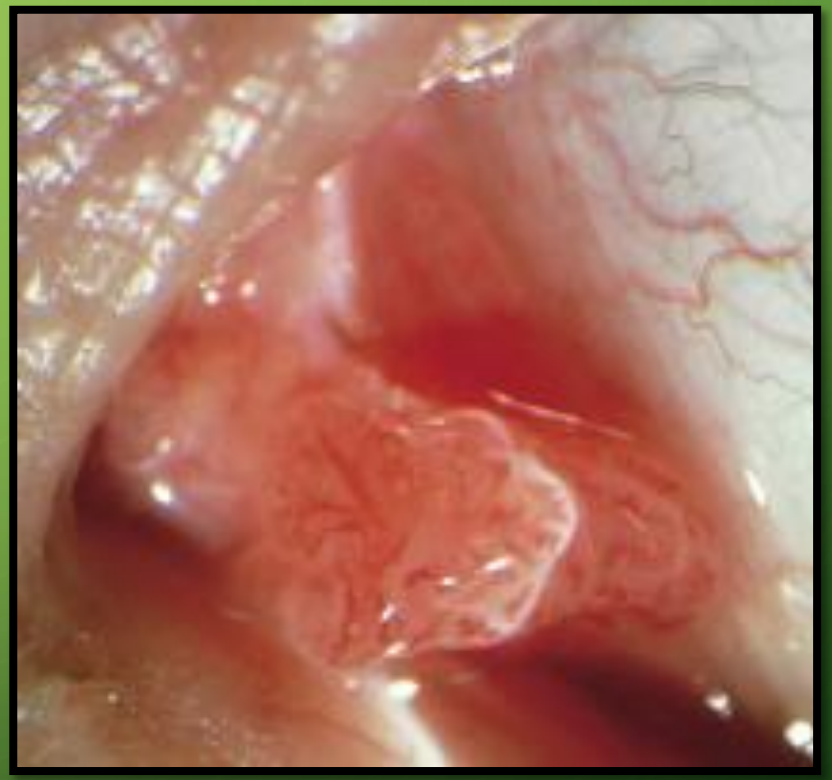
-Noninvasive OSSN: conjunctival or corneal interaepithelial neoplasia

-Invasive OSSN: squamous cell carcinoma

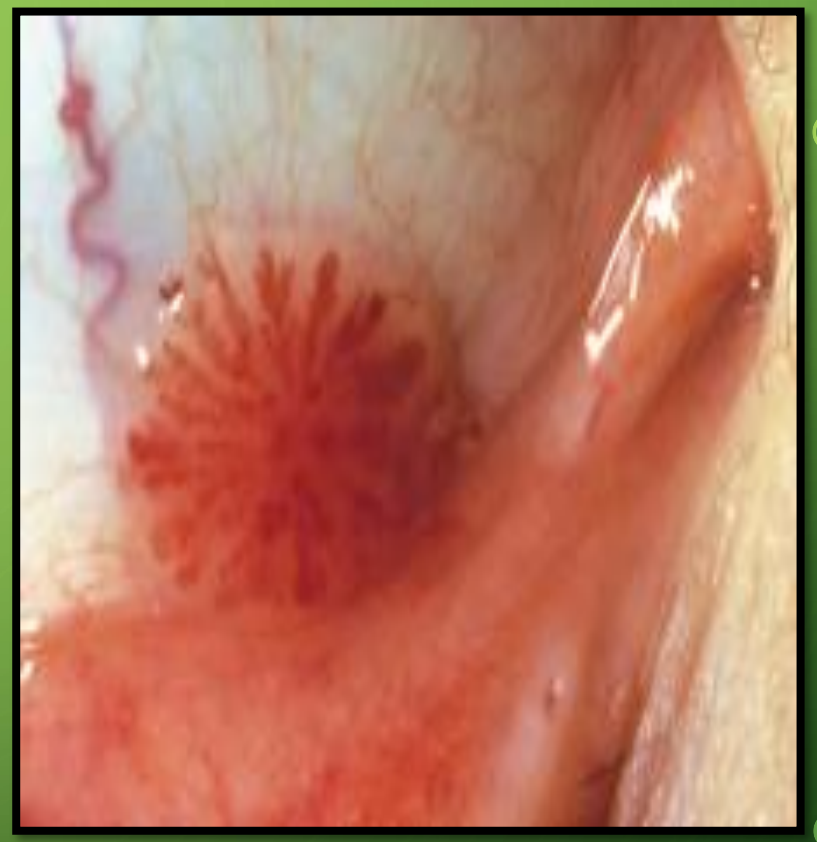
PEDUNCULATED PAPILLOMA:

Fleshy, exophytic growth with a fibrovascular core

It often arises in the inferior fornix but can also present on the tarsal or bulbar conjunctiva or along the plica semilunaris.



SESSILE PAPILLOMA :



Typically found at the limbus and has a flat base With its glistening surface and numerous red dots (resembles a strawberry)

The lesion may spread onto the cornea.

Signs of dysplasia:

leukoplakia(keratinization), symblepharon formation, inflammation, and invasion.

Conjunctival papilloma(pathogenesis):

Human papillomavirus (**HPV**), subtypes 6 and 11 (in children) or 16 (in adults), may initiate a neoplastic growth of epithelial cells with vascular proliferation that gives rise to a pedunculated conjunctival papilloma.

A sessile lesion, though also usually benign, may represent a dysplastic or carcinomatous lesion, especially when caused by HPV subtypes 16, 18, or 33

Conjunctival papilloma (management):

-Pedunculated papilloma that is small, cosmetically acceptable, and nonirritating may be observed

-Surgical excision with cryotherapy or cautery to the base of the lesion is curative in approximately 90% of cases(surgical manipulation should be minimized to reduce the risk of dissemination of the virus to uninvolved healthy conjunctiva)

- Adjunctive treatment with topical INF- α2b or oral cimetidine may be beneficial in cases of extensive or recalcitrant lesion

Conjunctival papilloma(management):

- Sessile limbal papilloma must be observed closely or excised.

- If the lesion enlarges or shows clinical features suggesting dysplastic or carcinomatous growth, excisional biopsy with adjunctive cryotherapy is indicated.

Ocular Surface Squamous Neoplasia (OSSN):

A wide spectrum of conjunctival and corneal squamous tumors that may have similar clinical findings but require biopsy for differentiation.

The traditional categorization of OSSN lesions:

-conjunctival or corneal intraepithelial neoplasia(**CIN**)

-**squamous cell carcinoma**(on the basis of histologic criteria)

OSSN(Risk factors):

- ultraviolet light exposure
- prior skin cancer
- older age
- male sex
- smoking
- HPV and HIV
- Systemic immunosuppression

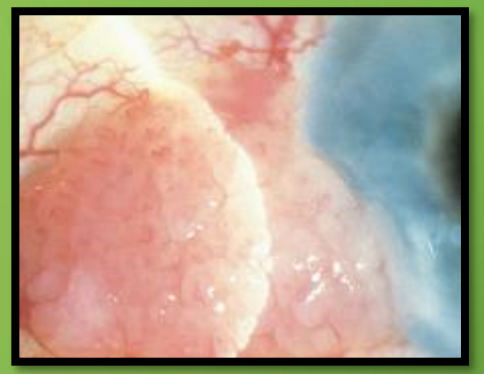
Noninvasive OSSN: Conjunctival or corneal intraepithelial neoplasia (CIN)

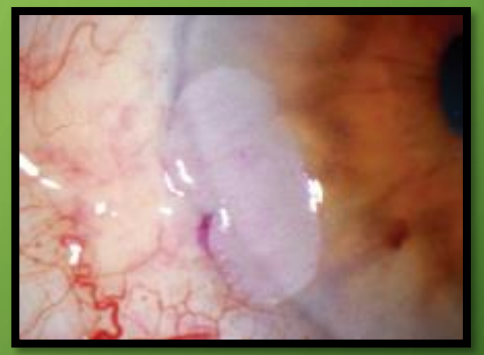
- In CIN, the dysplastic process **does not involve the underlying basement membrane**

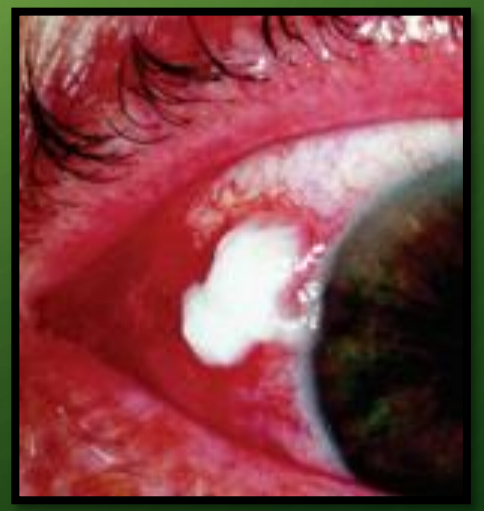
- CIN is considered a **premalignant** condition that is at risk of transforming into squamous cell carcinoma

CIN :

- Slow-growing tumors that are nearly always centered at the **limbus**.
- Mild **inflammation** and abnormal **vascularization** may accompany CIN
- Large feeder blood vessels indicate an increased probability of invasion beneath the epithelial basement membrane.

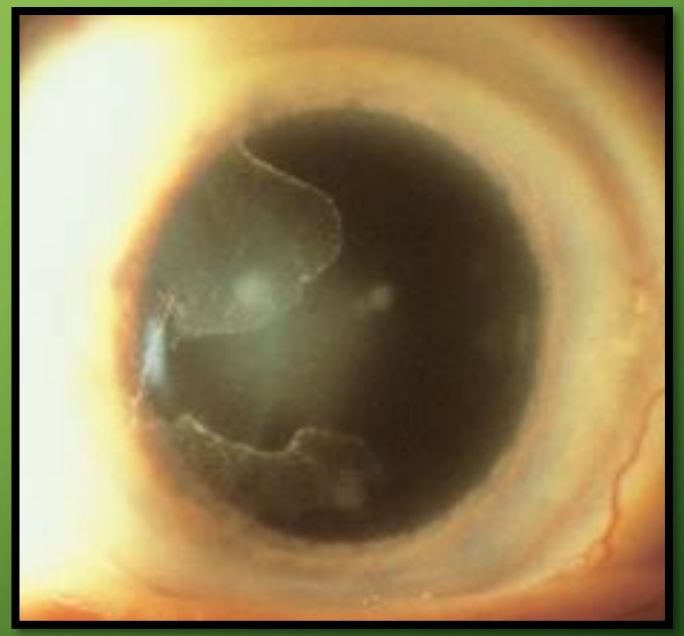






CIN(CORNEAL INVOLVEMENT):

- Translucent, **mildly elevated gray epithelial sheet** that is based at the limbus and extends onto the cornea
- The edges of corneal lesions have characteristic **pseudopodia like extensions**
- Topical rose Bengal and lissamine green staining can help define the extent of the lesion.

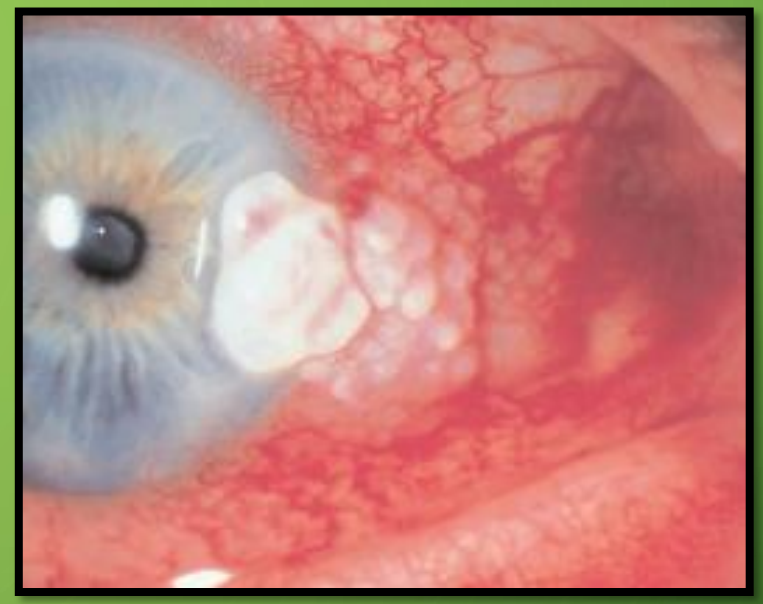


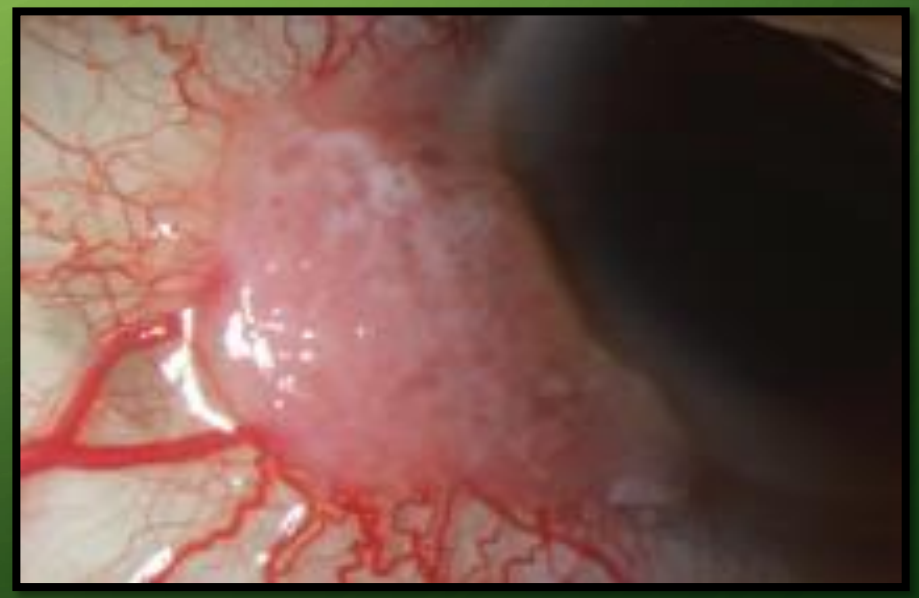
INVASIVE OSSN:(SCC)

- In squamous cell carcinoma (SCC), involvement **extends beyond the basement membrane** into stroma, with metastatic potential.
- SCC is more common and aggressive in patients with **compromised immunity** and in those with **xeroderma pigmentosum.**

SCC:

- A plaquelike, gelatinous, or papilliform growth in **limbal and bulbar conjunctiva**, usually in the interpalpebral fissure zone.
- A broad base is often present along the limbus.
- It may appear **leukoplakic**.
- **Engorged conjunctival vessels** suggest malignancy.





OSSN(MANAGMENT) :

- All OSSN lesions should be regarded as possible carcinoma with metastatic potential because it may be difficult to distinguish dysplasia from invasive SCC clinically.

- Stable OSSN with benign appearance can be observed with **meticulous follow-up** exams including drawings, photographs, and imaging with OCT .

- Lesions that are growing or appear suspicious for malignancy should be treated with **surgical excision and/or topical chemotherapy**

OSSN(MANAGEMENT) :

- Success rates for treatment with topical INF-α2b, MMC, or 5-FU are similar at more than 85%, comparable to success rates seen with wide-margin surgical excision followed by cryotherapy.
- SCC can grow into the iris, trabecular meshwork, or the orbit, providing a portal to systemic circulation and metastasis
- Orbital invasion may require orbital exenteration(Radiation therapy may be indicated as adjunctive treatment in select cases).

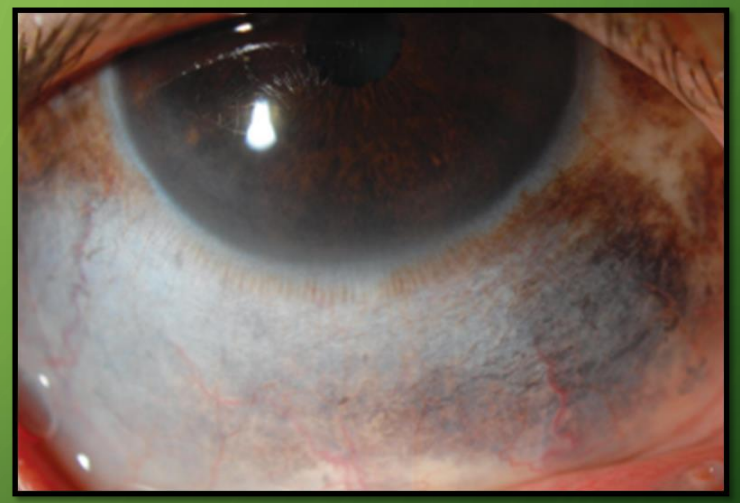
TOPICAL CHEMOTHERAPY:

- MMC can be used for a shorter duration than the other 2 agents (INF-α2b / 5-FU)typically for weeks rather than months but it may result in more severe adverse effects.
- MMC 0.2mg/ml is typically administered 4 times daily for 1 week, followed by a 1-week structured treatment interruption, for a maximum of 3 or 4 treatment cycles.
- The ocular pain and surface toxicity associated with topical chemotherapy can be reduced with fluorometholone eyedrops once or twice per day.

BENIGN PIGMENTED LESIONS:

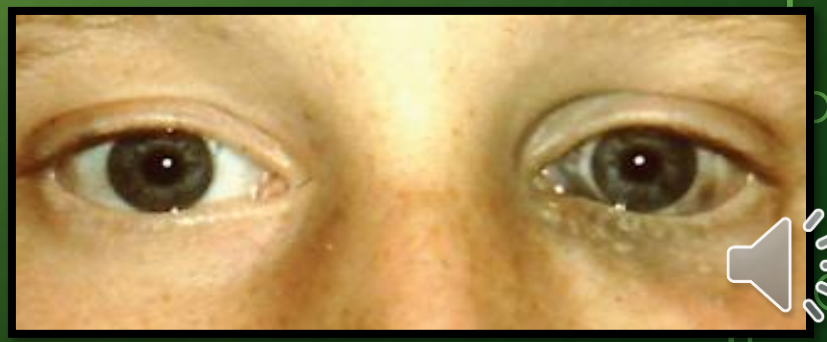
Ocular melanocytosis:

- focal proliferation of subepithelial melanocytes.
- Congenital melanosis of the **episclera** occurs in approximately 1 in every 2500 individuals and is more. common in Black, Hispanic, and Asian populations.
- Patches of episcleral pigmentation appear slate gray through the normal conjunctiva and are immobile and **usually unilateral**.



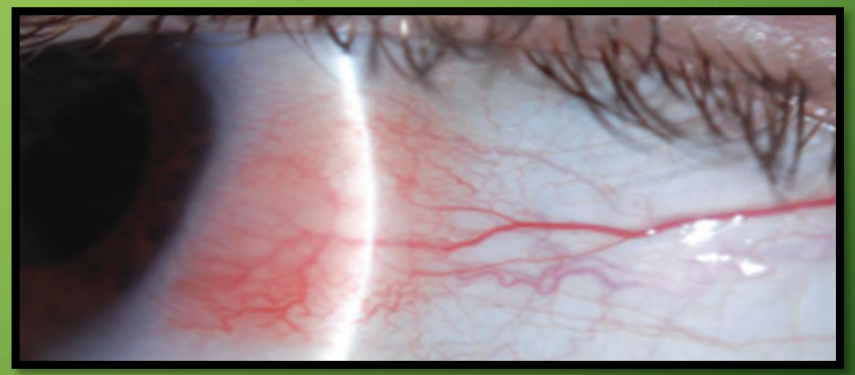
OCULODERMAL MELANOCYTOSIS OR NEVUS OF OTA

- In approximately 50% of patients with ocular melanocytosis, ipsilateral dermal melanocytosis and a proliferation of dermal melanocytes is present in the periocular skin of the first and second dermatomes of the fifth cranial nerve .
- Approximately **5% of cases are bilateral**
- In **10%** of patients with ocular melanocytosis, **secondary glaucoma** occurs in the affected eye
- Malignant transformation is rare.



CONJUNCTIVAL NEVUS:

- They arise during the first or second decade of life.
- Nevus near the limbus is usually almost flat and nevi appearing else where tend to be elevated.



- **Intralesional cysts are present in 50% or more**

(seldom in conjunctival melanoma).

- Pigmentation of conjunctival nevi is variable. (15% of cases are amelanotic)
- Mild enlargement associated with hormonal influences can occur at puberty or pregnancy, creating a clinical impression of conjunctival melanoma.

CONJUNCTIVAL NEVUS:(MANAGEMENT)

They can be **followed every 6–12 months**(serial photography or drawings)

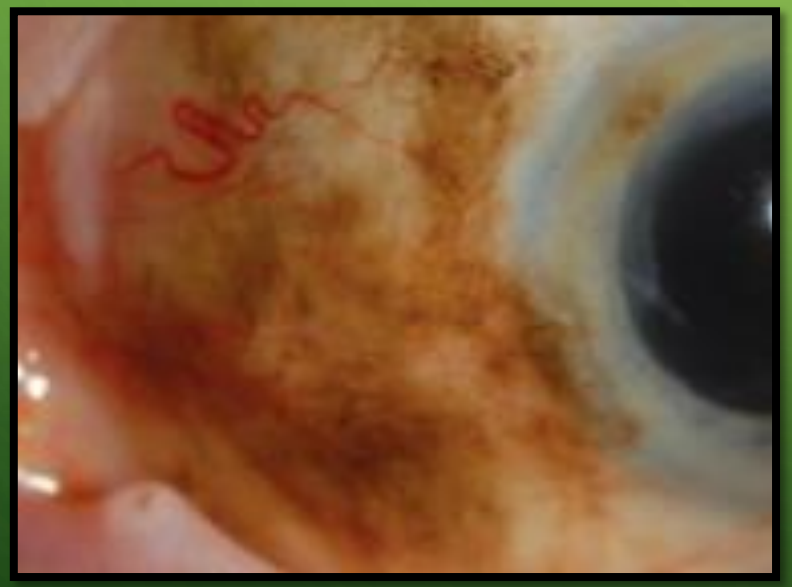
Patients should be instructed to periodically inspect the lesion, looking for changes in size, coloration, elevation, or vascularization

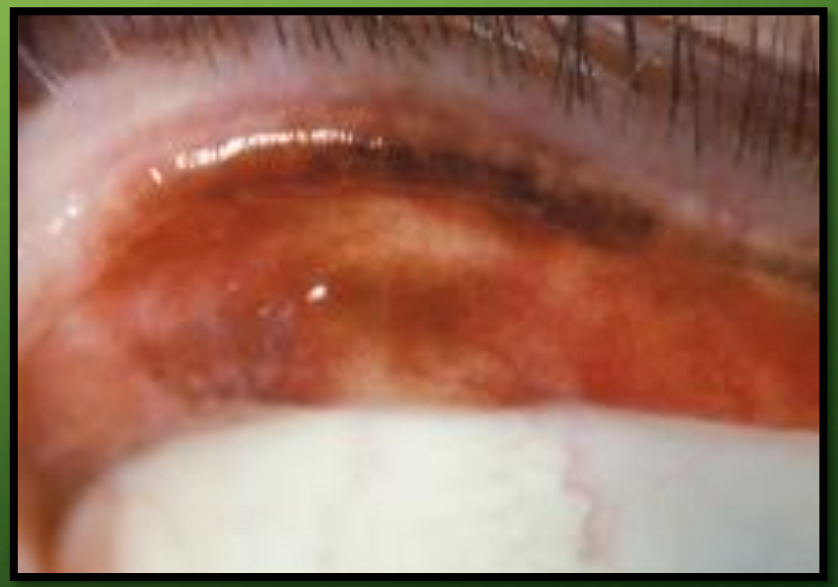
Lesions showing suspicious change or growth warrant an excisional biopsy

A biopsy can also be considered for pigmented lesions on the palpebral conjunctiva or cornea or in the fornix, because nevi are rare in these locations.

PRIMARY ACQUIRED MELANOSIS (PAM):

- Acquired noncystic, flat, patchy or diffuse, tan to brown pigmentation of the conjunctival epithelium
- PAM is usually unilateral or asymmetric if bilateral and is most often seen in individuals with fair skin.





PAM(MANAGEMENT):

- Most cases of PAM are benign, but a minority of cases may progress to melanoma.
- It is difficult to predict which lesions may progress, but a worse prognosis is associated with:
- larger size / caruncular, forniceal, or palpebral location / progressive enlargement / a nodular component / thickening / feeder vessels

PAM(MANAGEMENT):

- The most important finding in predicting progression to melanoma is the presence of cellular atypia.
- PAM without atypia has little malignant potential. These patients may be followed with examination every 6–12 months.
- PAM with mild atypia has a minimal risk of malignant transformation but should be followed more closely.
- PAM with moderate to severe atypia: 30% risk of progression to melanoma

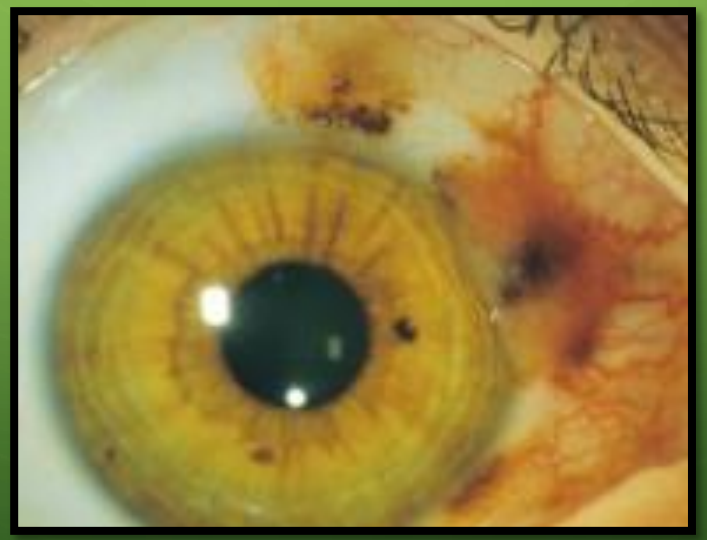
PAM(MANAGEMENT):

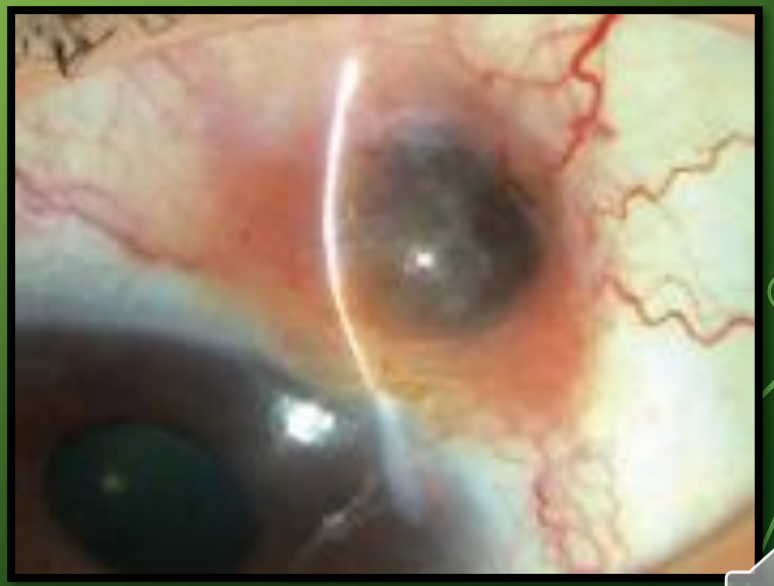
- Every effort should be made to eliminate all conjunctival pigment in patients with moderate to severe atypia.
- If the pigmentation is diffuse topical chemotherapy with MMC may be useful to treat the entire ocular surface.

CONJUNCTIVAL MELANOMA:

- Conjunctival melanomas may arise from PAM (70%) or nevi (5%) or they may arise de novo (25%).

- the overall mortality rate is 25%.





CONJUNCTIVAL MELANOMA:

- They are most commonly found in the bulbar conjunctiva or at the limbus.
- The degree of pigmentation is variable (25% amelanotic).
- Recurrent melanomas are often amelanotic, even if the primary tumor was pigmented.
- Because heavy vascularization is common, these tumors may bleed easily.
- They grow in a nodular fashion and can invade the globe or orbit.

CONJUNCTIVAL MELANOMA:

Poor prognostic indicators :

- location in the palpebral conjunctiva, caruncle, or fornix
- invasion into deeper tissues
- thickness >1.8 mm
- involvement of the eyelid margin
- lymphatic invasion
- Conjunctival melanomas may metastasize to regional lymph nodes, the brain, lungs, liver, and bone.

OCULAR SURFACE MELANOMA (MANAGEMENT):

- complete wide margin (2- to 4-mm) surgical excision and cryotherapy to conjunctival margins.

- Adjunctive treatments: radiotherapy and topical chemotherapy with MMC.

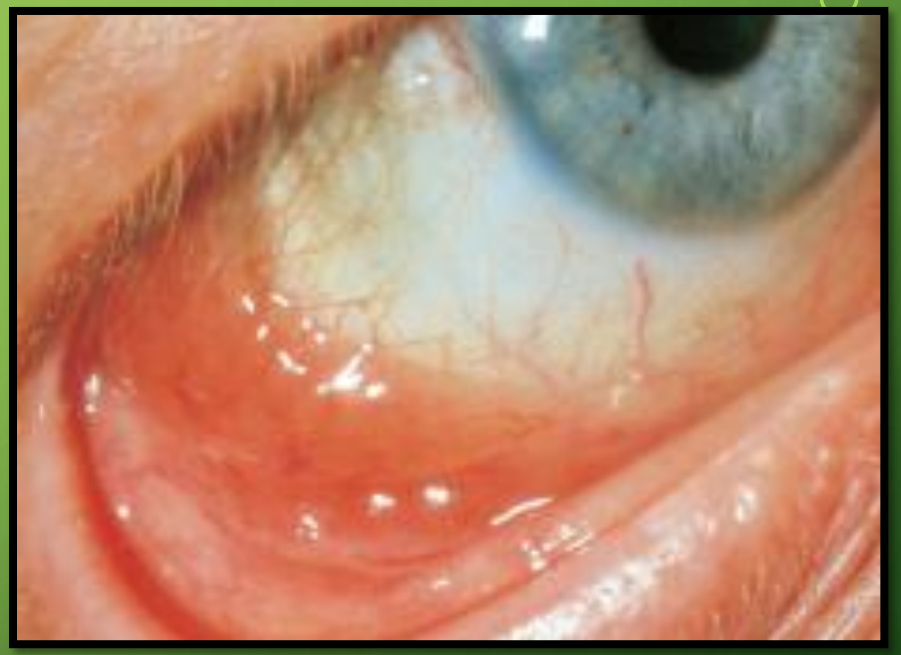
- Orbital exenteration is occasionally performed in cases of advanced disease.

CONJUNCTIVAL LYMPHOID HYPERPLASIA :

- Minimally elevated, salmon colored subepithelial tumor that usually has a smooth surface.

-The lesion is often moderately or highly vascularized.

- Lymphoid hyperplasia is clinically indistinguishable from conjunctival lymphoma and requires biopsy to differentiate.

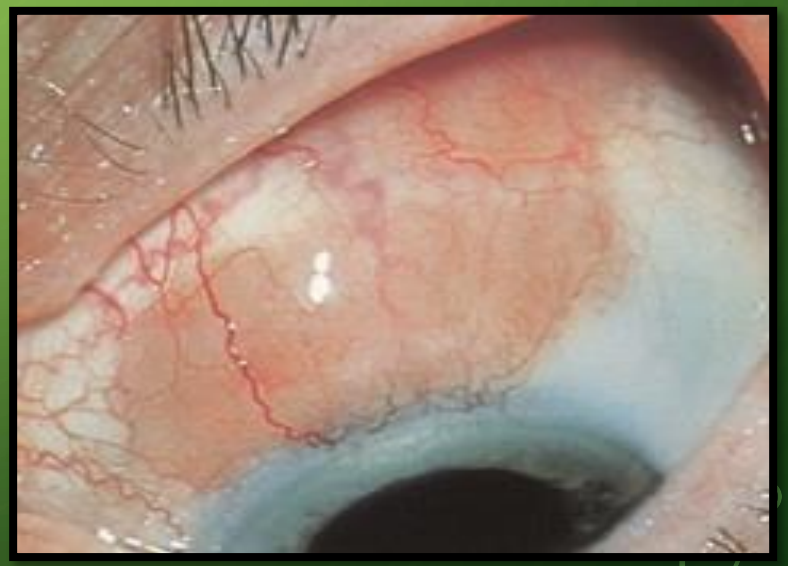


LYMPHOID HYPERPLASIA (MANAGEMENT):

- May resolve spontaneously
- These lesions can be treated with local excision, topical corticosteroids, or radiation.
- Because systemic lymphoma could potentially develop in a patient with an apparently benign polyclonal lymphoid lesion, general medical consultation is advisable.

CONJUNCTIVAL LYMPHOMA:

- The same clinical appearance as benign lymphoid hyperplasia.
- It appears as a mobile, salmon-pink mass on the conjunctiva.
- It is typically unilateral
  (20% of patients have bilateral lesions).
- Conjunctival lymphoma can also masquerade as a chronic follicular conjunctivitis.



CONJUNCTIVAL LYMPHOMA:

- It usually occurs in immunosuppressed individuals or in persons older than 50 years and patients with Sjogren syndrome.
- Some conjunctival lymphomas are limited to the conjunctiva; others occur in conjunction with systemic malignant lymphoma.
- Histopathology is required to differentiate conjunctival lymphoma from benign lymphoid hyperplasia.
- Conjunctival lymphoma predominately occurs as a B-cell non-Hodgkin lymphoma.

CONJUNCTIVAL LYMPHOMA: (MANAGEMENT):

- Patients should be referred to an oncologist for systemic evaluation (underlying systemic lymphoma: 31% of these patients).
- Small tumor: Remove completely.
- Local low dose external-beam radiation therapy.
- Intralesional INF-α2b.
- Systemic chemotherapy is required for the treatment of systemic lymphoma.