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Illustrated Manual of CORNEA

Diagnosis & Treatment

Uma Sridhar



Forewords

Christopher J Rapuano

Gullapalli N Rao

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Contents

1. **Slit Lamp and Examination Techniques** 1
   Kunwar Vikram Singh Dhaliwal, Uma Sridhar
2. **Anatomy of Conjunctiva, Cornea, Sclera, and Tear Film** 17
   Uma Sridhar
3. **Drawing the Cornea** 25
   Uma Sridhar
4. **Ocular Allergies** 29
   Uma Sridhar
5. **Conjunctivitis** 43
   Uma Sridhar
6. **Drug Toxicity** 71
   Uma Sridhar
7. **Dry Eye Disease** 79
   Hafsa Bashir, Jyoti Batra, Uma Sridhar
8. **Ocular Surface Disorders** 122
   Jyoti Ohri, Uma Sridhar
9. **Chemical Injury** 144
   Santosh Suman, Paras Mehta, Uma Sridhar
10. **Pterygium** 160
    Uma Sridhar
11. **Acne Rosacea** 179
    Uma Sridhar
12. **Contact Lenses** 189
    Yogeshwari Bansal, Uma Sridhar
13. **Infective Keratitis** 207
    Meena Lakshmipathy, Paras Mehta, Uma Sridhar
14. **Postoperative Infections** 319
    Uma Sridhar
15. **Trauma** 331
    Uma Sridhar
16. **Ectatic Disorders of Cornea** 340
    Uma Sridhar

17. Iridocorneal Endothelial Syndrome **369**
Aparna Rao, Uma Sridhar

18. Congenital Disorders **372**
Aparna Rao, Meena Lakshmipathy, Uma Sridhar

19. Peripheral Ulcerative Keratitis and Peripheral Corneal Disorders **388**
Paras Mehta, Uma Sridhar

20. Conjunctival and Corneal Degenerations **408**
Uma Sridhar

21. Corneal Dystrophy **427**
Uma Sridhar

22. Keratoplasty **452**
Santosh Suman, Paras Mehta, Uma Sridhar

23. Tumors of the Ocular Surface **496**
Shaifali Chahar, Fairooz P Manjandavida, Santosh G Honavar

24. Systemic Diseases Affecting the Cornea **535**
Uma Sridhar

25. Refractive Procedures **546**
Kanika Bhardwaj, Uma Sridhar

26. Corneal Tomography **568**
Uma Sridhar

27. Anterior Segment Optical Coherence Tomography **601**
Rajib Mukherjee, Uma Sridhar

28. Specular Microscopy **642**
Fareed Ahmad, Kunwar Vikram Singh Dhaliwal, Uma Sridhar

29. Clinical Confocal Microscopy **659**
Aravind Roy, Pravin K Vadavalli

30. Episclera and Sclera **666**
Shahana Mazumdar, Uma Sridhar

31. Differential Diagnosis **687**
Uma Sridhar

Index *749*

CHAPTER 23

Tumors of the Ocular Surface

Shaifali Chahar, Fairooz P Manjandavida, Santosh G Honavar

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INTRODUCTION

The ocular surface constitutes a dynamic anatomical and physiological interface comprising the eyelids, blink reflex, tear film, lacrimal glands, conjunctival lining over the bulbar and palpebral regions, corneal epithelium, and Bowman's layer.[1] This unified system plays a vital role in ocular protection, lubrication, and vision. The anatomical diversity makes the ocular surface a potential site for the development of a wide range of tumors. Neoplastic lesions may arise from epithelium, stroma, melanocytes, caruncle, or even secondary metastatic sources. These lesions are frequently encountered across various ophthalmic specialties, including general ophthalmology, cornea, and ocular oncology, and hence it is important to recognize and appropriately identify them. This chapter provides a comprehensive overview of ocular surface tumors, spanning the spectrum from benign to malignant lesions, and highlights current trends in their diagnosis and management.

ANATOMY

The conjunctiva is a delicate, transparent, and vascularized mucous membrane that lines the inner surface of the eyelids and extends to cover the anterior aspect of the globe. It is anatomically divided into three distinct regions: (1) The bulbar conjunctiva, which includes the corneoconjunctival junction or limbus; (2) the forniceal conjunctiva, forming the superior, inferior, medial and lateral conjunctival fornices; and (3) the palpebral conjunctiva, which lines the posterior aspect of the eyelids and continues to the mucocutaneous junction at the lid margins.

HISTOLOGY

Two primary structural layers are seen: The epithelium and the underlying stroma.

1. *Epithelium:* It transitions seamlessly from the corneal epithelium at the limbus and continues into the epidermis at the lid margin via the mucocutaneous junction. It is composed of stratified, nonkeratinized squamous cells. The bulbar and palpebral regions predominantly feature cuboidal cells, while the forniceal areas contain stratified columnar cells. Melanocytes are distributed within the basal layer, and goblet cells, most densely concentrated in the lower fornix, play a crucial role in mucin production.
2. *Stroma (substantia propria):* Beneath the epithelium lies a fibrovascular connective tissue framework composed of collagen, elastin, lymphatic channels, blood vessels, and nerves. It also contains the accessory lacrimal glands of Krause and is interspersed with immune cells including lymphocytes, plasma cells, mast cells, and neutrophils. The conjunctival stroma, like other mucosal tissues, is associated with conjunctiva-associated lymphoid tissue (CALT), supporting its immunological functions.

Caruncle: Located at the medial canthus, caruncle is a unique structure composed of both conjunctival and skin-type elements. Histologically, it includes conjunctival epithelium, hair follicles, sebaceous glands, sweat glands, and accessory lacrimal tissue.

Plica semilunaris: Adjacent to the caruncle, this crescent-shaped fold of conjunctiva features a thick epithelial covering and a richly vascularized stromal base.

CLASSIFICATION OF OCULAR SURFACE TUMORS

The tumors of conjunctiva are grouped into two major categories, i.e., congenital and acquired lesions. **Tables 1 to 3** summarizes classification of ocular surface tumors. The World Health Organization (WHO) classification of tumors of conjunctiva and caruncle

provides an evidence-based taxonomy to standardize diagnostic practices worldwide and to promote translational research on cancer. **Table 4** summarizes the 5th edition of the WHO classification (WHO Eye5) of tumors of conjunctiva and caruncle.[2]

CONGENITAL LESIONS OF THE OCULAR SURFACE

Choristomas

Choristomas are congenital anomalies characterized by the presence of histologically normal tissue located in an ectopic anatomical site (*Remember: Choristomas is normal tissue at abnormal location; hamartoma is abnormal tissue at normal location*). When composed of a single tissue type, they are termed simple choristomas, whereas lesions containing a heterogeneous mix of ectopic tissues are referred to as complex choristomas.

Among ocular surface lesions in children, epibulbar choristomas are the most frequently encountered. The most common subtypes include dermoid and dermolipoma, which often present at the limbus or in the superotemporal quadrant respectively. These lesions may occur in isolation or associated with eyelid or uveal coloboma. They can be a part of systemic syndromes such as Goldenhar syndrome or organoid nevus syndrome.[3]

TABLE 1: Classification of tumors of the ocular surface.

S. No	*Type*	*Subtypes*
1.	Congenital	• Choristomas • Hamartomas
2.	Acquired	• *Epithelial:* – Nonmelanocytic – Melanocytic • *Stromal:* – Lymphoproliferative – Vascular – Fibrous – Neural – Histiocytic – Myogenic – Lipomatous • Caruncular • Metastatic and secondary

Dermoid

Dermoids are congenital, benign epibulbar growths most commonly located at the inferotemporal limbus. They are considered a type of simple choristoma composed of dermal elements and represent one of the most frequently encountered ocular surface tumors in pediatric patients.

Clinical Presentation

They typically appear as well-defined, yellowish-white, and firm masses. Fine hair may be seen protruding from the surface, especially on slit-lamp examination, a feature that can help clinch the diagnosis **(Figs. 1A and B)**. The size can range from small, localized nodules to large lesions extending across the cornea, involving the anterior chamber or even the iris. When the corneal surface is significantly involved, these lesions can induce high astigmatism and lead to amblyopia if not addressed during the visual development period. Classic grading system is used to grade the dermoid based on size and extent of corneal involvement. Corneal dermoid is also a known entity.

TABLE 2: Epithelial tumors of conjunctiva.

S. No.	*Type*	*Benign*	*Malignant*
1.	Nonmelanocytic	• Squamous papilloma • Reactive hyperplasia • Keratoacanthoma • Dacryoadenoma • Hereditary intraepithelial dyskeratosis • Keratotic plaque • Actinic keratosis	• Conjunctival intraepithelial neoplasia (CIN) • Squamous cell carcinoma
2.	Melanocytic	• Conjunctival melanocytic nevi • Complexion-associated melanosis (CAM) • Primary acquired melanosis (PAM)	Conjunctival melanoma

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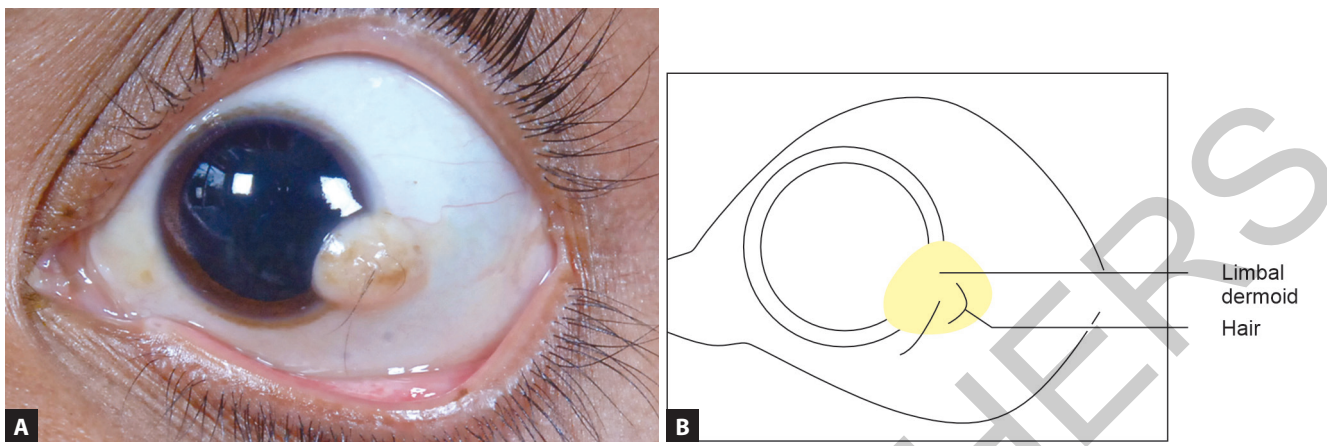
TABLE 3: Stromal tumors of conjunctiva.

S. No.	*Types*	*Benign*	*Malignant*
1.	Lymphoproliferative	Benign reactive lymphoid hyperplasia	Lymphoma
2.	Vascular	• Capillary hemangioma • Cavernous hemangioma • Varix • Racemose malformation • Lymphangiectasia • Lymphangioma • Hemangiopericytoma • Pyogenic granuloma	• Kaposi's sarcoma • Malignant hemangioendothelioma
3.	Fibrous	• Fibroma • Nodular fasciitis • Benign fibrous histiocytoma	• Fibrosarcoma • Malignant fibrous histiocytoma
4.	Neural	• Neurofibroma • Schwannoma	
5.	Histiocytic	• Xanthoma • Xanthogranuloma	
6.	Myxoid	• Myxoma • Conjunctival stromal tumor (COST)	
7.	Myogenic		Rhabdomyosarcoma
8.	Lipomatous	Lipoma	Liposarcoma
9.	Others	Amyloidosis	• Metastatic • Secondary tumors • Leukemic infiltrates

TABLE 4: The World Health Organization (WHO) Eye5: The 5th edition of the WHO classification of tumors of conjunctiva and caruncle.

1.	Tumor-like lesions and choristomas of the conjunctiva	*Cysts of conjunctiva and caruncle:* • Epithelial conjunctival inclusion cyst *Reactive, epithelial, and degenerative conjunctival lesions:* • Reactive epithelial hyperplasia • Papillary and follicular conjunctivitis • Pterygium and pinguecula *Choristomas:* • Epibulbar choristoma (dermoid, dermolipoma, and complex choristoma) • Epibulbar osseous choristoma	
2.	Epithelial tumors of conjunctiva	*Benign:* • Squamous papilloma • Oncocytoma • Hereditary benign intraepithelial dyskeratosis	*Premalignant and malignant:* • Conjunctival squamous intraepithelial neoplasia and carcinoma in situ • Conjunctival squamous cell carcinoma • Adenosquamous carcinoma
3	Melanocytic conjunctival tumors	*Benign:* • Benign epithelial melanosis • Junctional, compound, and subepithelial nevi • Inflamed juvenile conjunctival nevi • Blue nevus • WNT-activated deep penetrating/plexiform melanocytoma (nevus) • Combined nevus	*Premalignant and malignant:* • Conjunctival melanocytic intraepithelial neoplasia • Conjunctival melanoma

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Figs. 1A and B: Limbal dermoid with hair on the surface.

Histology

It is a simple choristoma, composed of dense fibrous connective tissue covered by nonkeratinized conjunctival epithelium. Deeper portions may include dermal structures such as hair follicles, sebaceous glands, and, occasionally, adipose tissue or cartilage depending on the lesion's depth **(Fig. 2)**.

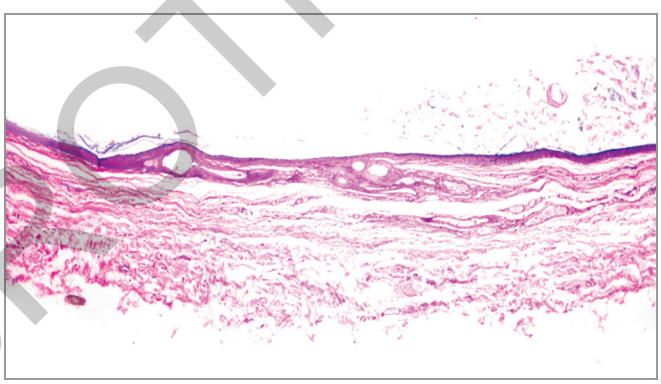


Fig. 2: Microphotograph of a dermoid (OM ×4) with dense fibrous tissue lined by conjunctival epithelium with deeper dermal elements including hair follicles and sebaceous glands.

Treatment

Observation is sufficient for very small, nonprogressive, and asymptomatic dermoids, unless parent or patient is concerned about the cosmesis. Surgical excision is recommended when the lesion interferes with vision, induces significant astigmatism, causes persistent irritation, dellen formation, or for cosmetic indications. Superficial lesions can be managed by lamellar keratosclerectomy followed by amniotic membrane transplantation. For deeper or full-thickness defects, lamellar or penetrating corneoscleral grafts may be required. While surgical removal improves cosmesis, visual outcomes depend on the degree of preexisting astigmatism and timely amblyopia management.

Systemic Associations

Dermoids may be isolated or associated with syndromes such as Goldenhar syndrome, CHARGE syndrome, VATER syndrome, SCALP syndrome, and nevus sebaceous of Jadassohn.[3] Systemic associations are more common in bilateral presentations **(Figs. 3A and B)**.

Dermolipoma

Dermolipoma is a congenital lesion that typically remains asymptomatic and may go unnoticed until adolescence or adulthood. It is considered a simple choristoma composed predominantly of adipose tissue and is most commonly located in the superotemporal quadrant of the conjunctiva, near the lateral canthus.

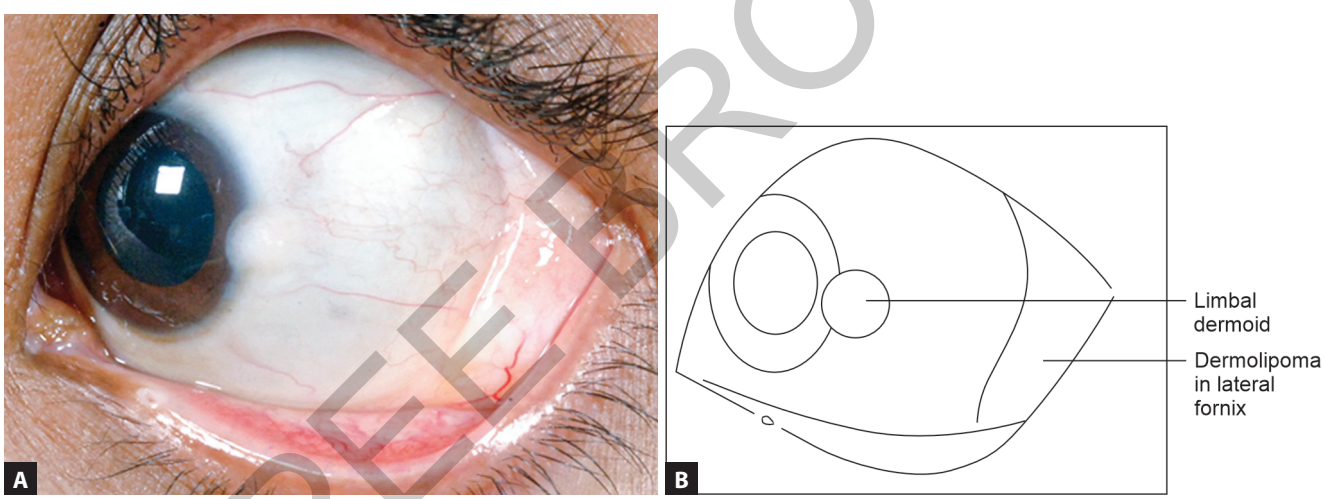
Clinical Presentation

Patients often present with a soft, whitish-yellow, and nontender subconjunctival fluctuant mass that appears to protrude most commonly from the superotemporal fornix, sometimes extending posteriorly into the orbit or anteriorly toward the limbus **(Figs. 4A and B)**. Surface examination often reveal fine hair. Most common differential is herniated orbital fat, a yellow mass seen in superotemporal area, which is an acquired condition, more commonly seen in older individuals, is freely mobile, often reducible into the orbit, and lack cilia/surface hair. Anterior surface of dermolipoma overlying the bulbar region is concave/flat and that of orbital fat prolapse is convex. Although

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Figs. 3A and B: Goldenhar syndrome: Apart from a limbal dermoid and preauricular tags, note the presence of bilateral upper lid colobomas.



Figs. 4A and B: Yellow-white smooth lesion in the lateral fornix indicating dermolipoma.

typical location is superotemporal, inferotemporal and bilateral lesions can also be encountered.

Dermolipoma manifesting as a yellow-white smooth lesion in the lateral fornix. Also note small limbal dermoid.

Histology

Dermolipomas are lined by conjunctival epithelium and contain mature adipose tissue intermixed with collagenous stroma **(Fig. 5)**. Occasional dermal adnexal elements such as hair follicles, sebaceous glands, or even accessory lacrimal gland tissue may be found within the lesion.

Management

Most dermolipomas do not require treatment unless they are cosmetically disfiguring, cause discomfort or raise concern about progression. In such cases, conservative surgical debulking of the visible portion can be performed. Care must be taken to avoid aggressive excision due to the lesion's proximity to lacrimal gland and extraocular muscle, and potential for deep extension. The ocular surface is typically reconstructed using an amniotic membrane graft following removal.

Other forms of simple choristomas involving the ocular surface include osseous choristoma and lacrimal

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gland choristoma. These both are rare congenital lesions; most commonly located in the superotemporal quadrant of the eye.

Complex Choristoma

Complex choristomas are congenital lesions composed of multiple tissue types originating from more than one embryonic germ layer. They are typically unilateral and can vary widely in their extent and tissue composition.

Clinical Presentation

These lesions can range in size from small, localized nodules to large, extensive masses involving the bulbar conjunctiva and cornea. Their clinical appearance depends on the predominant tissue elements, leading to variability in color, consistency, and surface features. In more extensive cases, they may encroach upon the visual axis or cause surface irregularity and induce astigmatism.

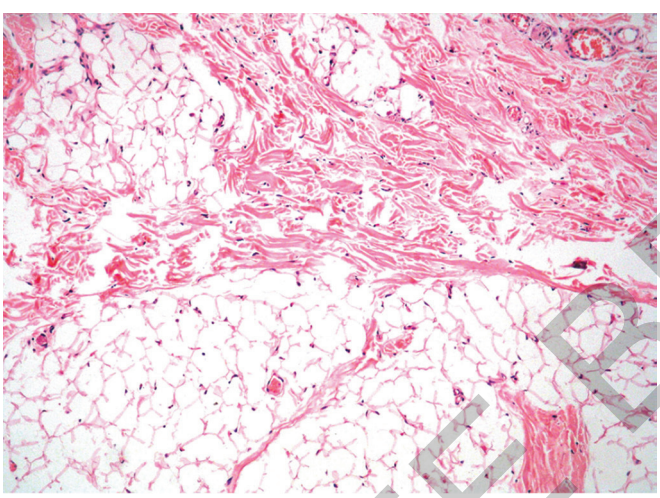


Fig. 5: Microphotograph of dermolipoma (OM ×10) showing conjunctival epithelium lining its surface and subepithelial tissue with collagenous connective tissue and adipose elements.

Histology

Microscopically, complex choristomas may contain a combination of ectodermal and mesodermal derivatives such as adipose tissue, collagen, cartilage, smooth muscle, lacrimal gland, nerves, and blood vessels, along with hair follicles and pilosebaceous units.

Management

Small and asymptomatic lesions may be managed conservatively with regular monitoring. Larger or symptomatic lesions, particularly those affecting the visual axis or causing ocular irritation, may require surgical excision and appropriate ocular surface reconstruction.

Systemic Associations

Complex choristomas may be seen in association with syndromic conditions such as organoid nevus syndrome, which is characterized by the presence of cutaneous lesions like nevus sebaceous of Jadassohn **(Figs. 6A and B)**.[4] Cutaneous features of nevus sebaceous and alopecia help clinch the diagnosis. Systemic evaluation is imperative. Cutaneous lesions can show malignant changes on follow-up.



Figs. 6A and B: Complex choristoma in a patient with organoid nevus syndrome.

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ACQUIRED LESIONS OF CONJUNCTIVA

Benign Tumors of the Epithelium: Nonmelanocytic

Squamous Papilloma

Squamous papilloma is one of the most frequently encountered benign epithelial tumors of the conjunctiva. It can develop at any age but is more commonly seen in children and young adults, with a slight male predominance.[5]

Etiopathogenesis: In pediatric cases, these lesions are typically associated with human papillomavirus (HPV), particularly subtypes 6, 11, and occasionally 16. Vertical transmission during childbirth through an infected birth canal is believed to be a mode of inoculation. In contrast, adult-onset papillomas may or may not be linked to HPV infection and can be influenced by immunocompromised states or chronic irritation.[6]

Clinical features: Squamous papillomas appear as pedunculated or sessile, soft, fleshy lesions with a frond-like or finger-like surface architecture. They are generally pink or red in color and may be solitary or, in some cases, multiple or bilateral. In children, lesions tend to occur in the inferior fornix or bulbar conjunctiva. Adult lesions typically arise near the limbus and are more commonly sessile. Although many cases are asymptomatic, larger lesions may lead to foreign body sensation, discharge, bleeding, or cosmetic disfigurement. As the lesion grows, it can encroach upon the cornea and obstruct the visual axis.

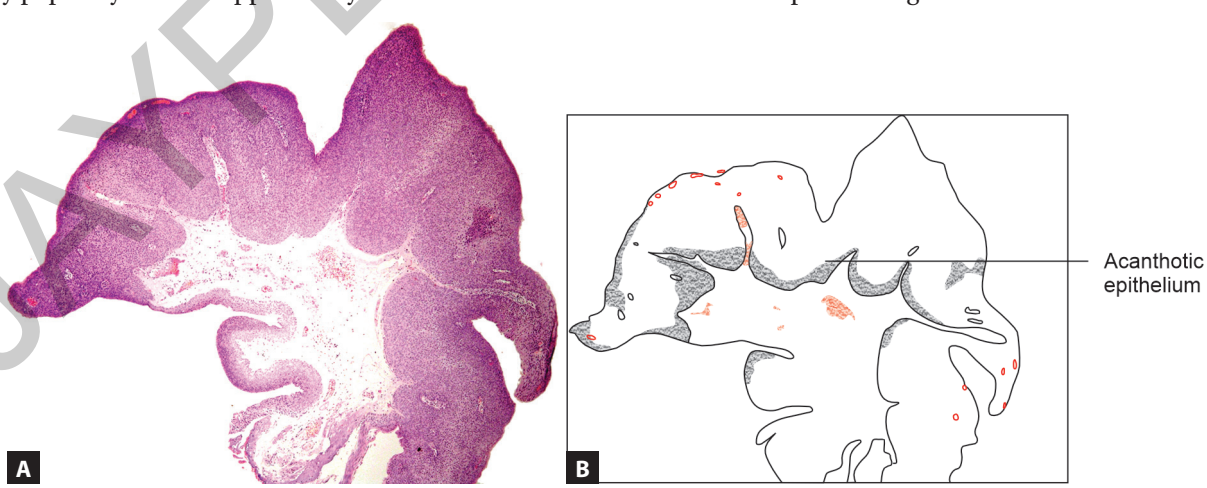
Histopathology: Microscopically, squamous papillomas display papillary fronds supported by a fibrovascular core and covered by acanthotic nonkeratinized squamous epithelium **(Figs. 7A and B)**. Goblet cells may be seen, and the basement membrane remains intact. HPV DNA has been demonstrated in the majority of childhood papillomas via immunohistochemical and molecular methods.[6] Adult lesions may exhibit mild epithelial dysplasia and keratinization, sometimes raising concern for premalignant change. A variant with inverted growth pattern has been noted to carry a higher risk of malignant transformation.

Management: Small lesions, particularly in children, may regress spontaneously and can be monitored if asymptomatic. For larger or symptomatic growths, complete surgical excision using a no-touch technique is preferred to minimize viral dissemination. Adjunctive cryotherapy is often applied to the lesion base and surrounding conjunctiva.[7] In select cases, especially recurrent or diffuse disease, topical antiviral and immunomodulatory treatments such as interferon (IFN) alpha-2b or mitomycin C (MMC) may be used.[8] Other therapeutic approaches reported include laser ablation and immunotherapy with agents like dinitrochlorobenzene. Oral cimetidine has also shown promise in managing refractory or recurrent cases by modulating T cell activity and enhancing immune clearance.

Reactive Epithelial Hyperplasia

(Pseudoepitheliomatous hyperplasia and pseudocarcinomatous hyperplasia)

It is a benign reactive inflammatory proliferation of the conjunctival epithelium that arises as a response to concurrent or preexisting stromal inflammation such as



Figs. 7A and B: Microphotograph of squamous papilloma (OM ×4). The lesion shows numerous vascularized papillary fronds lined by acanthotic epithelium.

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pterygium, pinguecula, allergic conjunctivitis, or foreign body.[7]

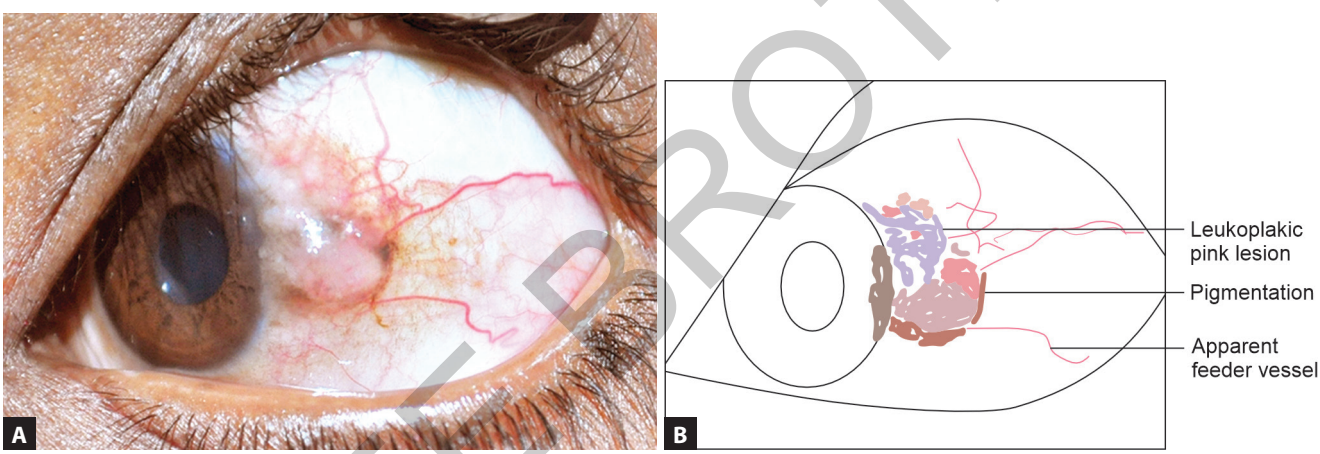
Clinical presentation: These lesions typically appear as elevated, pinkish, leukoplakic plaques, and most often located in the limbal region **(Figs. 8A and B)**. Though benign in nature, their clinical appearance may resemble more serious conditions, particularly conjunctival squamous cell carcinoma (SCC), making accurate differentiation essential.

Histology: On microscopic examination, reactive hyperplasia shows marked epithelial thickening characterized by acanthosis, hyperkeratosis, or parakeratosis **(Figs. 9A and B)**. Subepithelial chronic inflammation is usually present. While mitotic activity may be noted, cytologic atypia or basement membrane breach is absent, which helps distinguish it from true dysplastic or malignant lesions.

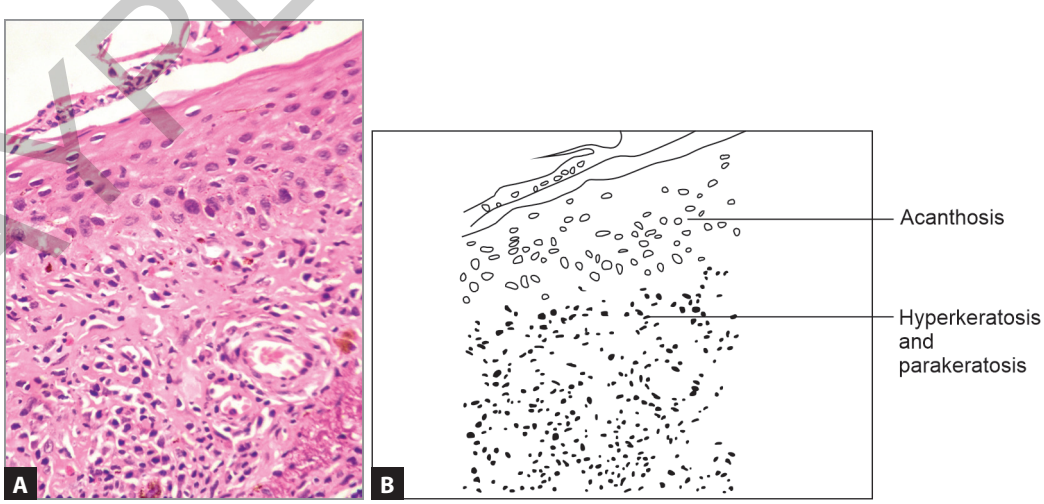
Management: Given the potential for clinical overlap with squamous neoplasia, excision is generally recommended to both alleviate symptoms and establish a definitive diagnosis. Excision is often accompanied by adjunctive cryotherapy to reduce recurrence risk.[7]

Keratoacanthoma

Keratoacanthoma is considered a variant of conjunctival pseudoepitheliomatous hyperplasia. Although benign, it is sometimes thought to represent a low-grade form of SCC. Clinically, it presents as a rapidly growing elevated



Figs. 8A and B: 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 (OSSN).



Figs. 9A and B: Microphotograph of the same patient as in **Figures 8A and B** showing hyperkeratosis and parakeratosis along with massive acanthosis (OM ×40).

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lesion with surface hyperkeratosis or leukoplakia. Complete surgical excision with adjunctive cryotherapy is the recommended treatment.[9]

Dacryoadenoma

Dacryoadenoma is an uncommon lesion typically seen in children and young adults. Clinically, it presents as a translucent, fleshy pink mass involving the bulbar, forniceal, or palpebral conjunctiva. Histologically, it originates from the conjunctival surface epithelium, growing inward into the stroma and forming glandular lobules that resemble normal lacrimal gland architecture, but with an abundance of goblet cells. The preferred treatment is complete surgical excision.[10]

Hereditary Benign Intraepithelial Dyskeratosis

Hereditary benign intraepithelial dyskeratosis (HBID) is a rare, autosomal dominant disorder affecting mucous membranes, including the conjunctiva and oral cavity. It was originally described in the Haliwa-Saponi Native American community, but sporadic cases have also been reported among other ethnic groups including Caucasians and African Americans.[11]

Clinical features: Ocular involvement usually manifests during the first decade of life as bilateral, elevated, gelatinous, V-shaped plaques on the bulbar conjunctiva near the limbus, most commonly in the nasal or temporal quadrants. The lesions are often vascularized and may cause chronic irritation. In advanced cases, extension onto the cornea can result in vascularization and scarring, leading to decreased vision.

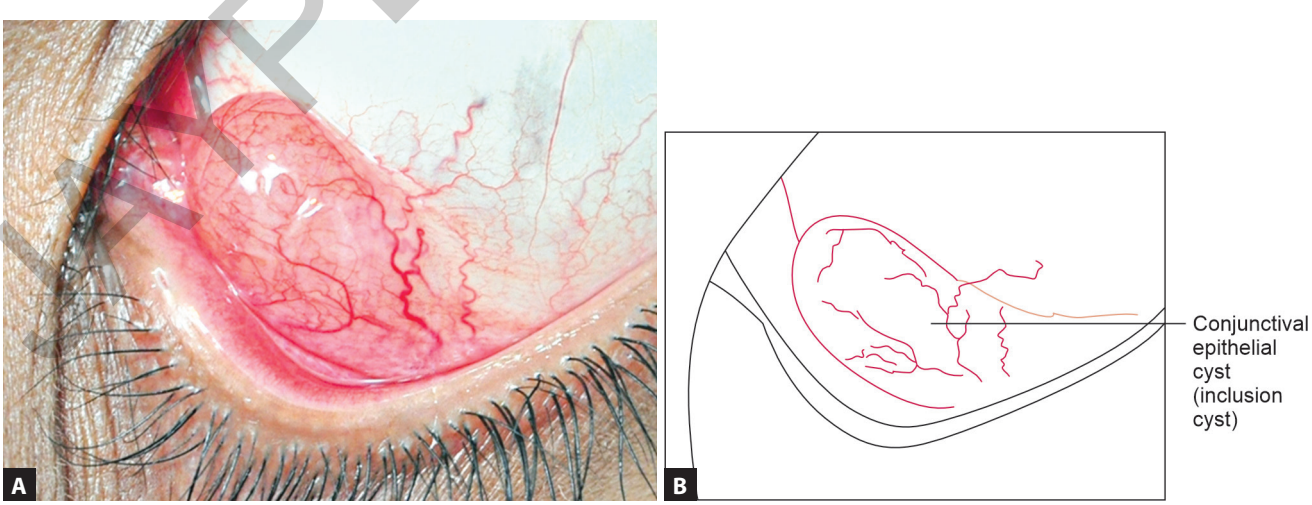
Histopathology: Microscopically, HBID shows epithelial acanthosis with prominent dyskeratosis and intraepithelial eosinophilic bodies. There is often an associated chronic inflammatory infiltrate in the underlying stroma. The dyskeratosis in HBID is benign and lacks features of malignancy, although the histologic appearance can sometimes raise concern for epithelial neoplasia.

Management: Mild or asymptomatic cases can be observed with supportive care including lubricating drops or short courses of topical corticosteroids during symptomatic flares. Larger lesions that threaten the visual axis or cause significant symptoms may require surgical excision with ocular surface reconstruction.

Conjunctival Epithelial Cysts

Conjunctival epithelial cysts are benign, fluid-filled lesions that may be congenital or acquired, with the latter being more frequently encountered in clinical practice. They typically arise from inclusion of conjunctival epithelium due to trauma, surgery, inflammation, or spontaneously.[7]

Clinical features: These cysts present as smooth, dome-shaped, and translucent lesions filled with clear or slightly turbid fluid **(Figs. 10A and B)**. They are often located on the bulbar or forniceal conjunctiva and may be solitary or multiple. While most are asymptomatic, larger cysts can cause foreign body sensation, ocular discomfort, or



Figs. 10A and B: Conjunctival inclusion cyst—smooth translucent lesion with turbid fluid.

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cosmetic concerns. In rare instances, cysts may rupture or become secondarily infected.

Histology: Histologically, inclusion cysts are lined by nonkeratinized stratified squamous conjunctival epithelium. The lumen may contain mucin, keratinous debris, or exfoliated epithelial cells. Ductal cysts, which originate from accessory lacrimal glands, are typically lined by a double layer of cuboidal epithelium and often contain periodic acid–Schiff (PAS)-positive secretions.

Management: Small, asymptomatic cysts may be managed conservatively with observation. Surgical excision is indicated when the cyst enlarges, becomes symptomatic, or poses cosmetic issues. Careful dissection is essential to avoid rupture and reduce recurrence.

Keratotic Plaque

Keratotic plaques are benign, elevated lesions of the conjunctival surface that present as white or grayish patches, typically located on the interpalpebral bulbar conjunctiva near the limbus. They are often associated with chronic environmental exposure or ocular surface irritation.[7]

Clinical features: These lesions appear as flat or slightly raised, opaque areas with a dry or rough surface texture. Patients are generally asymptomatic, and the lesion is often discovered incidentally during routine examination. There is no significant vascularity or infiltration, and they do not typically cause discomfort or visual impairment.

Histology: Microscopic examination reveals hyperplasia of the conjunctival epithelium with acanthosis and surface keratinization (hyperkeratosis or parakeratosis). Unlike premalignant lesions, keratotic plaques lack dysplasia or cellular atypia.

Management: Given their benign nature and extremely low malignant potential, keratotic plaques can be safely observed in most cases. Surgical excision may be considered for diagnostic clarification, persistent irritation, or cosmetic reasons.

Actinic Keratosis

Actinic keratosis of the conjunctiva is considered a premalignant epithelial lesion, most commonly arising due to chronic exposure to ultraviolet (UV) radiation. It shares histologic and etiologic features with cutaneous actinic keratosis and typically affects individuals with significant sun exposure history.[12]

Clinical features: The lesion typically appears as a flat or slightly elevated, white or gray plaque with a rough or frosted surface. It is most often seen in the interpalpebral region of the bulbar conjunctiva, frequently overlying areas of chronic inflammation such as pinguecula or pterygium. The lesion may resemble conjunctival intraepithelial neoplasia (CIN), making clinical differentiation challenging **(Figs. 11A and B)**. Rose bengal staining can help in differentiating; wherein positive staining is seen in cases of OSSN.



Figs. 11A and B: Actinic keratosis, a focal leukoplakic lesion seen in the interpalpebral area. It can easily be misdiagnosed as pinguecula.

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Histology: Microscopically, actinic keratosis shows epithelial thickening with acanthosis, parakeratosis, and variable degrees of keratinization. Mild dysplasia may be present, but there is no invasion through the basement membrane. The adjacent stroma may show solar elastosis due to chronic UV damage.

Management: When clinical suspicion for dysplasia or malignancy exists, complete excision with a margin of surrounding normal tissue is advised, typically accompanied by cryotherapy. In cases with low concern for progression, careful observation may be a reasonable approach with serial photographic documentation and follow-up.

OCULAR SURFACE SQUAMOUS NEOPLASIA

Ocular surface squamous neoplasia represents a spectrum of benign, premalignant, and malignant epithelial dysplastic disorders involving the conjunctiva and cornea. It is an umbrella term encompassing lesions ranging from mild dysplasia and carcinoma in situ to invasive SCC. OSSN is the most common malignant tumor of the ocular surface.[13] Historically, it has also been referred to by terms such as intraepithelial epithelioma, Bowen's disease of the conjunctiva, or Bowenoid epithelioma.

Epidemiology

The incidence of OSSN varies geographically and is significantly higher in regions near the equator, likely due to increased UV radiation exposure. The condition is more common in older individuals and shows a male predominance. Global variability of case incidence remains pronounced, with prevalence ranging from <0.2 to 35 per million.[13]

Conjunctival intraepithelial neoplasia constitutes roughly 39% of all premalignant and malignant lesions of the conjunctiva and represents approximately 4% of all conjunctival pathologies.[14] It predominantly affects males, with about 75% of cases occurring in this group, and is most commonly diagnosed in older individuals.

Etiology

Multiple etiologic factors have been implicated in OSSN, including:

- Prolonged exposure to ultraviolet B (UVB) radiation, which induces DNA damage and mutagenesis. Lee et al. reported an association between cumulative lifetime exposure to solar UV radiation and an increased risk of developing OSSN.[13]
- Infection with HPV, especially subtypes 16 and 18. Current evidence does not demonstrate a statistically significant correlation between anti-HPV antibody status and conjunctival neoplasia, suggesting that HPV infection alone is unlikely to be sufficient for the development of OSSN.
- Immunosuppression, particularly in human immunodeficiency virus (HIV)-positive individuals. Incidence of OSSN has increased since acquired immunodeficiency syndrome (AIDS) epidemic in sub-Saharan African countries.[14]
- Inherited disorders such as xeroderma pigmentosum and Papillon–Lefèvre syndrome.
- *Stem cell theory:* Lee et al. proposed that OSSN may originate from the limbal transition zone, an area rich in epithelial stem cells responsible for regenerating both the corneal and conjunctival surfaces.[13] They suggested that disruptions or alterations in this zone, potentially triggered by environmental or genetic factors, could lead to disordered maturation and neoplastic transformation. This concept builds upon Tseng's hypothesis, which emphasized the high proliferative capacity and longevity of limbal stem cells as contributing factors in tumor genesis.[15]
- Other risk factors include older age, light-colored hair and eyes, dry eye disease, ocular surface trauma, and smoking. Vitamin A deficiency compromises ocular surface integrity, facilitating HPV entry through microabrasions and triggering epithelial changes.

Clinical Features

Distinguishing between the various histological subtypes of OSSN can be clinically challenging, as their appearances often overlap. The majority of cases are unilateral and typically present in older adults, manifesting as chronic ocular redness and irritation. Visual impairment usually occurs only when the lesion becomes large enough to involve the cornea. Bilateral presentation has been documented with systemic associations including xeroderma pigmentosum and in immunocompromised individuals.

Lesions most commonly develop in the interpalpebral area, particularly at the limbus, though they may arise from any region of the conjunctiva or even extend onto the cornea. Clinically, they often present as fleshy, sessile, or

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slightly elevated nodular masses, accompanied by surface keratin, intrinsic vascularity, prominent feeder vessels, and secondary inflammatory changes.[7,13] Rose bengal staining is a useful adjunct in delineating the extent of the lesion **(Figs. 12A and B)**. Tumor extension onto the corneal surface from the limbus may appear as a subtle, grayish, and superficial opacity with a wavy and convex leading edge. This zone of corneal involvement is often avascular but may contain fine vascular loops. Corneal OSSN without bulbar conjunctival involvement can occur involving the corneal epithelium with a progressive convex edges. While most lesions are nonpigmented, pigmented variants of conjunctival SCC have also been reported.

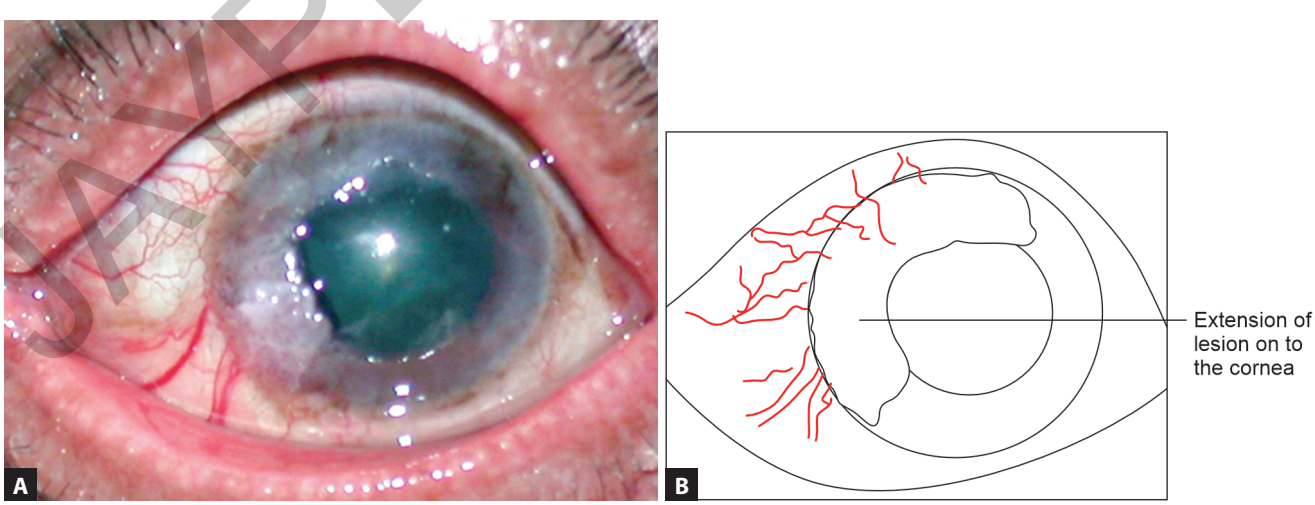
Ocular surface squamous neoplasia exhibits a variety of morphological subtypes, which may present independently or in combination **(Figs. 13 and 14)**.

These include:

- Placoid forms, such as:
  - Gelatinous
  - Leukoplakic plaque-like
  - Papilliform
  - Velvety
- Nodular lesions
- Pigmented
- Diffuse and poorly circumscribed lesions



Figs. 12A and B: Ocular surface squamous neoplasia (OSSN). External photography showing a limbal and nodular lesion with surface keratin, intrinsic vascularity, feeder vessels, and rose bengal stain positivity.



Figs. 13A and B: Ocular surface squamous neoplasia of diffuse gelatinous type with specks of keratin inferonasally.

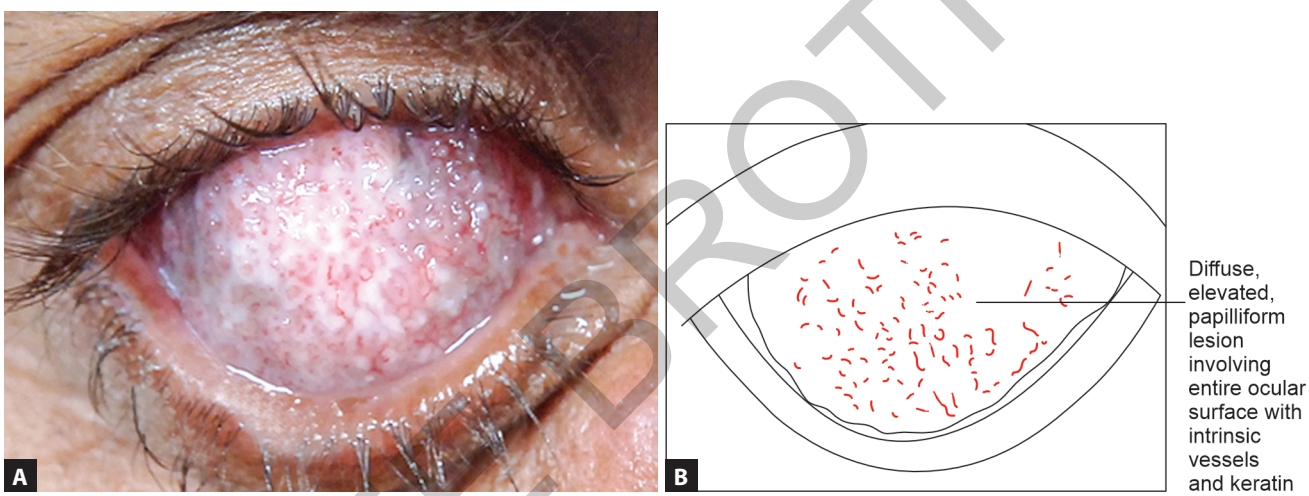
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Despite these descriptive categories, there are no definitive clinical criteria that reliably differentiate between CIN and invasive SCC. However, certain features may raise clinical suspicion for invasive disease. These include:

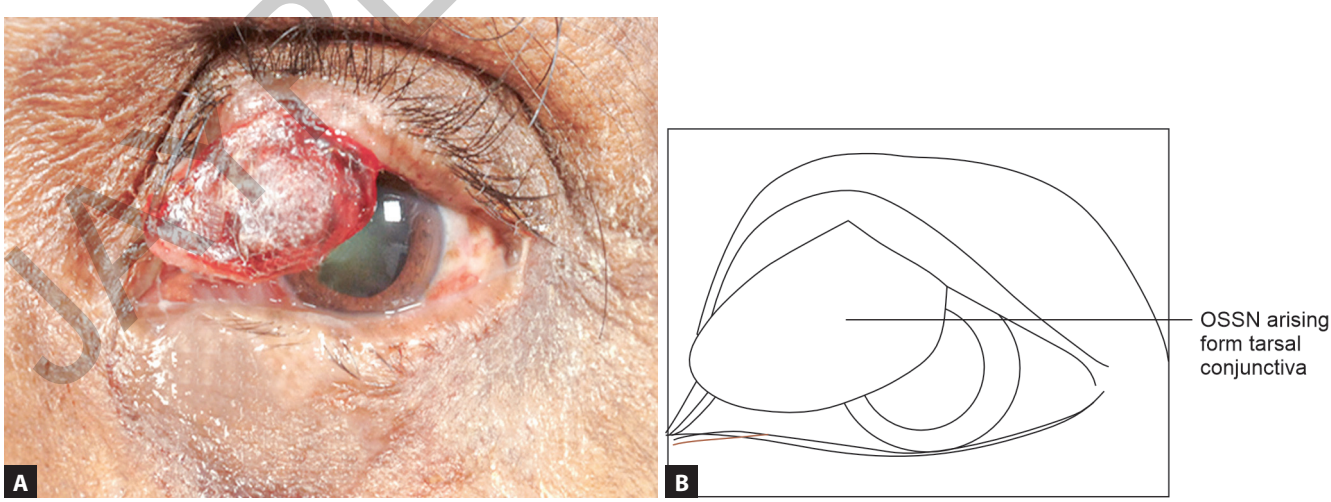
- Prominent leukoplakia
- Presence of feeder vessels and intrinsic vascularity
- Nodular appearance with increased thickness
- Firm attachment to the underlying sclera (scleral fixity)

Examination of the tarsal conjunctiva is critical in suspected or confirmed SCC cases, as lesions can be multifocal or involve areas not readily visible without eyelid eversion **(Figs. 15A and B)**. In more advanced cases, scleral invasion and intraocular extension tumor may occur that may simulate a necrotizing scleritis **(Figs. 16A and B)**. Orbital invasion is not uncommon in extensive disease, particularly when the lesion involves the caruncle or fornices. Radiologic imaging is recommended in such cases to assess for orbital and extraocular muscle involvement.

Regional lymph node metastasis, though uncommon, can occur, and distant metastasis has been reported in rare cases. The American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system is used to classify OSSN based on tumor size, location, and extent of local and systemic spread.[16]

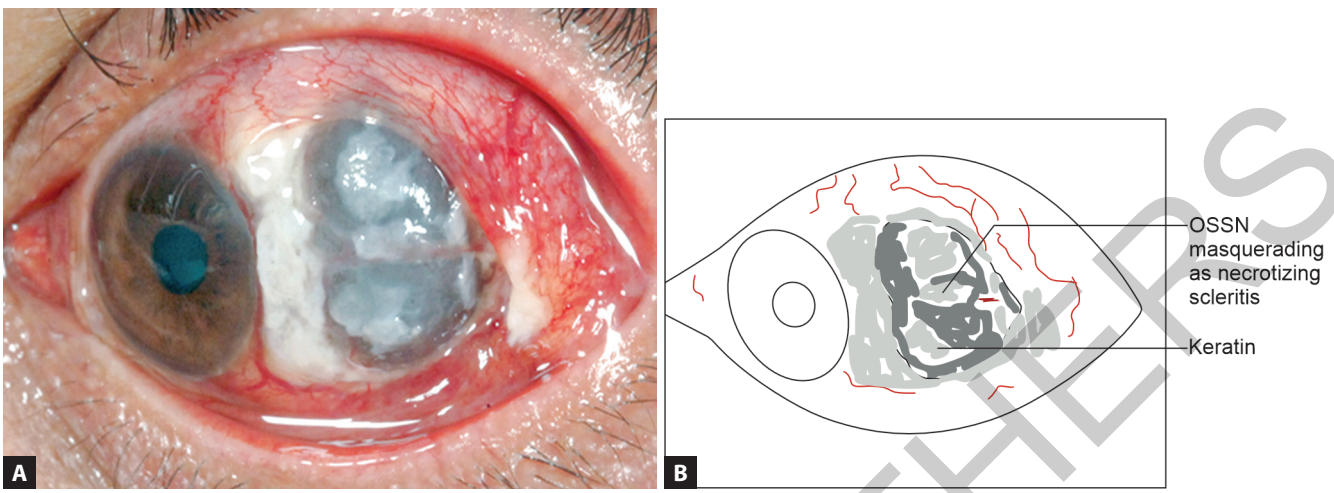


Figs. 14A and B: Ocular surface squamous neoplasia—diffuse, elevated, papilliform lesion involving the entire ocular surface with exuberant intrinsic vessels and diffuse keratin.



Figs. 15A and B: Ocular surface squamous neoplasia—sessile nodular type arising from the tarsal conjunctiva (unusual site) in an immunocompromised patient.

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Figs. 16A and B: Ocular surface squamous neoplasia masquerading as necrotizing scleritis. Note presence of keratin.

Anterior Segment Optical Coherence Tomography (AS-OCT) is a valuable noninvasive diagnostic tool, providing high-resolution imaging. In the evaluation of OSSN, a sharp demarcation between normal and abnormal epithelium, along with epithelial thickening and increased hyper-reflectivity in the lesion area helps in diagnosing the lesion.[17]

In the presence of exuberant surface keratin, it is difficult to identify the thickness and depth. Ultra high-resolution AS-OCT is designed for precision in imaging. With the current resolution of these devices, OSSN can be accurately identified and distinguished from other ocular surface lesions, demonstrating excellent morphological correlation with histopathology.[17]

Histology

Gold standard for diagnosing OSSN is histopathological analysis after excision **(Figs. 17A to C)**. Histopathological analysis plays a critical role in distinguishing between the various stages of lesions within the OSSN spectrum.[15]

Dysplasia

Dysplastic changes are categorized as mild, moderate, or severe based on the degree of cellular atypia and the proportion of epithelial thickness involved. These changes typically begin in the basal epithelial layer and progress upward, with the superficial layers often retaining normal architecture. There is loss of cellular polarity and an increase in nuclear-to-cytoplasmic ratio, but the basement membrane remains intact.

- *Carcinoma in situ:* In this form, the entire thickness of the epithelium exhibits loss of maturation and cellular disorganization. The basement membrane remains intact, which helps differentiate it from invasive carcinoma, though histologic distinction can sometimes be subtle. Mitotic figures are frequently observed, and surface keratinization may be present.
- *Invasive SCC:* This is characterized by disruption of the epithelial basement membrane and invasion into the underlying substantia propria. Histologically, there is pronounced pleomorphism, atypical mitotic activity, and dyskeratosis. Keratin pearls which are concentric collections of keratinized cells, may be present within the tumor mass. The surrounding stroma often shows inflammatory infiltrate and nests or islands of atypical epithelial cells infiltrating the connective tissue.

Certain histopathological variants of invasive SCC are associated with more aggressive behavior and poorer outcomes.[15] These include:

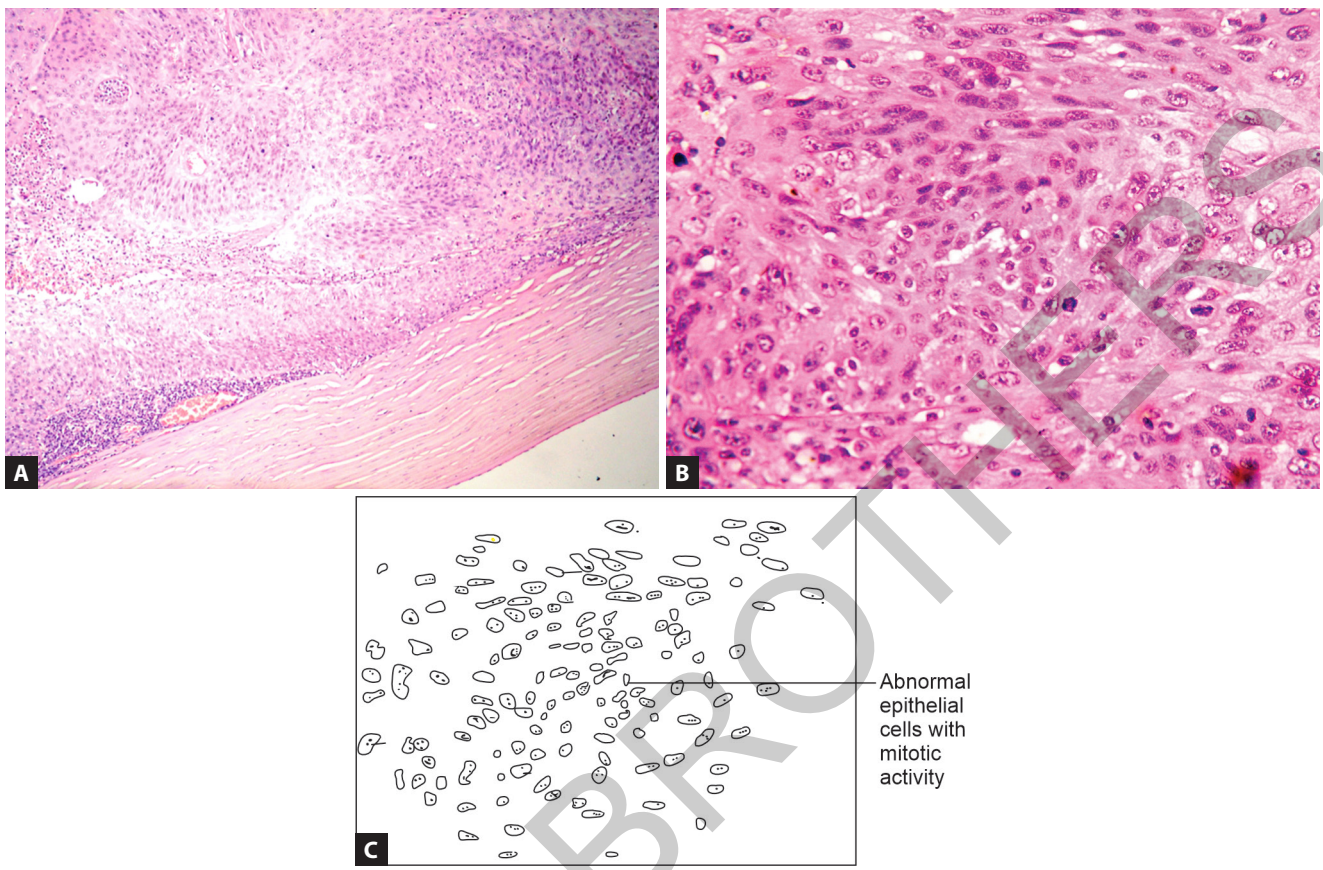
- Spindle cell squamous carcinoma
- Mucoepidermoid carcinoma
- Adenoid SCC

Treatment

Surgical Management—"No-touch" Technique

The preferred surgical approach for OSSN involves excision using the "no-touch" technique. The lesion is removed with a 4 mm clearance from its microscopically visible margins. If the cornea is involved, an alcohol-assisted superficial epithelial keratectomy is performed,

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Figs. 17A to C: Microphotograph of ocular surface squamous neoplasia showing abnormal epithelial cells with mitotic activity [OM ×10 (Fig. 17A), OM ×40 (Fig. 17B)].

maintaining a 2 mm margin beyond the microscopically visible tumor. Tumor manipulation is avoided to reduce the risk of tumor seeding. Cryotherapy using a double-freeze-thaw cycle is applied to the bulbar conjunctival margins. In the presence of scleral adherence suggestive of deeper invasion, superficial lamellar sclerectomy is additionally performed. Limbal cryotherapy should not exceed 6 clock hours to avoid limbal stem cell deficiency. For larger excisions, ocular surface reconstruction is often necessary, typically using amniotic membrane transplantation **(Figs. 18A and B)**.[18-20] When the limbus is extensively involved, simple limbal epithelial transplantation (SLET) may be combined with excision to restore ocular surface integrity.

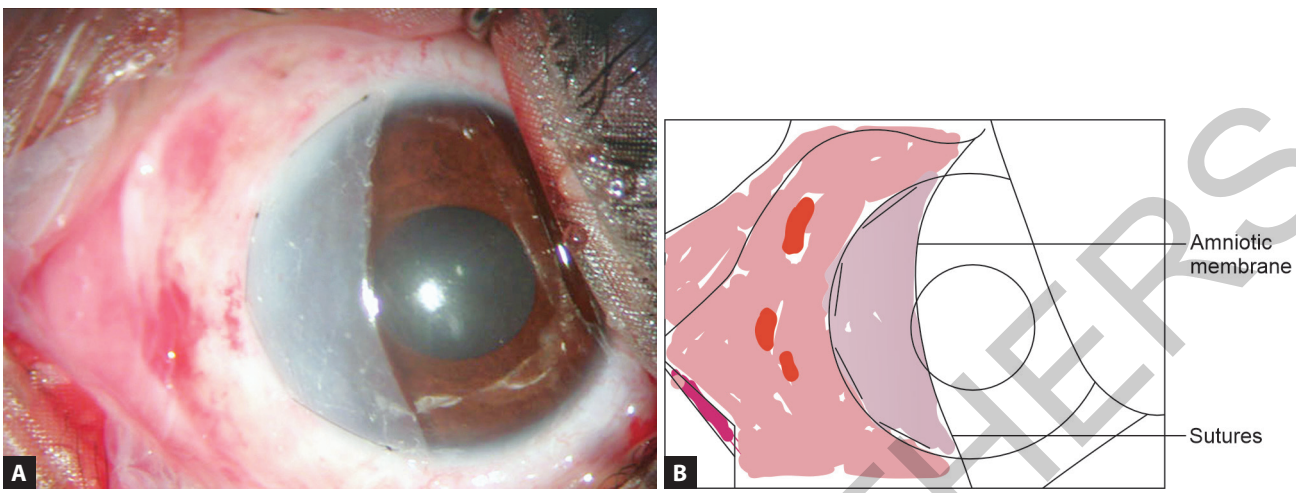
Medical Therapy—Topical Antineoplastic Agents

Several topical agents are used either as primary therapy, adjunct to surgery, or in cases where surgery is not feasible.[21]

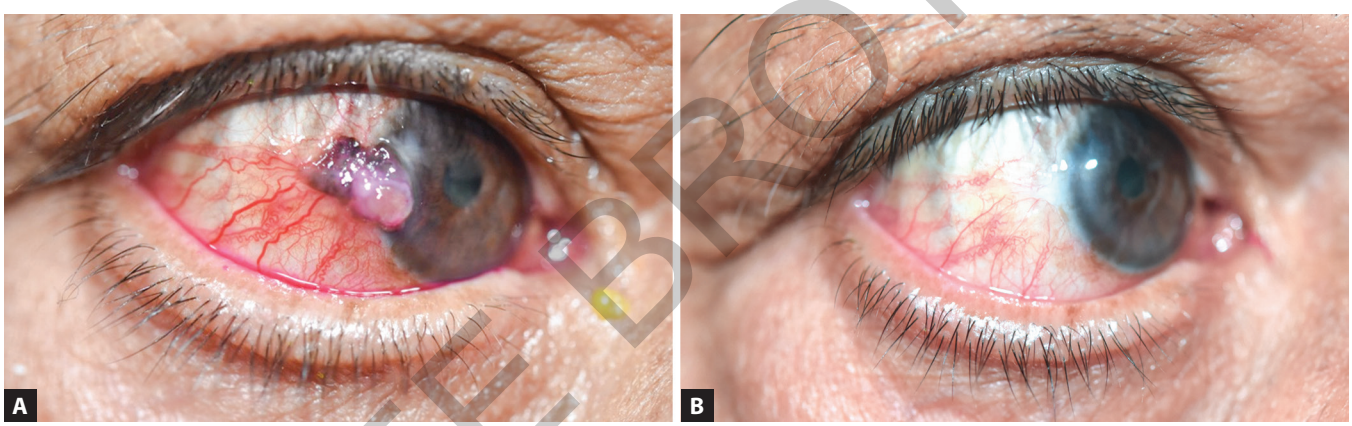
Interferon alpha-2b: This is currently the most widely accepted immunomodulatory treatment for OSSN. Its mechanism of action involves stimulation of interleukin-2 (IL-2) and interferon-gamma (IFN-γ) production and suppression of IL-10, enhancing immune recognition of dysplastic and neoplastic cells. It also exhibits antiproliferative and antiviral effects. It is generally well tolerated with minimal side effects compared to other chemotherapeutic options.

It is used either as a primary agent (immunotherapy), prior to surgery to reduce the size of the lesion (immunoreduction) or as long-term therapy in immunocompromised individuals for controlling recurrence (immunomodulation). Most common dosage used as topical formulation is 1 million IU/mL, administered four times daily until complete clinical resolution. For ensuring complete resolution of the subclinical disease, the cycle is typically continued 1–2 months post apparent clinical resolution. Reported

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Figs. 18A and B: Ocular surface squamous neoplasia—immediate postoperative appearance of a patient with a large tumor following excision and ocular surface reconstruction with amniotic membrane transplantation.



Figs. 19A and B: Medical management of ocular surface squamous neoplasia (OSSN). OSSN (A) managed with topical and intralesional interferon alpha-2b, showing complete resolution (B).

success rates range from 85 to 100%.[22] For large or thick lesions, intralesional injections of 3–10 million IU may be employed **(Figs. 19A and B)**.[23] Long-term topical therapy may help reduce recurrence in immunosuppressed patients through sustained immunomodulatory activity.[24] A transient flu-like illness remains the most common side effect after intralesional injections that is treated with oral antipyretics postinjection.

5-fluorouracil (5-FU): 5-FU is a pyrimidine analog that inhibits thymidylate synthase, thereby blocking DNA synthesis. This leads to reduced ribonucleic acid (RNA) and protein production, resulting in impaired cellular growth and apoptosis.[25] It is typically used as a 1% solution, applied topically four times a day. Different regimens can be employed to avoid ocular surface reaction. Commonly employed cyclical regimen is 2 weeks on and 2 weeks off the drops. However, 1 week on and 3 weeks off is also in clinical practice.[26] Common adverse effects include conjunctival hyperemia, eyelid erythema, and punctate epithelial erosions. Studies have demonstrated that 5-FU is highly effective as a primary treatment for OSSN, achieving resolution rates between 82–100% and recurrence rates as low as 6–14%. When compared to topical IFN α-2b, 5-FU offers comparable outcomes in terms of tumor resolution, recurrence rates, and time to clinical response.[27] It is the second line of management in lesions unresponsive to IFN α-2b, preferred over MMC.

Mitomycin C: MMC is an alkylating agent with antineoplastic and antibiotic properties. Under aerobic conditions, it generates reactive oxygen species that lead to lipid peroxidation and cellular damage. It binds to DNA and inhibits its replication; at higher concentrations, it

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can also block RNA and protein synthesis. One commonly used regimen is the "rule of four"—0.04% solution applied four times daily, 4 days a week, for 4 weeks.[28] Side effects may include conjunctival congestion, superficial punctate keratitis, and, in cases of prolonged or improper use, scleral thinning or melt.

Cidofovir: An additional antiviral and antiproliferative agent with limited use, cidofovir has shown some efficacy in refractory OSSN.[29]

Appropriate case selection is imperative for starting patient on topical therapy.

Radiotherapy: Plaque brachytherapy using isotopes such as ruthenium-106 or strontium-90 is utilized as a primary or secondary management strategy. Inoperable invasive SCC can be treated with primary application of surface plaque.[30] Secondary management for microscopic residual or recurrent tumor after incomplete surgical excision is the most common indication. On histopathological examination if the base of the lesion is positive, secondary plaque brachytherapy is mandated.[30,31] In cases of orbital extension where surgical excision is not feasible, stereotactic external beam radiotherapy may be used, often in combination with systemic chemotherapy.

Other emerging therapies:
Anti-vascular endothelial growth factor (VEGF) therapy: Agents such as bevacizumab (5 mg/mL), applied topically four times daily for up to 8 weeks, or injected subconjunctival (2.5 mg in 0.1 mL weekly for two doses), may be used to reduce tumor vascularity.[32] Ranibizumab has also been explored for refractory invasive SCC, where three out of five patients responded to the treatment.[33]

Immune check-point inhibitors: For conjunctival and periocular SCC, literature on use of immune check-point inhibitors is limited. Pembrolizumab and cemiplimab (PD-1/PD-L1 inhibitor) have shown some success as reported in case series with advanced invasive SCC.[34,35] Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR), such as cetuximab, have shown promise in head and neck SCC. Their application in OSSN is under investigation due to the demonstrated EGFR overexpression in conjunctival squamous tumors.[35]

Prognosis

Ocular surface squamous neoplasia generally has a favorable prognosis with low rates of metastasis and disease-related mortality. However, recurrence remains a challenge. Historical data show recurrence rates of 17% for conjunctival dysplasia, 40% for carcinoma in situ, and 30% for invasive SCC following excision.[13] With current treatment protocols, local recurrence rates have decreased to approximately 5%, and regional lymph node metastasis occurs in about 2% of cases.[28] Aggressive histological variants such as mucoepidermoid and spindle cell carcinoma are associated with poorer outcomes. Because regional lymph node involvement may precede distant metastasis, careful lymph node examination is recommended at each follow-up visit.

BENIGN TUMORS OF THE EPITHELIUM: MELANOCYTIC

Conjunctival Melanocytic Nevus

Conjunctival nevus is the most frequently encountered melanocytic tumor of the conjunctiva.[36]

Etiology

These lesions occur across all racial groups but are more commonly reported in Caucasians (approximately 89%) compared to individuals of African (6%) and Asian (5%) descent. Nevi present at birth or within the first six months of life are classified as congenital, while those appearing later are termed acquired nevi.

Clinical Features

Conjunctival nevi usually become clinically apparent during childhood or adolescence, typically within the first two decades of life. They appear as solitary, unilateral, slightly elevated, and pigmented lesions located most often on the bulbar conjunctiva adjacent to the limbus. A hallmark diagnostic feature is the presence of intralesional cystic spaces, which may be visible clinically or on slit-lamp examination **(Fig. 20)**. Feeder vessels are observed in approximately 64% of cases, while intrinsic vascularity is seen in about 77% **(Figs. 21A and B)**.[14,36] In some cases, particularly during puberty, lesions may show episodic inflammation. Pigmentation varies significantly among lesions, and some may appear nearly nonpigmented.

Malignant transformation is rare, occurring in <1% of cases in Caucasian population.[36] Clinical features that should prompt suspicion of malignancy include adult-onset nevi, growth in nonbulbar locations such as the fornix, palpebral conjunctiva, caruncle, or plica

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semilunaris, recent increase in lesion size or pigmentation, increased thickness, and prominent feeder vessels. In rare instances, particularly in Caucasians, the lesion may be amelanotic.

The differential diagnosis includes primary acquired melanosis (PAM), conjunctival melanoma, and pigmented OSSN.

Histopathology

Histologically, conjunctival nevi are characterized by nests of pigmented melanocytes within the basal layer of the conjunctival epithelium. Depending on the stage of development, they are classified as junctional, compound, or subepithelial types **(Fig. 22)**. Balloon cells and spindle cells are distinct morphologic variants seen within these lesions. Immunohistochemical staining with markers such as HMB-45 and Ki-67 can assist in distinguishing benign nevi from malignant melanocytic lesions.[37] Described clinicopathological variants include spitz nevus, blue nevus, balloon cell nevus, and inflamed juvenile conjunctival nevus (IJCN).[37]

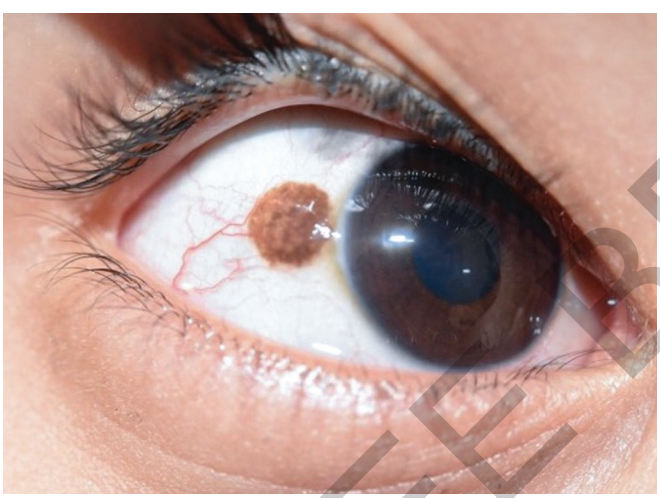


Fig. 20: Conjunctival melanocytic nevus: Slightly elevated, pigmented lesion with intralesional cysts, and a feeder vessel.

Management

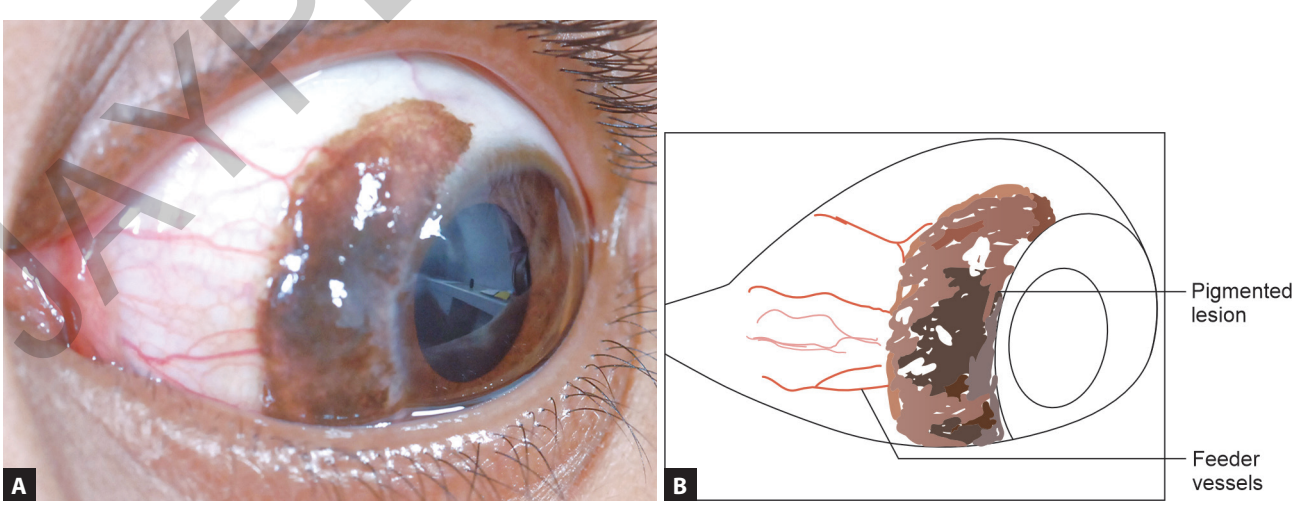
Most conjunctival nevi can be monitored annually with slit-lamp examination and photographic documentation. Excision biopsy is indicated when there is documented growth, clinical suspicion of malignancy, or for cosmetic reasons.

Complexion-associated Melanosis

This is a benign pigmentary condition commonly seen in individuals of African and Asian descent. It is the result of increased melanin production by melanocytes rather than an increase in melanocyte number.

Clinical Features

Complexion-associated melanosis (CAM) typically presents as bilateral, flat, and patchy brown pigmentation of the conjunctiva. The pigmentation is most prominent around the limbus and often encircles it completely (360 degrees) **(Fig. 23)**. It may extend onto the adjacent bulbar conjunctiva or peripheral cornea. Involvement of the palpebral conjunctiva or fornices is less common. Pigmentation is sometimes more concentrated near the entry points of anterior ciliary vessels or intrascleral nerves (Axenfeld loops), where melanocytes are more active.



Figs. 21A and B: Conjunctival nevus. Note excessive pigmentation, presence of intralesional microcysts, and feeder vessels.

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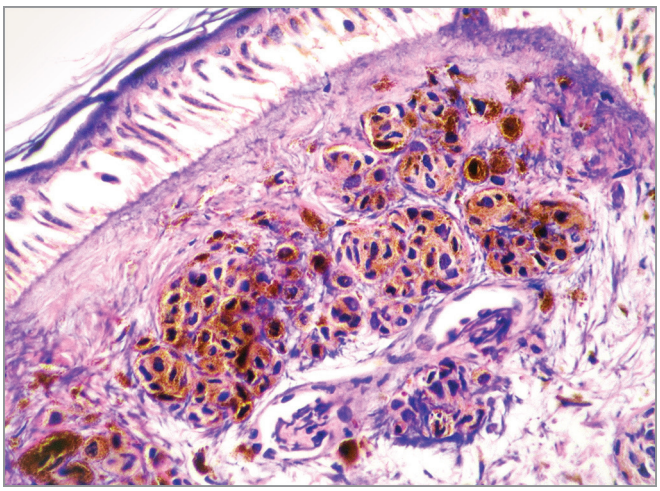


Fig. 22: Microphotograph of a subepithelial nevus showing clumps of melanocytes with no cellular atypia (OM ×40).

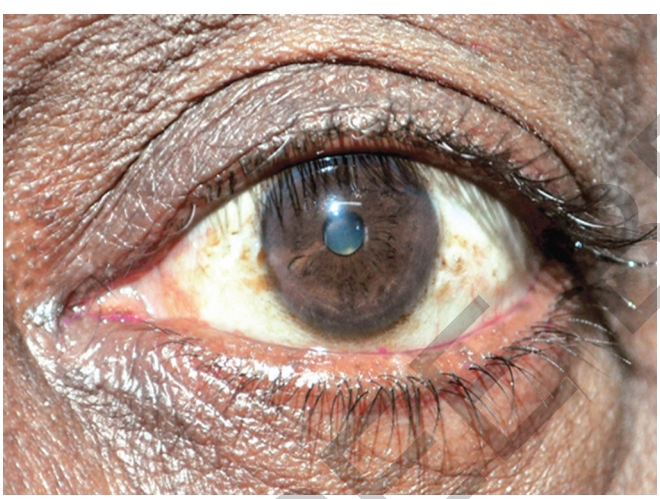


Fig. 23: Complexion-associated melanosis. Note the pigmentation in the perilimbal area.

Asymmetry or rapid growth should raise suspicion, as it may signal the risk of conjunctival melanoma.[38]

Management

Since the risk of malignant transformation is exceedingly low, no treatment is necessary. Regular observation and photographic documentation are adequate in most cases.

Primary Acquired Melanosis

Primary acquired melanosis is a benign melanocytic proliferation within the conjunctival epithelium. The earliest clinical reference to this lesion dates back to 1892 when Hutchinson referred to it as a "senile freckle".[39] It was later termed "precancerous melanosis" by Reese in 1966 and subsequently revised to "benign acquired melanosis" by Zimmerman. The WHO officially adopted the term "primary acquired melanosis" in its 1980 International Classification of Tumors.[40]

The nomenclature reflects its features; "primary" implies no known systemic or local cause; "acquired" differentiates it from congenital lesions; and "melanosis" denotes proliferation of melanocytes rather than pigment deposition from other sources.

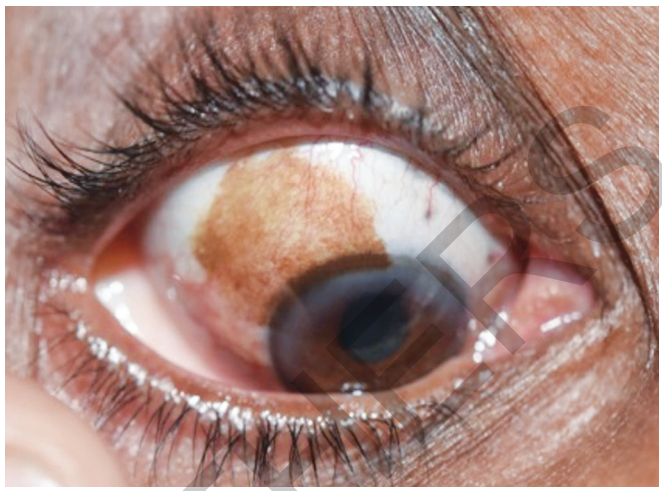


Fig. 24: Primary acquired melanosis (PAM)—flat, patchy, pigmented lesion, and mostly unilateral.

Etiology

Primary acquired melanosis is more commonly observed in individuals with fair complexions, and chronic sun exposure is believed to contribute to its development. It has also been reported in association with neurofibromatosis.[41] Additional risk factors include cigarette smoking and systemic hypertension, both of which have been independently linked to its onset.[39]

Clinical Features

Primary acquired melanosis typically presents in middle-aged to elderly adults, though cases in young adults may also occur, pediatric cases are rare. Clinically, it appears as a unilateral, flat, patchy, and golden brown to dark brown pigmentation that may be solitary, multifocal, or diffuse **(Fig. 24)**. The interpalpebral conjunctiva is most commonly involved, but lesions may also occur on the palpebral or forniceal conjunctiva. Rare amelanotic variants (PAM sine pigmento) have also been described.

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