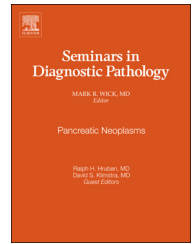


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Epithelial, non-melanocytic and melanocytic proliferations of the ocular surface



Wajiha J. Kheir, MD^{a,b}, Michael T. Tetzlaff, MD, PhD^{c,d},
Margaret L. Pfeiffer, MD^{a,e}, Kaustubh Mulay, MD^f, Omar Ozgur, MD^a,
Gail Morrell, APN^a, Bitu Esmaeli, MD^{a,*}

^aOrbital Oncology and Ophthalmic Plastic Surgery, Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1488, Houston, Texas 77030

^bDepartment of Ophthalmology, American University of Beirut, Beirut, Lebanon

^cDepartment of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas

^dDepartment of Translational and Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

^eRuiz Department of Ophthalmology and Visual Science, The University of Texas, Medical School at Houston, Houston, Texas

^fNational Reporting Centre for Ophthalmic Pathology (NRCOP), Centre For Sight, Hyderabad, India

ARTICLE INFO

Keywords:

Ocular surface

Conjunctiva

Cornea

Papilloma

Ocular surface squamous neoplasia

Intraepithelial neoplasia

Nevus

Primary acquired melanosis

Melanoma

ABSTRACT

Ocular surface tumors are commonly encountered by ophthalmologists and ophthalmic pathologists. These tumors have varied clinical manifestations. In this article, we discuss the most commonly encountered non-melanocytic and melanocytic ocular surface tumors, with emphasis on their common clinical features, morphologic patterns, and prognostic factors.

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The ocular surface includes the conjunctiva and cornea. Primary tumors at that site may be acquired or congenital and they include a variety of epithelial, stromal, hematolymphoid, and secondary lesions (Table 1). These lesions can cause significant morbidity and also have the potential to be life-threatening. In this brief review, we consider the epidemiological, clinical, and histopathological features of the non-melanocytic and melanocytic tumors of the ocular surface.

Histology

Considering the functional, embryological and anatomical aspects of this region, the “ocular surface system” encompasses the surface and glandular corneal and conjunctival epithelium, accessory lacrimal glands, Meibomian glands, the apical and basal matrices, the lacrimal glands with the lacrimal drainage system, the eyelashes, and the glands of Zeis and Moll.

* Corresponding author.

E-mail address: besmaeli@mdanderson.org (B. Esmaeli).

Table 1 – Epithelial tumors of the ocular surface.

Non-melanocytic
Benign
Squamous papilloma
Keratoacanthoma
Pseudoepitheliomatous hyperplasia
Oncocytoma
Dacroadenoma
Pre-malignant
Conjunctival corneal intraepithelial neoplasia (CCIN)
Malignant
Squamous cell carcinoma
Melanocytic
Benign
Complexion-associated melanosis (racial melanosis)
Secondary melanosis
Ocular melanocytosis
Nevi
Primary acquired melanosis
Pre-malignant
Melanoma in situ
Malignant
Malignant melanoma

Conjunctiva

The conjunctiva functions to produce the mucous component of the tear film and helps to attach the globe to the eyelids. Anatomically, the conjunctiva is divided into 3 zones—the palpebral conjunctiva (lining the inner surface of the eyelids), the forniceal conjunctiva (lining the superior and inferior fornices) and the bulbar conjunctiva (covering the sclera). Histologically, it consists of a non-keratinizing, stratified squamous or columnar goblet cell-containing epithelium, separated from the underlying substantia propria by a basement membrane (Fig. 1). The epithelium is 2–3 layers thick with the basal layer containing a variable number of melanocytes. In addition to a rich vascular and lymphatic network, the substantia propria contains conjunctiva-associated lymphoid tissue (CALT), constituting a mucosal immune system.

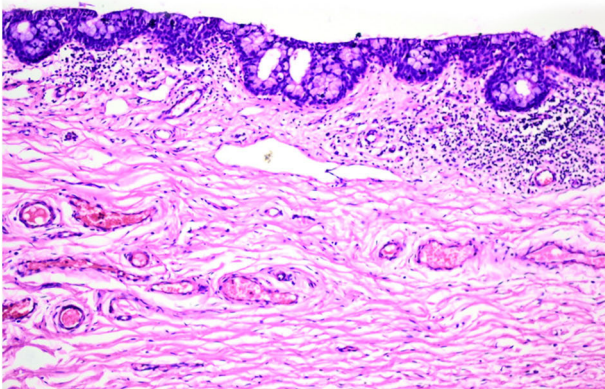


Fig. 1 – Conjunctiva with a non-keratinizing, stratified squamous or columnar goblet cell-containing epithelium and underlying substantia propria.

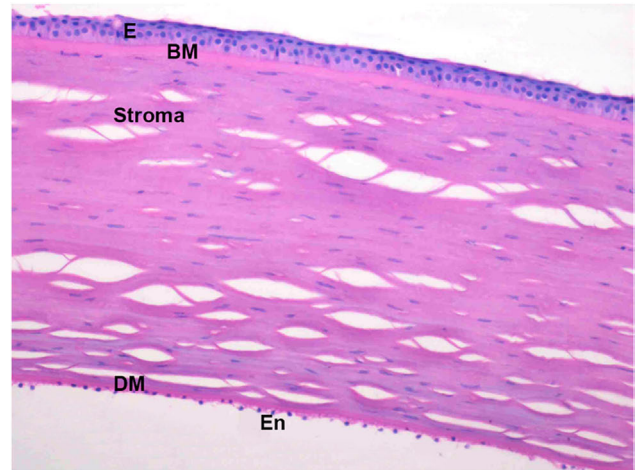


Fig. 2 – Layers of the cornea—(top to bottom) epithelium (E), Bowman's membrane (BM), stroma, Decemet's membrane (DM), and endothelium (En).

Cornea

The cornea is a transparent and avascular tissue that acts as an optical medium for light to enter the eye (Fig. 2). The stratified squamous, non-keratinized corneal epithelium is 3–6 layers thick. Posterior to it is the Bowman's membrane (anterior limiting membrane), an acellular band of collagen. The corneal stroma accounts for 90% of its thickness and comprises a lattice-like arrangement of collagen fibrils with sparsely distributed keratocytes. Posterior to the stroma is Descemet's membrane, a modified basement membrane of the corneal endothelium and the posterior-most corneal layer.

The corneal endothelium is a squamous or cuboidal monolayer responsible for exchange of fluid between the aqueous humor and the corneal stroma. Unlike the corneal epithelium, the corneal endothelium lacks a capacity for regeneration. Recently, Dua et al.¹ have identified a novel, acellular pre-Descemet's layer (Dua's layer); it plays a role in formation of such posterior corneal lesions as acute hydrops, descematomyces, and pre-descemet's dystrophies.

Epithelial tumors

Epithelial ocular surface tumors may be melanocytic or non-melanocytic (Table 1).

Non-melanocytic epithelial tumors

Squamous papilloma

Squamous papillomas are common benign tumors that are seen in both children and adults. They present most commonly in the inferior fornix as solitary or multiple, sessile or pedunculated, pink to red fleshy lesions with finger-like projections (Fig. 3).² Testing with the polymerase chain reaction (PCR) has shown an association with human papilloma virus (HPV) in 44–92% of these lesions, most commonly

with HPV types 6 and 11 in children and 16 and 18 in adults.^{3,4} Microscopically, papillomas are characterized by a frond-like growth pattern with fibrovascular cores (Fig. 3). Koilocytosis and dysplasia of varying degrees may be seen. Clinical differential diagnoses include keratoacanthoma, epithelial hyperplasia, ocular surface squamous neoplasia (OSSN), and pyogenic granuloma. Papillomas have very low malignant potential, with only rare reports of carcinomas developing in them.⁵

Pseudoepitheliomatous hyperplasia (PEH)

PEH is an exaggerated reactive epithelial hyperplasia in which cellular cords extend into the underlying stroma. It may thus simulate the pattern of squamous cell carcinoma (SCC). Although PEH may be idiopathic in nature, most cases are associated with prior inflammation as seen in lesions such as pterygium, pinguecula, and chronic conjunctivitis. Microscopically, PEH is characterized by florid proliferation of the surface epithelium, with invagination into the substantia propria. Finger-like projections, with keratin pearls and inflammatory infiltrates, are typical (Fig. 4) and distinction from SCC may be difficult. Histopathologic examination is best done with a properly oriented section. The invasive epithelial cells in SCC display a degree of cytologic atypia, but those in PEH do not.

Zorovnaya and Black⁶ suggested used an immunohistochemical panel of p53, matrix metalloproteinase-1 (MMP1), and E-cadherin as an adjunct to morphological assessment in difficult cases. p53 and MMP-1 staining is more diffuse and intense in SCC as compared with PEH, but labeling for E-cadherin is lesser in SCC.⁶ p63 immunostains are less discriminatory.⁷

Ocular surface squamous neoplasia (OSSN)

OSSN was first described by Lee and Hirst in 1995, and is the most common non-melanocytic neoplastic process in the conjunctiva and cornea. The term refers to a spectrum of lesions originating from the squamous epithelium and ranging from low-grade dysplasia to invasive carcinoma.^{8,9} The term conjunctival–corneal intraepithelial neoplasia (CCIN) encompasses non-invasive squamous epithelial neoplasms of the conjunctiva and cornea: mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ.

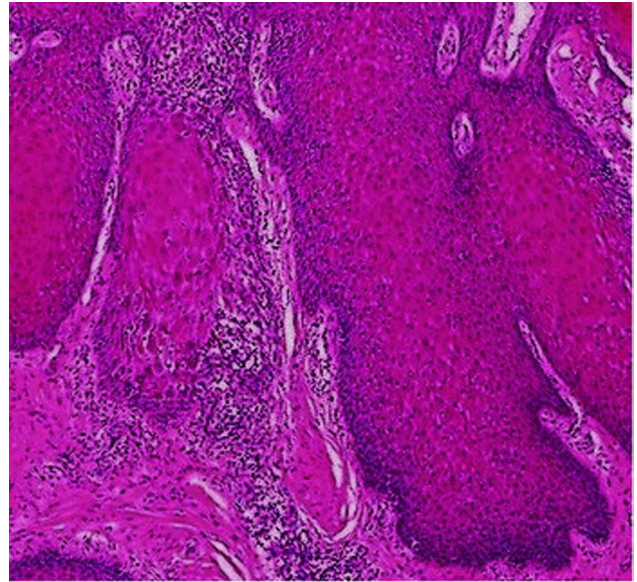


Fig. 4 – Marked epithelial hyperplasia with finger-like downgrowths in pseudoepitheliomatous hyperplasia.

Epidemiology

Data on the incidence of OSSN are difficult to obtain; they vary geographically and have changed over time.^{10,11} In 1967, Templeton¹² studied the incidence of several ocular tumors in various Ugandan tribes and found the incidence of squamous carcinoma of the conjunctiva to be 0.07–0.28 per 100,000. Later reports give incidence rates of 1.9 per 100,000 in Australia in 1992,¹³ 0.03 per 100,000 in the United States in 1997,¹⁴ and 2.2 per 100,000 in Tanzania in 2010.¹⁵

In a recent analysis by Gichuhi et al.,¹⁰ Africa had the highest age-standardized incidence rate of OSSN, which is 9–10 times higher than that seen in Europe and North America. This difference is felt to be due to the increased prevalence of infection with the human immunodeficiency virus (HIV) in the African population.¹⁰ A distinction across continents also has been made regarding age and gender of patients with OSSN.^{10,16,17} In developed countries, older Caucasian men have been considered to have the highest risk for OSSN, presumably caused by cumulative ultraviolet (UV) light exposure.^{14,18} In contrast, younger women are at greatest risk in Africa.^{10,15,19}

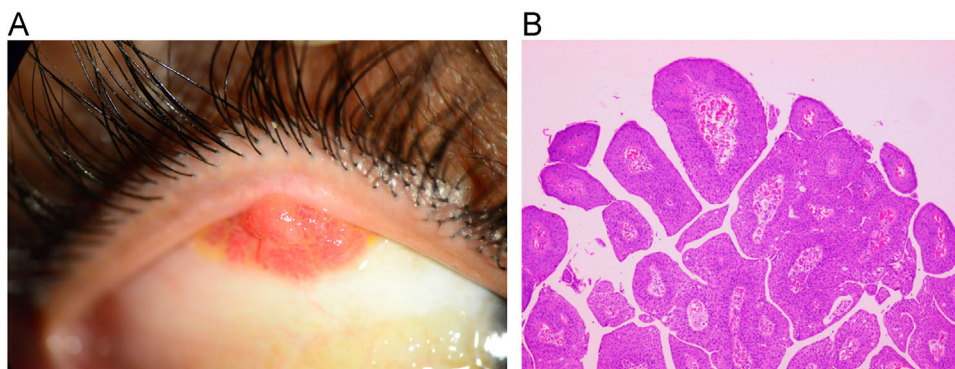


Fig. 3 – (A) Multiple, warty, finger-like projections of a conjunctival papilloma and (B) papillary hyperplasia of the conjunctival epithelium with fibrovascular cores.

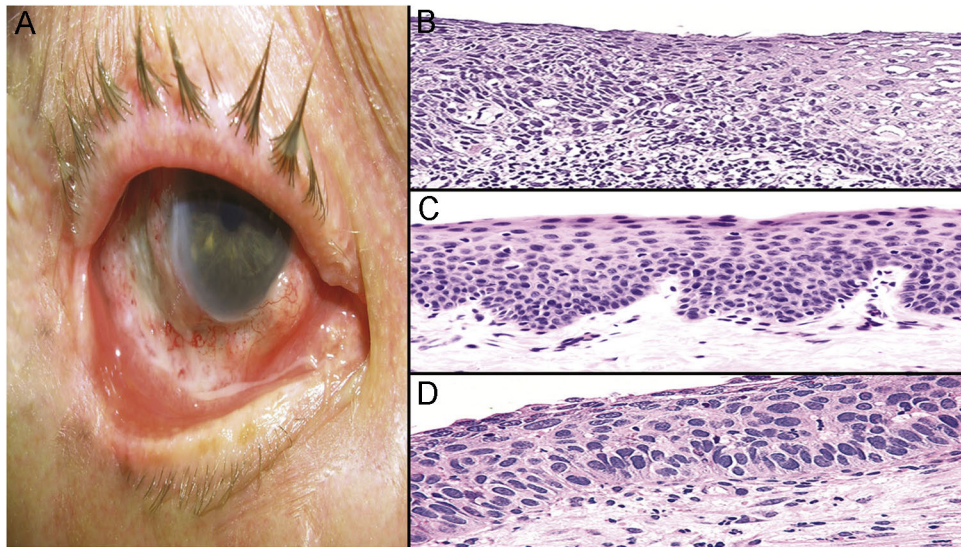


Fig. 5 – Conjunctival/corneal intraepithelial neoplasia (CIN) is shown in these images. The surface of the eye is hyper-vascularized and cloudy (A). Grade I CIN (B) shows modest nuclear atypicity with binucleated cells; perinuclear cytoplasmic clearing (koilocytosis) is focally apparent as well. Grade II lesions (C) demonstrate greater nuclear atypicity and hyperchromasia, and grade III CIN (D) manifests transepithelial marked nuclear atypia. It is synonymous with squamous carcinoma in situ.

Risk factors

The variability in incidence of OSSN may be related to differences in UV light exposure and infections with the human papilloma virus (HPV) and HIV. In 1996, Newton et al.²⁰ showed that there is a decreasing incidence of squamous cell carcinoma (SCC) of the eye (excluding the eyelids) with increasing geographic latitude, corresponding to decreased UV exposure. Sun et al.¹⁴ corroborated that association. Patients with OSSN often have other ocular findings that are consistent with prolonged sun exposure, such as pterygia, pinguecula, solar elastosis, and nuclear sclerosis.¹⁷ The link between UV exposure and OSSN is also associated with mutations in the p53 tumor suppressor gene in limbal²¹ and conjunctival SCCs.²² An additional link between OSSN and ultraviolet exposure is the observation that patients with xeroderma pigmentosum—a condition induced by faulty

repair of UV-induced damage to deoxyribonucleic acid—develop OSSN at a young age.²³

A more controversial association is that of OSSN and HPV infection. Several studies have detected HPV in a majority of OSSN cases^{24–27} with a relative absence of infection in control tissues.^{25,26} However, the sub-types of HPV detected, specifically the high-risk HPV types 16 and 18, have not been consistent. Scott et al. found either HPV 16 or 18 mRNA in all 10 examples of conjunctival/corneal intraepithelial neoplasia (CIN) using the polymerase chain reaction (PCR).²⁵ Carrilho et al.²⁷ detected HPV by PCR in 11 of 19 OSSN specimens (58%) of which only 3 were HPV 16 or 18. Asadi-Amoli et al.²⁶ found no HPV 16 or 18 in 44/46 OSSN specimens that were positive for HPV. In a report from India, Manderwad et al.²⁸ observed no HPV in 57 OSSN specimens using PCR, but they only used assays for HPV 16 and 18. Guthoff et al.²⁹ saw no evidence of HPV in 31 OSSN lesions that were assessed with immunohistochemistry and PCR. It is

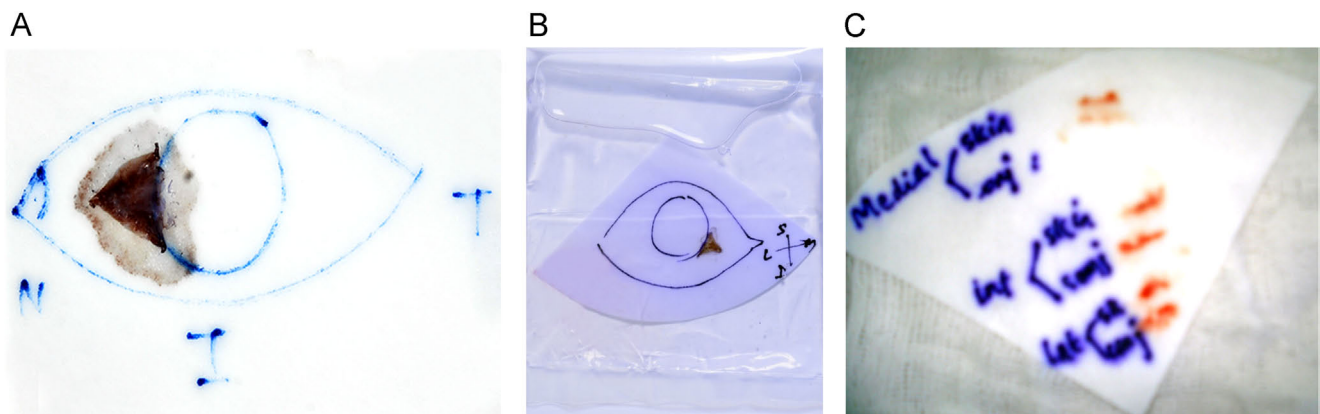


Fig. 6 – (A) Diagrammatic representation on a filter paper with the excised lesion, (B) transportation of the specimen in a polyethylene bag (note that adequate drying before transfer into the fixative prevents detachment of the specimen from the filter paper), and (C) separately sent resected margins.

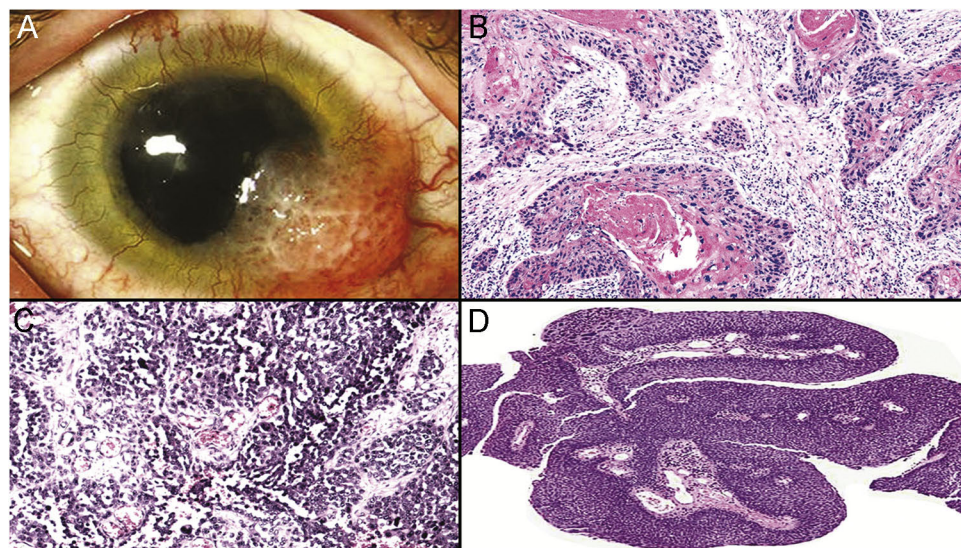


Fig. 7 – Invasive squamous-cell carcinoma of the limbus (A). Tumors of this type are most commonly of the keratinizing type (B), but they can also be adenoid and pseudovascular (C) or papillary (D).

also worth noting that HPV has been detected in normal conjunctival tissues.²⁴ It is possible that after it forms a complex with the protein encoded by p53,²⁵ HPV requires other cofactors to incite the development of OSSN.^{16,18,30}

Patients with immunocompromise that is caused by HIV have an increased risk of developing OSSN,^{10,11,19,31,32} and the high incidence of these tumors in Uganda and in other African countries has been attributed to infection with that agent.¹¹ Co-infection with HPV and exposure to sunlight may be contributing factors as well.^{11,19} OSSN lesions in HIV-positive patients are typically quickly growing, aggressive,¹⁹ large,⁹ and invasive.³³ In fact, OSSN may be the presenting sign of HIV infection in endemic areas¹⁸ as well as in the United States.³⁴ The association between HIV and OSSN has also been demonstrated in North America.³⁵ It is prudent to obtain HIV testing in cases of OSSN in high-risk patients³¹ or in those who are younger than 50 years.³⁴

Aggressive OSSN lesions occur in individuals who are immunodeficient for any reason.^{10,36,37} Shields et al.³⁶ studied 13 immunocompromised patients with conjunctival SCC that sometimes required exenteration or enucleation. Shelil et al.³⁷ reported a liver transplant recipient on immunosuppressants whose conjunctival SCC metastasized and proved fatal within a year of onset.

Other selected risk factors for OSSN are heavy cigarette smoking, fair skin, lightly pigmented irides, exposure to petroleum products, male gender, Caucasian race, residence within 30° latitude of the equator, and vitamin A deficiency.^{18,20}

OSSN occurs predominantly in adults. The average age of occurrence is 56 years with an age range of 4–96 years.⁸

Clinical features and diagnosis

OSSN has varied clinical presentations. It usually appears as fleshy elevations with a gelatinous, leukoplakic, or papilliform appearance, sometimes with corkscrew, tufted, and superficial feeder vessels.^{38–40} They are frequently located at the limbus,³⁸ involving both the cornea and conjunctiva (Fig. 5).⁴¹ Clinicians

face problems in separating early neoplastic lesions from others.³⁹ In fact, with the exception of tumor size, clinical features such as laterality, location, keratinization, pigmentation, vascularization, and corneal invasion have not shown any linkage with the probability of malignancy.³³ Furthermore, benign and malignant lesions may coexist, such as in rare cases of concomitant pterygia and OSSN.⁴²

The standard method for diagnosis of OSSN is histopathologic assessment of a surgical biopsy. Other approaches have been explored in recent years, such as vital staining, impression cytology, *in vivo* confocal microscopy (IVCM), ultrasound biomicroscopy (UBM), and ultra-high resolution ocular coherence tomography (UHR-OCT).⁴³ In some analyses, the topical application of stains such as methylene blue⁴⁴ and 1% toluidine blue,⁴⁵ coupled with clinical examination, had a high sensitivity for the detection of OSSN. IVCM has a limited scan width and is unreliable in the detection of invasion,⁴³ therefore, it has had variable success in separating benign and malignant lesions.^{39,46} Impression cytology is a relatively non-invasive method of sampling tissue, but it is limited to the evaluation of surface cells only. UBM is useful for large lesions but it has low resolution and is operator dependent. UHR-OCT has shown promise in the diagnosis of OSSN,^{43,47} and the possible application of gold nanorod technology in that context may improve its performance.⁴⁸ However, UHR-OCT is still considered investigational and is not widely available outside of selected research centers. It also poorly penetrates thick lesions and may be unreliable for the detection of invasive carcinoma.⁴³

Histopathological features

A complete pictorial documentation of the lesion is important, with comments on the status of the surgical margins. A diagram is made on filter paper (Fig. 6), and the excised specimen is placed over the paper with the mucosal surface up and laterality indicated appropriately. The specimen and the filter paper are allowed to dry for 2–4 min and then

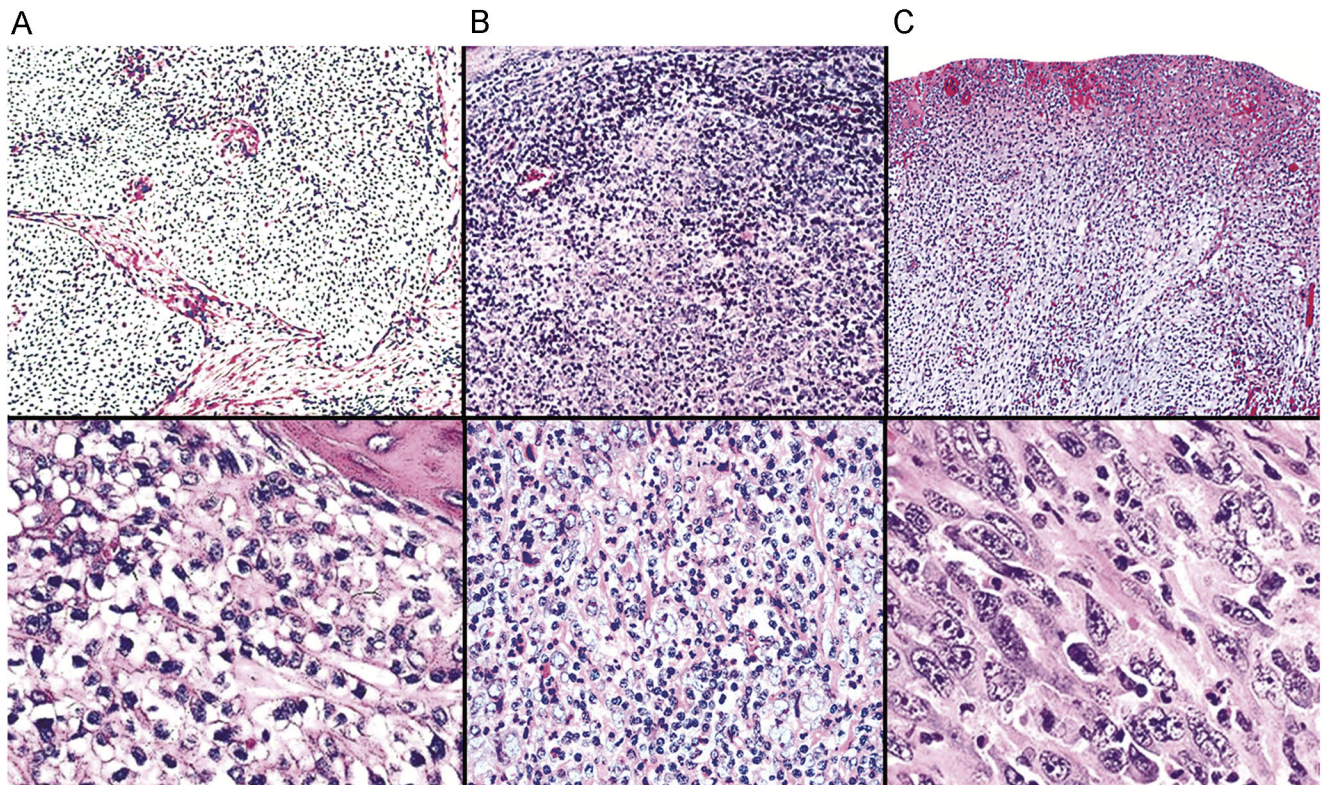


Fig. 8 – Other histological variants of conjunctival squamous-cell carcinoma (SCC) are depicted here. They include clear-cell SCC (A); lymphoepithelioma-like SCC (B); and sarcomatoid (spindle-cell) SCC (C).

transferred to a polyethylene bag containing 10% neutral-buffered formalin (Fig. 6). If margins have been sampled separately, they can be handled in a similar manner (Fig. 6). All margins should be processed separately and the remainder of the tissue is processed in its entirety.

Dysplasia of the conjunctival or corneal epithelium is generically designated as CCIN (Fig. 5). Grade I CCIN shows the presence of binucleated epithelial cells, nuclear folding, and nuclear

hyperchromasia, sometimes with perinuclear clearing of the cytoplasm (Fig. 5). Grade II lesions occupy at least one-half of the epithelial thickness, with greater nuclear irregularity; mitoses are often present as well. If full-thickness epithelial dysplasia is present with an intact basement membrane, the lesion is classified as grade III CCIN or carcinoma in situ (CIS) (Fig. 5).⁴⁹ Those tumors that penetrate the epithelial basement membrane and grow into the underlying stroma are invasive SCCs (Fig. 7).

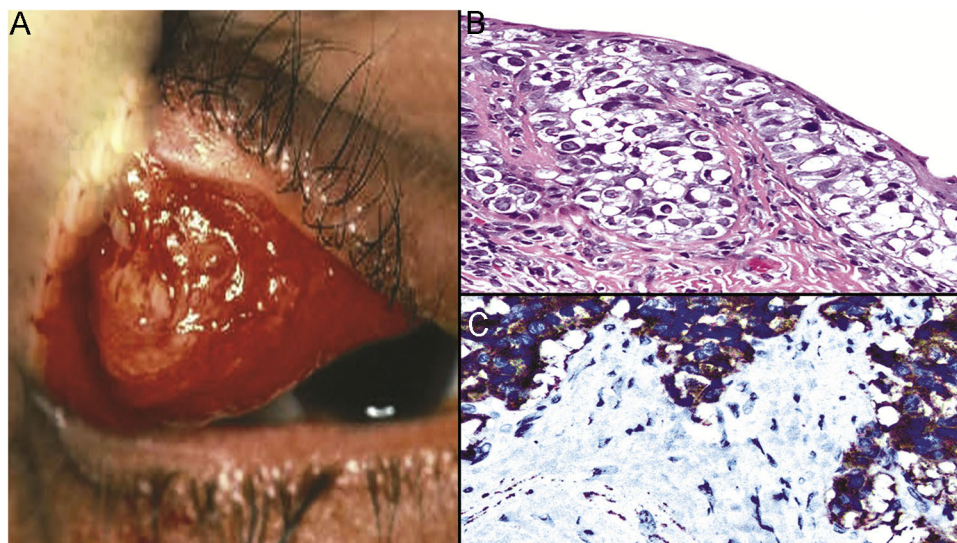


Fig. 9 – Sebaceous carcinoma may occasionally manifest in the conjunctiva (A) with pagetoid intraepithelial growth in the absence of a discrete mass in the eyelids (B). Immunostaining for adipophilin (C) shows labeling of the multiple cytoplasmic vacuoles in the tumor cells.

Table 2 – American Joint Committee on Cancer (AJCC) staging system for conjunctival carcinomas (TNM).

Primary tumor (T)	
TX	primary tumor cannot be assessed
T0	no evidence of primary tumor
Tis	carcinoma in situ
T1	tumor 5 mm or less in greatest dimension
T2	tumor >5 mm. in greatest dimension, without invasion of adjacent structures
T3	tumor invades adjacent structures (excluding the orbit)
T4	tumor invades the 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 nodes (N)	
NX	regional lymph nodes cannot be assessed
N0	no regional lymph node metastasis is present
N1	regional lymph node metastasis is present
Distant metastasis (M)	
MX	distant metastasis cannot be assessed
M0	no distant metastasis is present
M1	distant metastasis is present

Although most OSSN lesions are localized,³⁸ patients with invasive SSC are at increased risk for intraocular invasion, orbital involvement, and distant metastasis.^{38,41,50} Microscopically, the lesions comprise infiltrating nests of malignant squamous cells with associated fibrosis and lymphohistiocytic inflammation. The latter features are helpful in distinguishing invasion from tumor extension along glandular structures. With progressively higher grade, SCCs may invade as single cells rather than nests and may also assume a fusiform and pleomorphic cellular appearance (sarcomatoid SCC) (Fig. 8).

Most malignant OSSN lesions are keratinizing SCCs.⁵¹ Other histological variants include spindle-cell carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like carcinoma,⁵¹ adenoid squamous cell carcinoma⁵² and clear-cell squamous carcinoma^{53,54} (Fig. 8). The last of those subtypes may be similar microscopically to sebaceous carcinoma⁵³; however, it comprises cells with single intracytoplasmic vacuoles, rather than showing the multivesicular image of sebaceous tumors (Fig. 9).

A distinction between clear-cell SCC and sebaceous carcinoma can be achieved using immunohistochemical studies

for adipophilin, demonstrating intracytoplasmic vacuoles in sebaceous carcinoma only (Fig. 9). That marker is absent or it assumes a non-specific granular staining pattern in squamous cell carcinoma.⁵⁵ Some authors have also suggested that immunostaining for androgen receptor protein is helpful in recognizing sebaceous tumors in this context.⁵⁶ Histopathologic prognostic features include morphologic type, status of the resected margins, invasion of conjunctival aspect of the base of the biopsy, scleral invasion (if included in the biopsy or sent separately), lymphovascular invasion and perineural tumor spread.

Spindle-cell carcinoma and mucoepidermoid carcinoma (MEC) of the conjunctiva are potentially aggressive tumors, and immunohistochemical studies for keratin may be necessary to identify the first of those variants.³⁸ The identification of mucoepidermoid carcinoma of the ocular surface can pose a challenge for clinicians, because such lesions may produce minimal mucin in an epibulbar location.⁵⁷ Rapid growth or recurrence are clues to the identification of this rare entity, which is associated with a higher incidence of intraocular and orbital invasion.⁵⁸ Morphologically, one sees areas of gland formation that are juxtaposed to foci of squamous differentiation in MEC. Intracytoplasmic mucin can be demonstrated with histochemical stains such as the mucicarmine method, the digested periodic acid-Schiff technique, or the colloidal iron procedure.

In a retrospective case series by Yousef and Finger,⁵⁰ the size of the tumor (>5 mm in diameter), a high American Joint Committee on Cancer (AJCC) T substage (Table 2), extension onto the cornea (>2 mm), and scleral, intraocular, or orbital invasion were associated with adverse behavior. Galor et al.⁵⁹ found a higher risk of recurrence in AJCC T2 and T3 tumors as compared with T1; high-grade tumors (CIS and SCC); and tumors with tarsal involvement. Tumor-associated lymphangiogenesis has also been linked to the risk of local recurrence.⁶⁰

Melanocytic surface tumors

Conjunctival melanocytic lesions include melanosis, melanocytic nevi, primary acquired melanosis (PAM), ocular melanocytosis, and malignant melanoma.

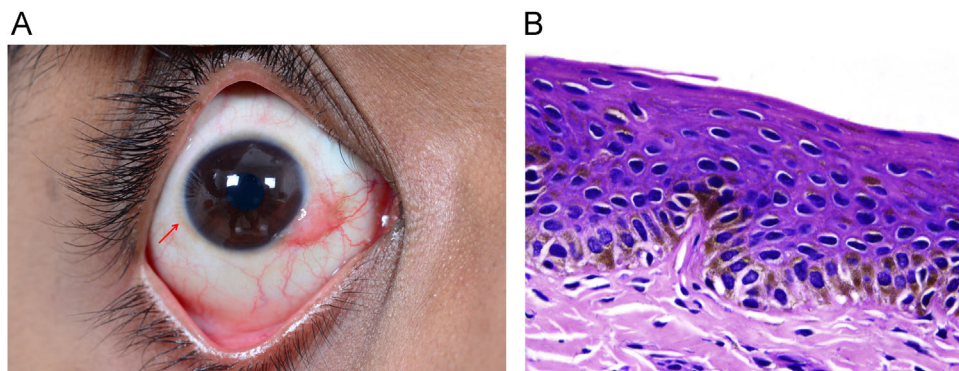


Fig. 10 – (A) Complexion associated melanosis presenting as a peri-limbal pigmentation (arrow) in a patient with conjunctival benign reactive lymphoid hyperplasia. (B) Supranuclear location of melanin in the basal cells of the conjunctival epithelium.

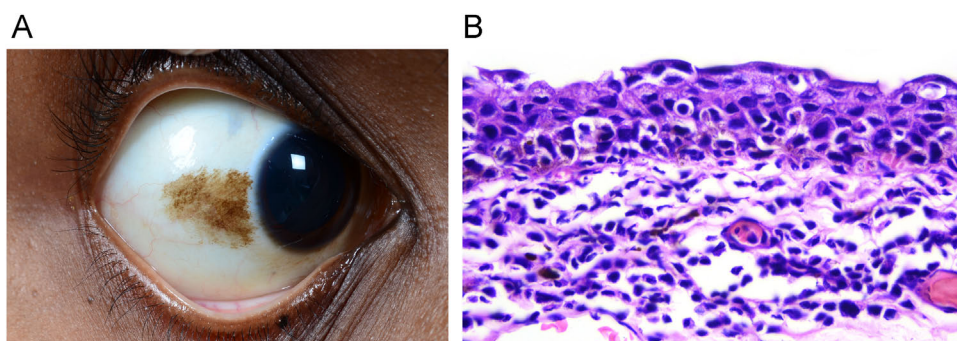


Fig. 11 – (A) Patchy, inter-palpebral pigmentation in primary acquired melanosis (PAM) and (B) PAM with atypia characterized by linear proliferation of atypical melanocytes.

Complexion-associated melanosis (CAM; “racial” melanosis)

CAM is common and it presents with bilateral, flat, diffuse pigmentation of the conjunctiva, concentrated in the limbus. One may also see variable pigmentation of the perilimbal bulbar conjunctiva and cornea (Fig. 10).¹ Microscopically, CAM is characterized by increased melanin production in the basal epithelial layer with or without accompanying dendritic melanocytes. Cytoplasmic melanin is typically supranuclear in location (Fig. 10).

Primary acquired melanosis (PAM)

PAM presents in middle-aged individuals with unilateral, superficial, patchy, diffuse, or multifocal pigmentation in the inter-palpebral, sun-exposed conjunctiva (Fig. 11). Microscopically, it is characterized by augmented melanin production without an increase in the number of melanocytes, or,

alternatively, by hyperplasia of dendritic melanocytes with melanin synthesis.⁶¹

It is important to determine whether cytological atypia is present in PAM, because 13% of such cases with severe atypia evolve to melanoma.⁹ PAM with atypia (PAMA) is microscopically characterized by linear, nested, or pagetoid arrangements of atypical melanocytes. They are larger than basal keratinocytes and show varying degrees of nuclear aberrancy (Fig. 11).⁶¹ PAMA may be graded as mild, moderate, or severe morphologically, or as “low risk” and “high risk.” If the atypical melanocytes replace >75% of the epithelial thickness, the lesion is considered as synonymous with melanoma in situ.^{62,63} Kenawy et al.⁶⁴ developed a scoring system for conjunctival melanocytic intraepithelial neoplasia (C-MIN), based on the pattern of horizontal epithelial involvement, vertical depth of melanocytic infiltration of the epithelium, and the degree of cellular atypia. The last of those elements considers cellular and nuclear diameters; the presence of nucleoli; and mitotic activity (Table 3). Two drawbacks exist for this scoring system: a lesion could be given a score of zero and yet be labeled as C-MIN and because the system scores the vertical extent twice (growth pattern and vertical spread, a risk of over scoring the lesion exists.⁶¹

Table 3 – Scoring system for conjunctival melanocytic intraepithelial neoplasia (C-MIN).

Parameter	Score
Growth pattern	
Basal	1
Pagetoid	2
Isolated nests	3
Confluent nests	4
Vertical intra-epithelial spread	
No vertical spread	0
Less than half thickness of epithelium involved	1
50–90% epithelium involved	2
More than 90% epithelium involved	3
Melanocytic atypia	
Nucleus and cytoplasm size less than that of basal keratinocyte	0
Nucleus of melanocyte is of the size of a basal keratinocyte	1
Cytoplasm of melanocyte greater in size than basal keratinocyte	1
Presence of nucleoli and/or mitoses	1
Total score	
Score 5 or more is melanoma in situ	10
Score < 5 is C-MIN with atypia	

Secondary melanosis

Secondary melanosis is similar to complexion-associated melanosis microscopically. It may result from the use of such

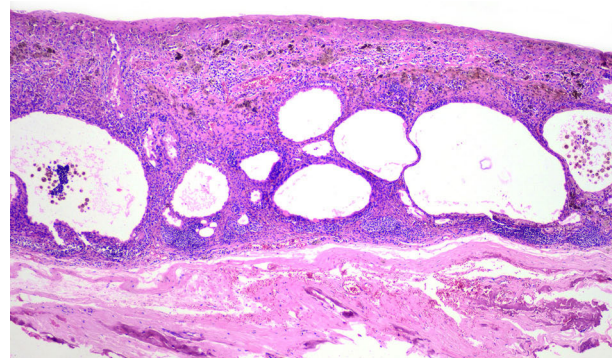


Fig. 12 – (A) Compound cystic nevus in a 20-year-old male patient and (B) sub-epithelial nevocytic proliferation with focal junctional activity and cystic downgrowths of the conjunctival epithelium.

drugs as chlorpromazine; chronic conjunctival inflammation; and effects of various other ocular surface lesions including papillomas, pterygium, pingecula, and OSSN.⁶¹

Melanocytic nevi

Melanocytic nevi (MN) are the commonest benign melanocytic tumors of the conjunctiva, and they have various clinical presentations. MN usually involve the bulbar conjunctiva and have a brown or tan appearance. Slit-lamp examination demonstrates entrapped cysts in some of them. The overall risk of MN evolving to melanoma is roughly 1%. Nevi may be classified as intra-epithelial, junctional, compound, or sub-epithelial based on the location of the abnormal cells. Of particular interest in this category is the “compound cystic nevus,” characterized by junctional and sub-epithelial nevocytic nests and the cystic down-growth of conjunctival epithelium (Fig. 12). Combined, blue, cellular blue and balloon-cell nevi have also been reported in the conjunctiva.^{65–68} It is a peculiarity of MN that they show a greater degree of cellular and nuclear heterogeneity than that seen in cutaneous nevi. This feature should not be used in isolation as justification for a diagnosis of melanoma.

Ocular melanocytosis (*melanosis oculi*)

Ocular melanocytosis is a congenital, unilateral, periocular pigmented lesion resulting from the abnormal migration of melanocytes. Melanocytosis may involve the sclera, iris, choroid, eyelid, and temporal fossa, and appearing as patches of scleral and episcleral brown to gray pigment.^{2,69} Microscopically, one sees fusiform or dendritic melanocytes in the episcleral tissue without epithelial involvement. Patients with uveal involvement have a significant risk for subsequent uveal melanoma.

Melanoma

Conjunctival melanoma is rare, accounting for 2–6.6% of melanocytic malignancies in the eye.⁷⁰ It affects Caucasians predominantly, is classically unilateral, and may occasionally be amelanotic. The most common site of occurrence is at the limbus in the interpalpebral bulbar conjunctiva but the palpebral conjunctiva, plica, caruncle, and fornix may also be affected.⁶¹ Most commonly, conjunctival melanoma arises from PAM or MN, but some examples are malignant *ab initio*.⁷⁰

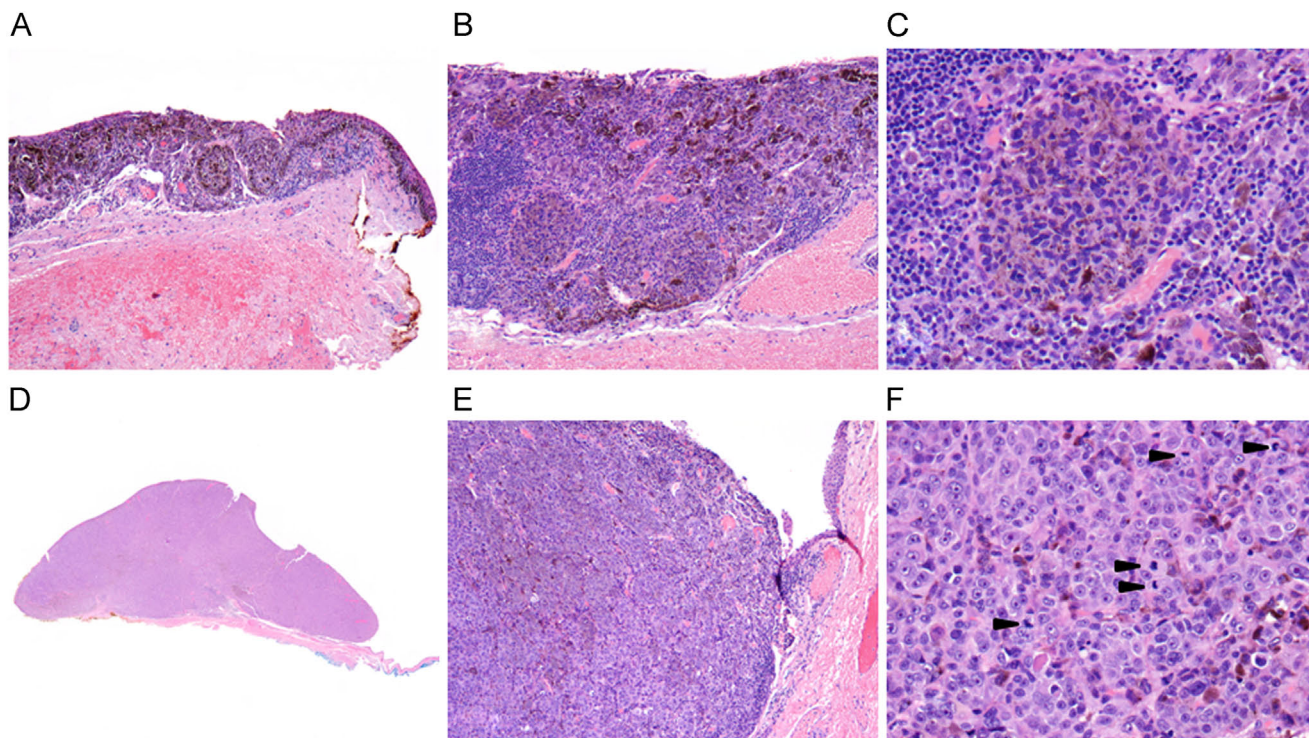


Fig. 13 – (A) Scanning magnification of eyelid tissue with a confluent intraepithelial proliferation of atypical melanocytes replacing the basilar epithelium with upward pagetoid migration and a brisk underlying lymphohistiocytic inflammatory infiltrate in the superficial submucosa. (B and C) Higher power examination reveals invasive melanoma into the submucosa with an associated lymphohistiocytic inflammatory response. The tumor cells exhibit cytologic atypia, including increased pale eosinophilic cytoplasm (some with intracytoplasmic pigment) and variably elongate-ovoid, hyperchromatic nuclei. (D) Scanning magnification of eyelid tissue effaced by a proliferation of malignant epithelioid melanocytes forming an expansile nodule in the submucosa. (E and F) Higher power examination reveals a densely cellular proliferation of cytologically malignant epithelioid melanocytes with increased pale eosinophilic cytoplasm and enlarged oval nuclei with prominent nucleoli. Scattered mitotic figures (arrowheads) are evident throughout the lesion.

Microscopically (Fig. 13), conjunctival melanomas may comprise small round (nevoid), spindle, or epithelioid cells. They exhibit some degree of nuclear atypia, often with prominent nucleoli. Melanin pigment may or may not be apparent, and mitoses are usually sparse.

Clinical factors associated with a poor clinical outcome include an unfavorable location (fornix, palpebral conjunctiva, medial bulbar conjunctiva, caruncle, and plica semilunaris); tumor thickness, presence of histologic ulceration, size >10 mm; and multifocality.^{61,71} Adverse histopathologic factors include deep invasion, epithelioid cytology, and lymphovascular invasion. Mutations in conjunctival melanoma may involve the *N-RAS*, *BRAF*, and *TERT* genes.^{72–74}

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