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Squamous Neoplasia of the Conjunctiva: The New TNM Classification by the American Joint Committee on Cancer (AJCC)

By Hugh D. McGowan, MD, FRCSC

Recently, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUCC) developed an update for the tumour, node, metastasis (TNM) classification of conjunctival intraepithelial neoplasia (CIN), carcinoma *in situ* (Cis), and squamous cell carcinoma (SCC).[1] This issue of *Ophthalmology Rounds* reviews this new classification and discusses the incidence, differential diagnosis, histopathology, staging, and care of patients with squamous neoplasia. This classification should provide better identification of prognostic risk factors and improve outcome analysis. Further, it allows clinicians the capability to more accurately classify clinical disease and pathological stage, thus enabling more appropriate application of treatment modalities.

Overview

Squamous neoplasia of the conjunctiva/cornea is a rare malignancy of conjunctival limbal stem cells, and management of this malignancy may affect the ultimate outcome. The clinical distinction of SCC of the conjunctiva, from other amelanocytic tumours of the conjunctiva, is based on certain clinical features of the tumour, and correct management requires an understanding of normal anatomy and histology of the cornea and conjunctiva, as well as knowledge of the principles of tumour management.

Treatment is centred on tumour excision with "minimal manipulation" and adjuvant cryotherapy, but new roles for topical chemotherapy and immunotherapy are emerging. Surgical margin assessment is increasingly enhanced with preoperative ultrasound biomicroscopy (UBM). Conjunctival SCC is associated with high recurrence rates and local invasion; positron emission tomography and computed tomography (PET/CT) scanning, as well as sentinel lymph node (SLN) assessment, play increasing roles in staging patients.

Pathophysiology

Squamous dysplasia and neoplasia of the squamous epithelium of the conjunctiva may present with several types of benign and malignant lesions, revealing a spectrum from low malignant potential to aggressive malignant behaviour with local invasion and possible distant metastasis. It is often difficult for the ophthalmologist to differentiate these lesions on clinical appearance alone, reinforcing the importance of accurate pathological assessment (Table 1).[2]

Benign lesions include keratotic plaque and actinic keratosis; these are difficult to distinguish from CIN, which has a higher potential to progress to SCC and invasive (inv) SCC. CIN consists of abnormal cellular proliferation limited to the epithelium and is evaluated as Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe). When the full thickness of the epithelium is involved, it is then referred to as Cis. Extension of atypical cells through the basement membrane into the substantia propria, abnormal epithelial cells with keratin production, and/or increased mitotic activity are referred to as invSCC. Histopathological variants include SCC, mucoepidermoid carcinoma, basal cell carcinoma (rarely), and spindle cell carcinoma.[3-5]

Incidence

Conjunctival SCC accounts for only 5% of all ocular malignancies;[3] whereas on the eyelid, basal cell carcinoma outnumbers SCC, 40:1, SCC of the conjunctiva is the most common conjunctival malignancy. Conjunctival squamous cell neoplasias occur more commonly in

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Table 1: Tumours of the surface epithelium in the conjunctiva[2]

Type of tumour	Number of cases
Benign	
Squamous cell papilloma	74
Keratotic plaque	9
Pseudocarcinomatous hyperplasia	9
Benign hereditary intraepithelial dyskeratosis	5
Intraepithelial neoplasia	
Actinic keratosis (solar keratosis)	149
Dysplasia	76
Carcinoma *in situ*	26
Malignant	
Squamous cell carcinoma	151
Basal cell carcinoma	1
Mucoepidermoid carcinoma	4
Adenocarcinoma	5

Frequency distribution of 509 tumours in the Registry of Ophthalmic Pathology 1984-1989 Armed Forces Institute of Pathology (AFIP)[2]

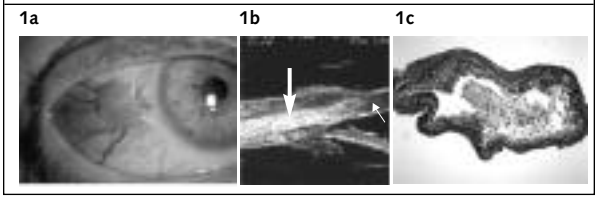
pale-skinned groups than in more pigmented groups, with an increased incidence in males (75%) vs females (25%), at a median age of 60 years.[3-5] The SCCs associated with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are seen at younger ages (average 35 years), are usually not in a bulbar location, and are more aggressive, clinically. Shields et al[6] reviewed a large clinical sample of conjunctival tumours and found that 219/1643 (13%) were epithelial in origin.

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) in the United States (US) for the years of 1984 to 2005, provided evidence of an increasing incidence of conjunctival SCC, especially in white male patients >60 years of age.[3] The incidence of SCC varies geographically (increasing with closer distance to the equator); for example, Uganda has 1.2 cases/100 000 persons/yr, compared to the United Kingdom with <0.02 cases/100 000 persons/year. This may suggest a role of ultraviolet (UV) light exposure in the etiology of these tumours. SEER data in the US indicates an incidence of 0.03/100 000 persons/yr, and the incidence increases 6-fold in association with HIV infection.[7,8] The lesions are more common in males and the elderly, with the majority occurring at the limbus. The etiology is multifactorial with risk factors including fair complexion, UV light exposure, atopic eczema, and infection with human papilloma virus (HPV), or HIV. Invasive disease may spread locally, with 2%-15% demonstrating intraocular spread and 12%-16% of cases progressing to orbital disease.[7,8]

Association with infectious agents

Conjunctival papillomas are associated with HPV infection in 58%–92% of cases.[8] The low-risk HPV types 6 and 11 are significantly more common than the high-risk HPV types 16 and 18, associated with high-grade cervical intraepithelial neoplasia and carcinoma. HPV-types 6 and 11 are also most frequently associated with benign dysplastic lesions.[8] Squamous carcinoma of the conjunctiva has an equivocal association with HPV types 16 and 18, but a very strong association with HIV infection. The role of HIV infection in SCC is uncertain, since

Figure 1: 1a: Bulbar conjunctival carcinoma with limbal involvement and increased vascularity. **1b:** Ultrasound microscopy (UBM) showing surface carcinoma interface with the bulbar sclera (large arrow), Bowman membrane, (small arrow). **1c:** Pathology showing nests of carcinoma cells replacing all of the normal layers of the conjunctival epithelium.



the pathogenesis is unclear as to whether immunosuppression or HIV itself is more causative.[8]

Mortality and morbidity

Estimates of overall tumour-related mortality at 10 years is in the range of 4%-8%.[3] Orbital exenteration rates are 6% at 5 years in the US, but are higher in HIV-endemic areas, with 13/23 cases (56%) reported in a case series in Zimbabwe.[9] Risk factors for death using multivariate analysis include local invasion (reflecting locoregional recurrence and brain involvement, not systemic metastasis; $P=0.004$) and pathology of perineural invasion ($P=0.05$).[10]

Clinical assessment

History

The history on the growth of conjunctival squamous dysplastic lesions is crucial and varies depending on tumour origin and location. SCCs that arise *de novo* at the limbus usually have a short horizontal growth phase followed by a more rapid vertical growth phase. SCCs that arise from intraepithelial neoplasia show growth and increasing vascularity in the original lesion (Figure 1). Papillomatous thickening followed by increased vascularity and adhesion to the underlying scleral tissue mark the onset of malignant degeneration in conjunctival intraepithelial neoplasia.[10]

Differential diagnosis

Benign tumours may arise from the conjunctival epithelium, such as: the pseudotumours, pinguecula and pterygium; benign tumors; squamous papilloma; keratotic plaque; actinic keratosis (solar keratosis); and dysplasia (Figure 2).[2,3] Malignant tumours include SCC, basal cell carcinoma, mucoepidermoid carcinoma, and adenocarcinoma. Other amelanotic tumours that may

Figure 2: Benign lesions: 2a: Keratotic plaque, leukoplakia, abnormal keratinization of squamous dysplastic lesion at the limbus of the right eye. **2b:** Squamous papilloma of the limbal conjunctiva showing vascularized fronds.

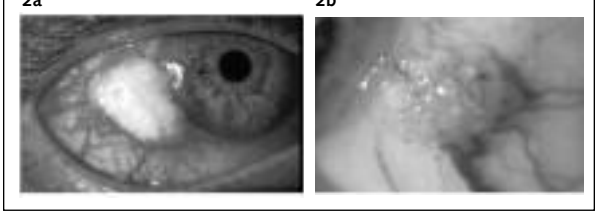
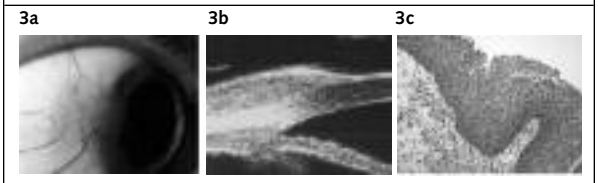


Figure 3: Malignant lesions: 3a: Limbal squamous cell carcinoma (SCC) showing a papillomatous pattern of growth with increased conjunctival vascularity (arrow). **3b:** UBM showing the interface between the SCC and the sclera in the proximity of the surgical limbus (arrow). **3c:** Histopathology of squamous intraepithelial neoplasia.



UBM courtesy of Dr. C.J. Pavlin, 2008.

clinically mimic SCC include a conjunctival pagetoid spread of sebaceous carcinoma, amelanotic conjunctival melanoma, reactive and atypical lymphoid hyperplasia, and conjunctival lymphoma.[2,3,6]

Slit-lamp biomicroscopy

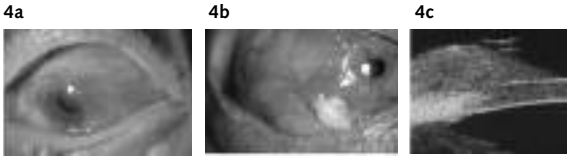
Clinical assessment should delineate the size of the lesion, its location, conjunctival mobility, vascularity, and association with the caruncle and nasolacrimal drainage system. Bulbar conjunctiva location is the most common, but lesions can occur in the forniceal, palpebral, and pretarsal conjunctiva, as well as the caruncle. SCC of the conjunctiva may appear identical to actinic keratosis as a leukoplakic lesion due to keratinization of the normally nonkeratinizing conjunctival epithelium.

Ultrasound biomicroscopy (UBM)

High-frequency (50 MHz) ultrasound imaging of conjunctival squamous dysplastic lesions allows for accurate measurement of the thickness of the tumour, which can be a predictor of survival.[11] Preoperative imaging can delineate the relation of the tumour to the structures of the cornea (intact Bowman layer, stromal invasion) and its relation to the underlying sclera (scleral invasion, emissarial vessel involvement; Figure 3). Typical nodular limbal squamous dysplastic tumours reveal a solid mass with low-level internal reflectivity, while more diffuse tumours are spread over a larger area with margins that are often difficult to accurately delineate.[11]

The preoperative UBM can aid the ophthalmic surgeon in determining the type and extent of superficial keratectomy and/or superficial sclerectomy required at the time of the initial tumour excision (Figure 4).[11]

Figure 4: 4a: Conjunctival SCC showing a corneal pannus pattern of growth. **4b:** Large conjunctival SCC showing a limbal papillomatous pattern of growth. **4c:** UBM showing relation of the SCC to the cornea, suggesting an intact Bowman layer.



UBM courtesy of Dr. C.J. Pavlin, 2008.

Table 2: Staging for conjunctival carcinoma[1]

1. Clinical classification (cTNM):	**Conjunctival carcinoma**
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[1]
T2	Tumor more than 5 mm. in greatest dimension, without invasion of adjacent structures[2]
T3	Tumor invades adjacent structures[2] (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
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
2. Pathological classification (pTNM):	**Conjunctival carcinoma**
Primary tumor (T)	
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Carcinoma *in situ*
pT1	Tumor(s) of bulbar conjunctiva, greatest dimension less than 5 mm.
pT2	Tumor(s) of bulbar conjunctiva, greatest dimension greater than 5 mm.
pT3	Tumor(s) of conjunctiva invading adjacent structures (excluding the orbit)
pT4	Tumor invades orbit with or without further extension
Regional lymph nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Regional lymph node metastasis
Distant metastasis (pM)	
pMX	Distant metastasis cannot be assessed
pM0	No distant metastasis
pM1	Distant metastasis
3. Stage group: No stage grouping recommended at this time.	
4. Histopathologic type:	
Carcinoma of the conjunctiva	
Conjunctival intraepithelial neoplasia (CIN)	
Squamous cell carcinoma	
Mucoepidermoid carcinoma	
Spindle cell carcinoma	
Sebaceous cell carcinoma including pagetoid (conjunctival) spread[12] (NEW)	
Basal cell carcinoma	

Table 2: Staging for conjunctival carcinoma *cont*[1]

5. Histopathologic grade: represents the primary tumor GX – Grade cannot be assessed G1 – Well differentiated G2 – Moderately differentiated G3 – Poorly differentiated G4 – Undifferentiated
6. Biomarkers (NEW) **a. Is the Ki-67 growth fraction less than or equal to 5%?** **b. Is the Ki-67 growth fraction between 5 and 10%?** **c. Is the Ki-67 growth fraction between 10 and 20%?** **d. Is the Ki-67 growth fraction between 20 and 50%?** **e. Is the Ki-67 growth fraction greater than 50%?**

Clinical staging

Clinical staging is based on assessment of the cancer by inspection; slit-lamp examination, palpation of regional nodes, and clinical photography are used, as well as UBM when intraocular invasion is suspected or the tumour is affixed to the globe. Standardized ultrasound is also helpful when intraocular or orbital invasion is suspected. Radiological examination (CT, magnetic resonance imaging [MRI], and PET/CT) can be used to examine regional node status, paranasal sinuses, orbit, brain, and chest. Ongoing studies are designed to clarify the role of sentinel node biopsy in the accurate staging of invasive squamous cell carcinoma.[1]

Staging also includes clinical classification and pathological classification as outlined by the AJCC;[1] this staging is applicable to conjunctival carcinomas with the natural history of lymphatic spread to regional nodes, the possibility of hematogenous metastases, as well as subsequent locoregional disease and metastatic disease (Table 2).

Histopathological findings

SCC of the conjunctiva consists of well-differentiated cells with exophytic growth of atypical epithelial cells. In advanced cases, the substantia contains inflammatory cells, as well as invading masses of atypical epithelial cells. There is great variation in the size, configuration and degree of differentiation of the invading cells; cells can be hyperplastic and hyperchromatic, keratinized cells, concentric collections of keratinized cells (horn pearls), exhibit loss of cohesiveness and atypical mitotic figures.[2] Immunohistochemical staining plays an important role in the assessment of malignant SCC tumours and current panels of antibody stains, emphasizing epithelial markers, include hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), cytokeratins AE1/AE3, epithelial membrane antigen (EMA), and low- and high-molecular-weight cytokeratins (CK-LMW, and CK-HMW).[13]

Ki67 protein is a cellular marker for proliferation and is detected with the monoclonal antibody, MIB-1; this marker provides a good measure of the tumour growth fraction. Mucoepidermoid carcinoma has varying portions containing mucous-secreting components that can be seen with mucicarmine, alcian blue, CAM5.2, and BRST-1 stains.[13,14] Spindle cell variants consist of spindle cells, as opposed to atypical epithelial cells, and show frequent desmosomes with electron microscopy.

Treatment

Surgical care

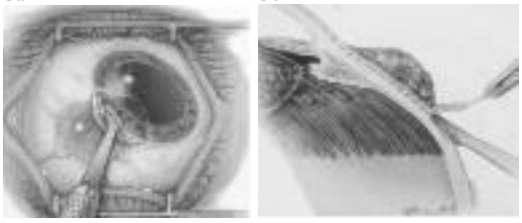
The recommended treatment of classic limbal conjunctival SCC includes "no touch" excisional tumour removal with a clear margin of 2-3 mm, alcohol (70%) epitheliectomy of adjacent corneal epithelium, and adjuvant double freeze-thaw cryotherapy to the tumour-free margins of the conjunctiva (Figure 5).[3,10,15,16] Not disturbing the tumour mass is an important goal, as well as using separate microinstruments for different sites so that pathology specimens are not contaminated. Tumours that have breached the Bowman layer of the cornea (seen on preoperative UBM) and with more adherence to the cornea may require a superficial keratectomy. Tumours adherent to the underlying sclera (immobile on clinical examination and the invasion noted on UBM) may require a superficial sclerectomy under the tumour base in the attempt to ensure complete excision. A dry surgical field should be maintained to promote adherence of any tumour cells to the excised mass. Adjuvant cryotherapy is applied in a specific manner with a double freeze-thaw technique to the underside of the conjunctival epithelial edges of the resection and the base of the scleral dissection.[10,15] Alcohol treatment to the scleral base has also been used.

Tunc et al[10] reported recurrence rates of 4.5% for CIN and 5.3% for SCC when the surgical technique included surgical removal with intraoperative surgical margins and adjuvant cryotherapy. Sudesh et al[15] reported a recurrence rate of 28.5% with surgical excision alone and 7.7% with surgical excision and cryotherapy. The technique of initial surgical management is an important factor in the reduction of recurrence (P=0.07), metastasis (P=0.03), and death (P=0.006), but only maintained statistical significance on univariate analysis.[16]

Tumours in other locations (fornix, palpebral, tarsal) should be excised with wider clear margins (3-4 mm), alcohol treatment to the base (70% appears less damaging to the Bowman layer), and cryotherapy (freezing for 10-20 seconds with probe temperatures approaching -30° to -40°C) applied to the conjunctival margins.[10,15,16] Conjunctival autogenous grafts, buccal mucosal grafts, or amniotic

Figure 5: "No touch" excisional biopsy technique of a limbal tumour. 5a: Corneal epitheliectomy **5b:** lamellar sclerectomy and tumour removal.

5a 5b



Courtesy of Dr. Jerry A. and Carol L. Shields[16]

membrane grafts may be necessary with larger resections, and in cases where symblepharon formation is a possible complication.[10,15,16]

Less commonly, cases can result in globe or orbital invasion and may require modified enucleation or orbital exenteration.[9,15,17] A meta-analysis of 9 publications on large series of exenterations between 1954 and 2005 indicated that 89/559 (16%) cases were for conjunctival SCC and required exenteration for advanced disease.[17] Risk factors predictive of orbital exenteration were positive margins at primary resection, perineural invasion, positive nodal status, and medial canthal tumour location.[17]

Topical chemotherapy

Recent publications have advocated the use of topical chemotherapy (mitomycin C, 5-fluorouracil, and interferon A) in the management of conjunctival SCC, primary acquired melanosis, conjunctival melanoma, and pagetoid invasion of sebaceous gland carcinoma.[3,18-20] All of these applications are presently "off-label" treatments, and although well supported in the literature, often present a challenge for the clinician to obtain drug plan coverage. Present recommendations advocate adjuvant therapy with 2-4 cycles of topical mitomycin C 0.04% qid, where 1 cycle consists of 7 days ontreatment and 7 days offtreatment to allow for epithelial recovery. Patients must place the topical drops while lying in the supine position and apply punctal occlusion for 5 minutes after drop placement. Some centres are now placing temporary punctal plugs to prevent antimetabolite effects on the nasolacrimal drainage system. Side effects include dry-eye syndrome, superficial punctate keratitis/keratopathy (SPK), toxic conjunctivitis, limbal stem-cell failure, and punctal stenosis.[3,18,19] The 5-fluorouracil dose is a solution of 1% in drops qid over 28 days.

Interferon alpha 2a[21] can also be administered topically to control epithelial malignancies with treatment regimens of 1 MU/mL concentrated drops applied qid, but treatment times may extend for months. The drops are well tolerated by patients over an extended time course.

Present recommendations suggest that topical chemotherapy (mitomycin C) as primary treatment is most effective for intraepithelial disease such as CIN and Cis.[18-21] It may also play a role as adjuvant therapy in cases with positive margins or pathological evidence of invasion after primary treatment with surgery and cryotherapy.

Radiation therapy

SCC of the conjunctiva is a radiosensitive tumour, but radiotherapeutic treatment has been limited to brachytherapy techniques either alone or as adjuvant therapy to support surgical resection. Kearsley et al[22] have had extensive experience in Australia using adjuvant radiation with strontium-90 after surgical resection and reveal excellent control rates with only 3/131 patients indicating a recurrence after a 30-Gy dose. Primary treatment with ruthenium-106 plaque brachytherapy was reported in a case where 320 Gy was delivered at the surface with no recurrence at 22 months.[23]

Sentinel lymph node (SLN) biopsy

Regional lymph node metastasis secondary to conjunctival SCC is a rare occurrence, involving the preauricular (intraparotid) nodes, submandibular, and deeper cervical nodes. Some patients may develop distant metastasis without prior nodal disease.[24] Wilson et al[24] reported a technique of SLN biopsy in conjunctival SCC that provided the detection of microscopic regional nodal disease and offered important staging information. Technetium (Tc-99m sulfur colloid) with an activity of 0.3 mCi (11.1 Mbq) in 0.2 mL is injected subconjunctivally around the base of the tumour and imaged with a handheld gamma probe at 20 minutes in the area of the regional nodes (intraparotid, preauricular, cervical, and submandibular). The identified nodes are surgically excised and assessed on histology with H&E and immunohistochemical stains (epithelial markers, cytokeratins: AE1/AE3, EMA, CK-LMW, CK-HMW) and with MIB-1 to assess Ki67 protein.

The staging information of positive nodes at the time of primary tumour resection would allow for earlier detection of those patients at risk of distant metastasis, and the possibility of offering systemic chemotherapy. Generally, SLN biopsies are only indicated in SCC of the conjunctiva when there is extensive primary disease or a high-risk presentation (T3 or T4; ie, local tissue involvement, fornix, medial canthal, intraocular, orbital). SLN biopsy is not usually used in routine cases, but are more indicated in other conjunctival malignancies, eg, melanoma, sebaceous cell, or Merkel cell carcinoma.

Conclusions

The comprehensive ophthalmologist will see few conjunctival SCCs in his/her career, but given the

high recurrence rates and the potential for local invasion that accompanies the disease, it is a diagnosis that should not be delayed or missed. A strong clinical suspicion is necessary when dealing with amelanotic lesions of the conjunctiva, but accurate history, slit- lamp examination, clinical photography, and close clinical follow-up can help differentiate conjunctival SCC from other similar lesions. Documented growth and increasing vascularity should lead to appropriate imaging with UBM[11] and initial treatment, including surgical resection as per Shields[16] with cryotherapy playing a significant role in reducing rates of local recurrence. SLN biopsy assessment will also play an increasing role in staging patients.[23]

Meticulous surgical resection with adjuvant cryotherapy remains the mainstay of treatment, but topical chemotherapy and adjuvant radiotherapy techniques will be instrumental for primary and secondary management. Systemic chemotherapy and/or immunotherapy may be offered to patients with nodal involvement at presentation and it is hoped that this will have a positive effect on long-term survival.

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