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Ocular Oncology: Malignant Melanoma of the Conjunctiva

By Hugh D. McGowan, M.D.

Malignant melanoma of the conjunctiva/cornea is a rare malignancy of conjunctival melanocytes, in which management may ultimately affect survival. Distinguishing malignant melanoma of the conjunctiva from other melanocytic tumours of the conjunctiva is based on certain clinical features of the tumour. Managing this malignancy correctly requires an understanding of the normal anatomy and histology of the cornea and conjunctiva, as well as knowledge of the principles of tumour management. Treatment is centered on "minimal manipulation" tumour excision with adjuvant cryotherapy, but there are emerging roles for topical chemotherapy and immunotherapy. Surgical margin assessment is increasingly enhanced with pre-operative ultrasound biomicroscopy (UBM). Conjunctival melanoma is associated with significant morbidity and mortality, and sentinel lymph node assessment plays an increasing role in the staging of patients.

Pathophysiology

Malignant melanoma of the conjunctiva arises from neuroectodermal-derived melanocytes in the basal layer of the conjunctiva and can show significant clinical variability. The majority (60%-75%) arise in pre-existing primary acquired melanosis (PAM); 20%-25% arise from pre-existing conjunctival nevi (junctional or compound); and 10%-25% arise *de novo* in normal-appearing conjunctival epithelium.[1-3] The majority (>90%) are melanotic, but some may present as amelanotic tumours.

Incidence

Conjunctival tumours occur more commonly in Caucasians than in pigmented races,[4] with an equal incidence in males and females at a median age of 62 years.[1] The estimated annual incidence in Denmark is 0.052 cases/100,000 compared to an incidence of 0.6 cases/100,000 for uveal melanoma. Singh et al reported an annual age-adjusted incidence of 0.012 cases/100,000 in the United States.[4] Conjunctival melanoma accounts for only 2% of all ocular malignancies. As with cutaneous melanoma, there is evidence from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) in the United States that the incidence of conjunctival melanoma increased between 1973 to 1999, especially in white male patients >60-years-old.[5] This may suggest that ultraviolet light exposure plays a role in the etiology of these tumours.

Mortality and morbidity

Estimates of overall tumour-related mortality at 10 years is 25%-26%.[1] A study by Paridaens et al demonstrated a 5-year survival rate of 83%-84% and a 10-year survival rate of 69%-80%.[3] Shields et al determined that the 5- and 8-year death rates were 7% and 13%, respectively (Table 1).[2] Recurrence rates were 39% at 5 years in the Moorfields study,[3] and 26% at 5 years and 51% by 10 years in the Philadelphia study.[2] Morbidity, measured by metastasis and exenteration rates, was 16% and 8%, respec-

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Table 1: Risks for local tumour recurrence, exenteration, metastasis, and death in patients with conjunctival melanoma[2]

	Length of follow-up		
Outcome	±5 years	±10 years	±15 years
Recurrence (%)	26	51	65
Exenteration (%)	8	16	32
Metastasis (%)	16	26	32
Death (%)	7	13	NA

NA = not available

tively, at 5 years. Risk factors for death using multivariate analysis included initial symptoms (reflecting tumour size; p=0.004) and pathology of malignant melanoma arising *de novo* (p = 0.05).[2]

Clinical assessment

History

The history of the growth of a conjunctival melanoma is crucial and varies, depending on the origin and location of the tumour. Melanomas that arise *de novo* at the limbus usually have a short horizontal growth phase followed by a more rapid vertical growth phase. Melanomas that arise from pre-existing nevi show growth and increasing vascularity of the original lesion (Figure 1). Nodular thickening followed by increased vascularity and adhesion to the underlying scleral tissue marks the onset of malignant degeneration in primary acquired melanosis.

Differential diagnosis

Tumours that arise from the melanocytes of the conjunctiva include nevus, the most common (Figure 2), racial melanosis, primary acquired melanosis, and malignant melanoma.[1]

The differential diagnosis of increased conjunctival pigmentation includes ocular melanocytosis, pigmented pterygium/pinguecula; Axenfelds nerve loops, silver-containing eye drops, mascara, adenochrome pigment, ochronosis, and alkaptonuria.[1] Pseudomelanoma presentation can be seen with extrascleral extension from ciliary body (CB) melanoma (Figure 3), anterior staphyloma of the sclera, subconjunctival foreign body (FB) with hemosiderosis, Cogan plaques at the insertion of the horizontal recti and hemorrhagic subconjunctival cysts post-trauma/surgery.[1]

Slit lamp biomicroscopy

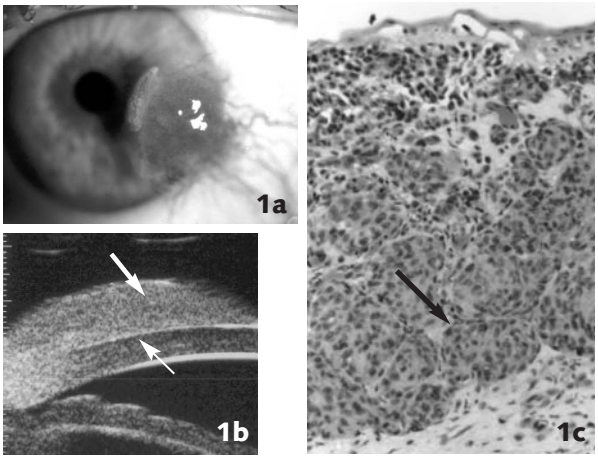
Clinical assessment with slip lamp should delineate size, location, conjunctival mobility, vascularity, and association with conjunctival nevi or primary acquired melanosis (PAM). Bulbar conjunctiva location is the most common, but tumours can occur in the forniceal, palpebral and pretarsal conjunctiva, as well as the caruncle.

Figure 1: Typical limbal conjunctival melanoma

1a: Limbal conjunctival melanoma with corneal involvement and increased vascularity

1b: Ultrasound biomicroscopy (UBM) showing corneal component of tumour (thick arrow) with intact Bowman's membrane (thin arrow).

1c: Pathology showing nests of melanoma cells (large arrow) replacing all of the normal layers of the conjunctival epithelium.



Ultrasound biomicroscopy (UBM)

High frequency ultrasound (50 MHz) biomicroscopy imaging of conjunctival melanoma allows for accurate measurement of the thickness of the tumour, which can be considered a predictor of survival.[6] Preoperative imaging can delineate the relation of the tumour to the structures of the cornea (intact Bowman's layer, stromal invasion) and the relation to the underlying sclera (scleral invasion, emissary vessel involvement; Figure 4). Typical nodular limbal melanoma tumours show a solid mass with low-level internal reflectivity, while more diffuse tumours are spread over a larger area and margins are often difficult to delineate accurately.[6]

Figure 2: Typical conjunctival nevus at the limbus in a 14-year-old female.

2a: Slit lamp exam of the nevus may show characteristic cystic changes.

2b: Pathology shows nevus cells in the stroma (thick arrow) under an intact conjunctival epithelium (thin arrow).

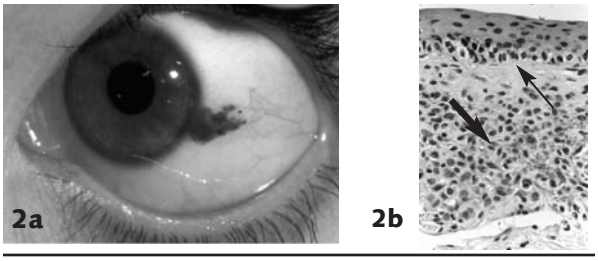
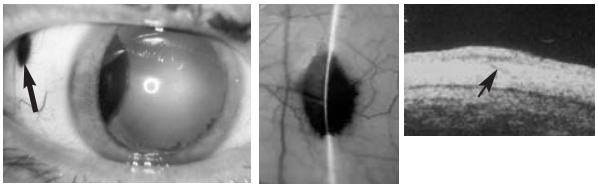


Figure 3: Extrascleral extension of a ciliary body (CB) melanoma simulating conjunctival melanoma

3a: Red reflex picture showing CB melanoma and pigmented scleral nodule (arrow).

3b: Higher magnification of the scleral nodule.

3c: UBM showing the emissarial vessel connection between the intraocular tumour and the scleral nodule (arrow). (UBM courtesy of Dr. C.J. Pavlin)



3a **3b** **3c**

The preoperative UBM can aid the ophthalmic surgeon with decisions as to the type and extent of superficial keratectomy and/or superficial sclerectomy required at the time of initial tumour excision.

Diagnostic biopsy and staging

Classic limbal melanoma tumours should be approached with complete surgical excision ("no touch" technique) combined with cryotherapy to the remaining tumour-free margins. 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.[2]

Staging includes clinical classification and pathological classification as outlined by the American Joint Committee on Cancer, and is applicable to conjunctival melanoma with the natural history of lymphatic spread to regional nodes and subsequent metastatic disease. This is in contradistinction to uveal melanoma in which nodal status is not an issue, given the absence of lymphatic drainage in the orbit posterior to the orbital septum.

Staging

The clinical classification for conjunctival melanomas is shown in Table 2; the pathological classification is shown in Table 3. There is no stage group at this time. The designation for histopathologic type is "malignant melanoma of the conjunctiva."

For "Histopathologic Grade," which represents the primary tumour, the following is used:

- GX – origin cannot be assessed
- G0 – Primary acquired melanosis (PAM)
- G1 – Malignant melanoma arises from nevus
- G2 - Malignant melanoma arises from PAM
- G3 - Malignant melanoma arising de novo.

Table 2: The clinical classification (cTNM) of conjunctival melanomas

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour(s) of bulbar conjunctiva, ≤1 quadrant
T2	Tumour(s) of bulbar conjunctiva, >1 quadrant
T3	Tumour(s) of conjunctival fornix, palpebral conjunctiva, or caruncle
T4	Tumour invades eyelid, cornea, orbit
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

American Joint Committee on Cancer (AJCC), *Cancer Staging Manual*, 5th edition;1998.

Table 3: The pathological classification of conjunctival melanomas

Primary tumour (pT)	
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pT1	Tumour(s) of bulbar conjunctiva, ≤1 quadrant, <2 mm in thickness
pT2	Tumour(s) of bulbar conjunctiva, >1 quadrant, ≤ 2 mm in thickness
pT3	Tumour(s) of conjunctival fornix, palpebral conjunctiva, or caruncle, >2 mm
pT4	Tumour invades eyelid, cornea, orbit
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

AJCC, *Cancer Staging Manual*, 5th edition;1998.

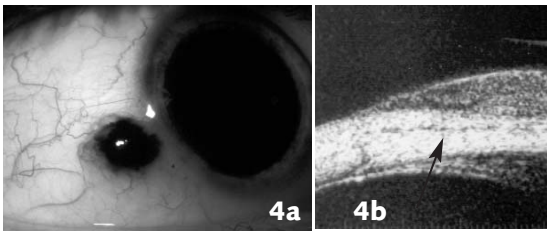
Histopathological findings

In malignant melanoma of the conjunctiva, abnormal melanocytes near the basal layer of the epithelium tend to grow in irregular nests. The tumour may involve the underlying stroma and replace all layers of normal conjunctival epithelium.[7]

Figure 4: Ultrasound assessment of a conjunctival melanoma

4a: Conjunctival melanoma arising from a pre-existing conjunctival nevus.

4b: The UBM shows possible early scleral invasion at the interface of the tumour and the outer sclera (arrow).



(Courtesy of Dr. C.J. Pavlin, published in *Ultrasound Biomicroscopy of the Eye*,1995)

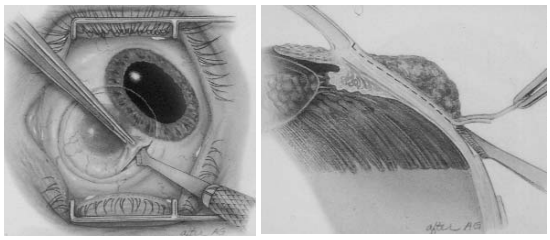
The melanoma cells are larger than nevus cells, have large nuclei with chromatin clumping in the periphery of the nuclear membrane, have distinct eosinophilic nucleoli, and may be a polyhedral, spindle, epithelioid, or balloon cell. The Callendar classification for melanoma, established for intraocular uveal tumours, does not apply to conjunctival melanoma. Immunohistochemical staining plays an important role in the assessment of malignant melanocytic tumours arising in nevi or PAM. Panels of antibody stains with Melan-A, HMB-45, and S100 help differentiate benign tumours (nevi), PAM without atypia (<1% chance for progression to melanoma), PAM with atypia (>50% chance for progression to melanoma), and malignant melanoma.[7,8] Immunohistochemical staining in conjunctival melanoma shows a diagnostic sensitivity of 100% with anti-S100 and anti-Melan-A, and 85% with anti-HMB-45.[8]

Treatment

Surgical care

The recommended treatment of a classic limbal conjunctival melanoma includes "no touch" excisional tumour removal with a 2-3 mm clear margin (Figure 5), alcohol epitheliectomy of adjacent corneal epithelium, and adjuvant double freeze-thaw cryotherapy to the tumour-free margins of the conjunctiva.[1,9,10] It is important that an attempt be made not to disturb the tumour mass and to use separate micro-instruments for different sites to ensure that pathology specimens are not contaminated. Tumours that have breeched Bowman's layer of the cornea (seen on preoperative UBM) and are more adherent to the cornea may require a superficial keratectomy. Tumours that adhere to the underlying sclera (immobile on clinical exam and invasion noted on UBM) may require a superficial sclerectomy under the tumour base in an effort to ensure complete excision. The surgical field should be dry to promote adherence of any tumour cells to the excised mass. Adjuvant cryotherapy with a double freeze-thaw technique is applied to the underside of the conjunctival epithelial edges of the resection and the base of the scleral dissection.[10] Alcohol treatment to the scleral base has also been used.

Figure 5: Figure 5a and b: "No touch" excisional biopsy technique of a limbal tumour



(Courtesy of Drs. Jerry A. and Carol L. Shields[9])

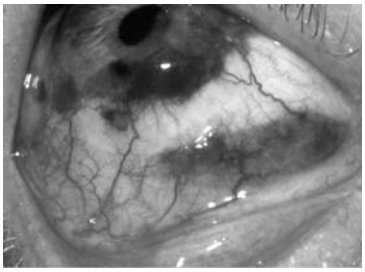
Tumours in other locations (fornix, palpebral, tarsal) should be excised with wider (3-4 mm) clear margins, with alcohol applied to the base, and cryotherapy to the conjunctival margins.[1,9] Conjunctival autogenous grafts, buccal mucosal grafts, or amniotic membrane grafts may be necessary with larger resections and in cases where symblepharon formation is a possible complication.[1,9]

Less commonly, cases can involve globe or orbital invasion and may require modified enucleation or orbital exenteration (Figure 6). Shields et al reviewed 20/151 (13%) cases of conjunctival melanoma that required exenteration for advanced disease.[11] In this series, clinical factors predictive of orbital exenteration were poor visual acuity (<20/200), amelanotic tumour, and extralimbal tumour location. Paridaens et al demonstrated that early exenteration did not improve life prognosis[12] and presently, it is reserved for palliative local control with or without regional node dissection.

Topical chemotherapy

Recent publications have advocated the use of topical chemotherapy (mitomycin C, 5-fluorouracil [5-FU] and interferon A) in the management of squamous cell carcinoma of the conjunctiva, PAM, conjunctival melanoma, and pagetoid invasion of sebaceous gland carcinoma.[1] Demirci et al found induced regression of conjunctival melanoma and primary acquired

Figure 6: High-risk conjunctival melanoma; extralimbal presentation and multifocal lesions of the bulbar conjunctiva with extension onto the cornea



(Courtesy of Dr. Brenda Gallie)

melanosis with atypia with application of 0.04% mitomycin C qid for 28 days as primary treatment, or 7 days as adjuvant treatment combined with excision and cryotherapy.[13] Present recommendations advocate treating PAM with atypia or small conjunctival melanoma with 2-4 cycles of topical mitomycin C 0.04% qid, where one cycle consists of 7 days on treatment and 7 days off treatment to allow for epithelial recovery. Patients insert the topical drops gtts while lying in a supine position and then 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 keratopathy (SPK), toxic conjunctivitis, and punctal stenosis.[1]

5-FU (1% eye gtts) has also been used to control superficial melanocytic proliferation, including PAM with atypia and superficial melanoma. Interferon (Intron A) can also be administered topically, usually to control epithelial malignancies, but it requires much longer treatment times (months).

Present recommendations suggest that topical chemotherapy (mitomycin C) as primary treatment is the most effective for intraepithelial disease such as PAM with atypia and small superficial melanoma. It may play a role as adjuvant therapy in cases with positive margins or pathologic evidence of invasion after primary treatment with surgery and cryotherapy.

Radiation therapy

Melanoma tends to be a radiation-resistant tumour requiring a total dose of 6,000-8,000 cGy delivered by custom-designed plaque radiotherapy. This is reserved for patients with diffuse tumours that are incompletely resected or with multiple recurrences.[1] Radiation plays the role of adjuvant or palliative treatment for conjunctival melanoma and there are no published reports comparing these treatments with surgical modalities.

Sentinel lymph node biopsy (SLN)

The frequency of regional lymph node metastasis secondary to conjunctival melanoma varies from 26% to 40% within 10 years of the diagnosis. The regional nodes involved include the pre-auricular nodes (73%), submandibular (9%), and deeper cervical nodes (18%); 26% of patients develop distant metastasis without prior nodal disease.[14]

Esmaeli et al reported an SLN biopsy technique that detects microscopic regional nodal disease and provides important staging information in conjunctival melanoma.[14] Technetium (Tc-99m sulfur colloid) with an activity of 0.3 mCi (11.1 Mbq) in 0.2 ml is injected subconjunctival around the base of the tumour and imaged with a hand-held gamma probe for 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 hematoxylin and eosin (H&E) and immunohistochemical stains (melan-A, HMB-45, MART-1) and with polymerase chain reaction (PCR) testing for mRNA tyrosinase.

The staging information of positive nodes at the time of primary tumour resection allows for earlier detection in patients at risk of distant metastasis and the possibility of offering systemic chemotherapy (eg, interferon).

Conclusions

The comprehensive ophthalmologist will see few conjunctival melanomas in his/her career but, given the significant morbidity and mortality that accompanies the disease, it is a diagnosis that cannot be delayed nor missed. A strong clinical suspicion is necessary when dealing with pigmented lesions of the conjunctiva, but accurate history, slit lamp examination, clinical photography, and close clinical follow-up can help differentiate conjunctival melanoma from other similar lesions. Documented growth and nodularity should lead to appropriate imaging (UBM) and initial treatment plays a significant role in reducing rates of local recurrence and metastasis. Sentinel lymph node assessment will play an increasing role in the staging of patients. Meticulous surgical resection with

adjuvant cryotherapy remains the mainstay of treatment, but topical chemotherapy regimens are instrumental for primary and secondary management. Systemic chemotherapy and/or immunotherapy may be offered to patients with nodal involvement at presentation and hopefully have a positive effect on long-term survival.

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