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Original Paper

Management of Conjunctival Melanoma: Critical Assessment of Sentinel Lymph Node Biopsy

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Key Words
Conjunctival melanoma · Aggressive form · Sentinel lymph node biopsy

Abstract
Conjunctival melanoma (CoM) is a rare and aggressive form of melanoma. There is a lack of consensus on a unified management plan for this disease. Recently, a few centers have adopted the regional sentinel lymph node biopsy into the staging process of CoM. This study presents a critical assessment of the role of sentinel lymph node biopsy in CoM and presents a simplified management algorithm based on high-risk clinical and pathological features.

Introduction

Conjunctival melanoma (CoM) is a rare and aggressive cancer that constitutes only 5–7% of all primary ocular melanomas [1, 2]. The Surveillance, Epidemiology, and End Results (SEER) noted a marked increase in the incidence of CoM, especially amongst white males, and that is most likely linked to an increase in UV light exposure [3]. CoM may originate from a nevus, primary acquired melanosis or arise de novo. Depending on its origin, size, location, histological features, lymph node involvement and systemic metastasis, the prognosis differs greatly. At 10 years' follow-up, the recurrence and mortality rates could be as high as 62 and 30%, respectively [4–6].

Like most rare diseases, the management of CoM lacks consensus on staging, systemic workup and follow-up protocol after the excision of the conjunctival tumor. Moreover, conducting multicenter trials with a large number of patients poses a great challenge. The

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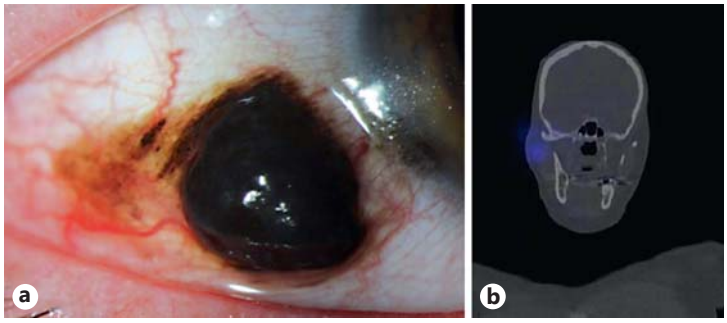

Fig. 1. a Slit-lamp photo of the right eye revealing a bulbar conjunctival mass with associated coarse pigment granules. **b** SPECT/CT image of the head and neck highlighting the enhancement of the SLN in the right parotid gland after subconjunctival technetium-99m injection.

current management of most patients with CoM includes tumor excision and cryotherapy to the margins [7]. Adjuvant topical chemotherapy or brachytherapy could be used in diffuse or deep infiltrative disease [8–11]. After excision, the patient is observed periodically for local or systemic recurrence. Once overt, systemic metastasis occurs and the prognosis is poor [12]. Sentinel lymph node (SLN) biopsy for staging and prognostication of the disease is only done in a few centers around the world [13–22]. Its impact on long-term survival is not known.

The purpose of this paper is to propose a management protocol of CoM by presenting a relatively common scenario that gets referred to an ocular oncology center. The protocol is based on published outcomes of patients who underwent SLN biopsy.

Case Presentation

A 51-year-old man was referred with a conjunctival lesion of the right eye that was noted to be growing in size over the course of a year. He reported that the lesion had been present for the past 2 years, but had grown significantly in the last 6 months. On presentation, the patient had a visual acuity of 20/20 in the right eye and 20/70 in the left eye (he had a history of an epiretinal membrane). Intraocular pressures were 13 mm Hg in both eyes. An examination of the right eye revealed a bulbar conjunctival mass measuring 5 × 3 × 2 mm in size, located 1 mm posterior to the corneoscleral limbus, extending from 8 to 9 o'clock (fig. 1). Coarse pigment granules were present and surrounding the tumor, extending 1 mm anteriorly into the cornea and 4 mm posterior to the posterior edge of the tumor. His fundus examination was otherwise within normal limits. The left eye was normal.

The patient was then scheduled for a combined procedure of conjunctival tumor excisional biopsy, map biopsies, cryotherapy and defect repair using an amniotic membrane graft and an SLN biopsy to stage the melanoma.

Procedure

Two hours prior to surgery, 0.5 ml of technetium-99m was injected subconjunctivally at the site of the lesion and SPECT/CT imaging was done to identify the SLN (fig. 1). During the first segment of surgery, viscoelastic was used to cover the unaffected cornea. Absolute alcohol was placed over the affected corneal epithelium and adjacent, 1 mm of normal epithelium was then copiously irrigated for 1 min. The epithelium was then scraped towards the limbus without disturbing the underlying Bowman's layer and stroma. Attention was then shifted to the bulbar component where a partial thickness scleral flap (30%) was used to dissect the tumor with 3 mm margins. The scleral dissection was performed out to the limbus. Finally, the corneal, limbal, and conjunctival components were excised as a single piece. Additionally, 1-mm strips of 3 conjunctival margins were then further excised and sent to pathology. Cryotherapy (double freeze thaw) was then applied to the conjunctival margins in an attempt to eradicate any microscopic disease. An amniotic membrane was then used to cover the scleral bed, and subconjunctival indocyanine green angiography was injected (0.5 ml) at the end of the first part of the procedure around the site of the tumor. Next, the SLN biopsy portion of the procedure was performed and the locations of the SLNs were confirmed intraoperatively by using both a

Table 1. Five-year recurrence and metastasis rates based on the AJCC classification of conjunctival melanoma [24, 25]

Primary tumor (T)		Five-year recurrence rate, %		Five-year metastasis rate, %	
		Shields et al.	Yousef et al.	Shields et al.	Yousef et al.
Tx	Primary tumor cannot be assessed				
T(0)	No evidence of primary tumor	–	–	–	–
T(is)	Malignant melanoma confined to conjunctival epithelium	–	–	19	–
T1	Malignant melanoma of the bulbar conjunctiva	44	11	27	–
T1a	<1 quadrant	34	17	–	20
T1b	>1 but <2 quadrants	52	5	44	–
T1c	>2 but <3 quadrants	47	6	–	33
T1d	>3 quadrants	60	20	–	–
T2	Malignant melanoma of palpebral conjunctiva, forniceal conjunctiva, and/or caruncle	78	35	33	–
T2a	<1 quadrant but not involving caruncle	–	40	–	–
T2b	>1 quadrant but not involving caruncle	83	49	50	–
T2c	<1 quadrant and involving caruncle	25	40	–	–
T2d	>1 quadrant and involving caruncle	80	38	–	–
T3	Malignant melanoma with local invasion	76	42	75	63
T3a	Globe	–	–	–	–
T3b	Eyelid	75	39	50	–
T3c	Orbit	–	–	80	80
T3d	Paranasal sinus	–	–	100	100
T4	Malignant melanoma with intracranial invasion	–	–	–	–

– = Data not reported.

gamma probe and the SPY Elite system (LifeCell, Bridgewater, N.J., USA) to detect the technetium-99m and indocyanine green angiography dyes, respectively (described previously by the authors) [16].

The results of the conjunctival biopsy confirmed a malignant melanoma of 1.2 mm Breslow thickness with >1 mitotic figure per 1 mm^2. It was of mixed cell type and was negative for ulceration. The margins and the SLN biopsies were all negative for melanoma. The patient was reassured and is being followed up every 3 months.

Discussion

In 2010, the American Joint Committee on Cancer (AJCC) published a new staging system of CoM [23]. Retrospective studies have confirmed the validity of the new staging system and showed that, as the stage of CoM progresses, the recurrence and metastasis rates increase progressively (table 1) [24, 25]. Overall, the major clinical prognostic indicators of CoM are TNM staging (including nonbulbar location and thickness of the tumor) and origin of the tumor (primary acquired melanosis and de novo vs. nevus) [25–27].

SLN biopsy for CoM staging is seldom performed, even though regional lymph nodes are the first site of metastasis in most cases of CoM [7, 28, 29]. Werschnik and Lommatzsch [12] reported that, once the lymph nodes are overtly involved in CoM, the prognosis is poor. These findings are similar to observations in cutaneous melanoma that have indicated that the strongest predictor of survival is the presence or absence of regional lymph node metastases [30, 31]. The presence of lymph node metastases decreases the 5-year survival rate by approximately 40% when compared to those who have no evidence of lymph node metastases [32].

SLN biopsy detects micrometastases when conventional methods of lymph node screening (e.g. ultrasound) may not, as the size of the lymph node is not enlarged with micro-

Table 2. Indications and characteristics of the patients who underwent SLN biopsies for CoM

Reference	n	Criteria for SLN biopsy	Positive SLN (%)	Thickness of CoM tumors with negative SLN Bx	Thickness of CoM tumors with positive SLN Bx	Location of CoM tumors with positive SLN Bx
Esmaeli et al. [21]	1	Not specified	0/1 (0)	0.95 mm	N/A	N/A
Wilson et al. [19]	1	Not specified	0/1 (0)	Not specified (recurrence tumor from PAM)	N/A	N/A
Esmaeli et al. [20]	1	Not specified	1/1 (100)	N/A	3.1 mm	Paralimbal
Nijhawan et al. [15]	5	Thickness (≥1 mm) Undetermined thickness (e.g. previously excised CoM at a different institution)	1/5 (20)	0.3 mm 1.2 mm 1.2 mm unknown	3.1 mm	Nonlimbal
Baroody et al. [13]	2	Not specified	2/2 (100)	N/A	4.5 mm 8 mm	Nonlimbal Nonlimbal
Savar et al. [18]	26	Thickness (≥1 mm) Recurrence of CoM Negative metastatic staging	4/26 (15)	2.7 mm (range 0.62–12.0)[a]	2.1 mm 3.8 mm 5.2 mm 6 mm	Nonlimbal Nonlimbal Nonlimbal Nonlimbal
Motomura et al. [22]	1	Not specified	0/1 (0)	3 mm	N/A	N/A
Maalouf et al. [17]	2	Not specified	0/2 (0)	1.2 mm 0.8 mm	N/A	N/A
Cohen et al. [14]	18b	Thickness (≥2 mm) Nonlimbal location	2/18 (11)	2.0 mm (range 1.0–13.0)	2.2 mm 10 mm	Nonlimbal Nonlimbal
Rubinstein et al. [16]	4	Thickness (≥2 mm) Ulceration on pathology ≥1 mitotic figure per mm^2	0/4 (0)	2.0 mm 3.4 mm 4.4 mm 4.4 mm	N/A	N/A
Total	61		10/61 (16.4%)	Overall mean: 2.4 mm	Overall mean: 4.8 mm	9/10 (90%) of patients with positive SNL were non-limbal in location

Bx = Biopsy.
[a] Four patients with eyelid skin melanoma are included in the mean of tumor thickness with negative SLN biopsies. [b] 4/22 patients were excluded since the SLNs were not identified during the biopsy procedure.

metastases [13, 15]. The procedure has a high safety profile with the most common complication being temporary weakness of the facial nerve that resolves spontaneously. Parotid sentinel node biopsy has a slight increase in the potential morbidity of facial nerve injury, albeit this rarely occurs when performed by an experienced surgeon [15].

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Table 3. High-risk features of CoM

High risk for metastasis and/or mortality	High risk for nodal involvement
Clinical	
Nonlimbal location	Nonlimbal location
Tumor thickness >2 mm	Tumor thickness >2 mm
Previous excision with positive margins	
Tumors arising from PAM or de novo versus nevus	
Local tumor recurrence	
Multifocal tumors	
Overt metastasis	
Histological	
Ulceration	Ulceration
Mitotic rate >1 per mm^2	Mitotic rate >1 per mm^2
Lymphovascular invasion	
Epithelioid cell type	
Microsatellitosis	

PAM = Primary acquired melanosis.

On the other hand, hematogenous spread without regional nodal involvement could occur in up to 30% of CoM patients [12, 33, 34]. Thus, SLN biopsy has limitations and the ophthalmologist should be cautious when counseling the patient because results could potentially be a false negative.

Indications for SLN Biopsy

Based on a literature review, there are 61 reported cases of CoM that underwent successful SLN biopsies (table 2). Positive SLN were present in 10/61 (16%) of cases, and negative results were present in 51/61 (84%) cases. The mean average tumor thickness with a positive sentinel node was 4.8 mm (range 2.1–10 mm), and with a negative sentinel node 2.4 mm (range 0.3–13 mm). None of the positive lesions was less than 2 mm in thickness. The location of the CoM with positive SLN was nonlimbal in 9/10 (90%) of cases.

High-risk features of CoM can be associated with either a higher risk of systemic metastasis and/or mortality or with a higher risk of nodal involvement (table 3). In our opinion, a SLN biopsy is indicated in the presence of ≥2 high-risk clinical and/or pathological features for nodal metastasis. Those include: (1) clinical features: tumor thickness >2 mm and nonlimbal location [16, 19, 20, 35], and (2) pathological features: ulceration and presence of >1 mitotic figure [36, 37].

Cohen et al. [14] reported that the SLN biopsy should be done subsequent to the conjunctival excision. Even though this was not done in our case, the authors agree with this suggestion as it allows for ample time for a critical review of the pathological specimens for high-risk features. An exception to that rule would be if the patient had a bulky disease (>2 mm in thickness or had excision of a high-risk CoM at an outside institution with histopathologic criteria for SLN biopsy).

Interpretation of SLN Biopsy in CoM

If the nodal involvement is negative, the patient can be reassured that a subclinical metastasis was not detected. A periodic observation every 3 months for the first year after resection and every 6 months thereafter is recommended at our institute. Additionally, the patient

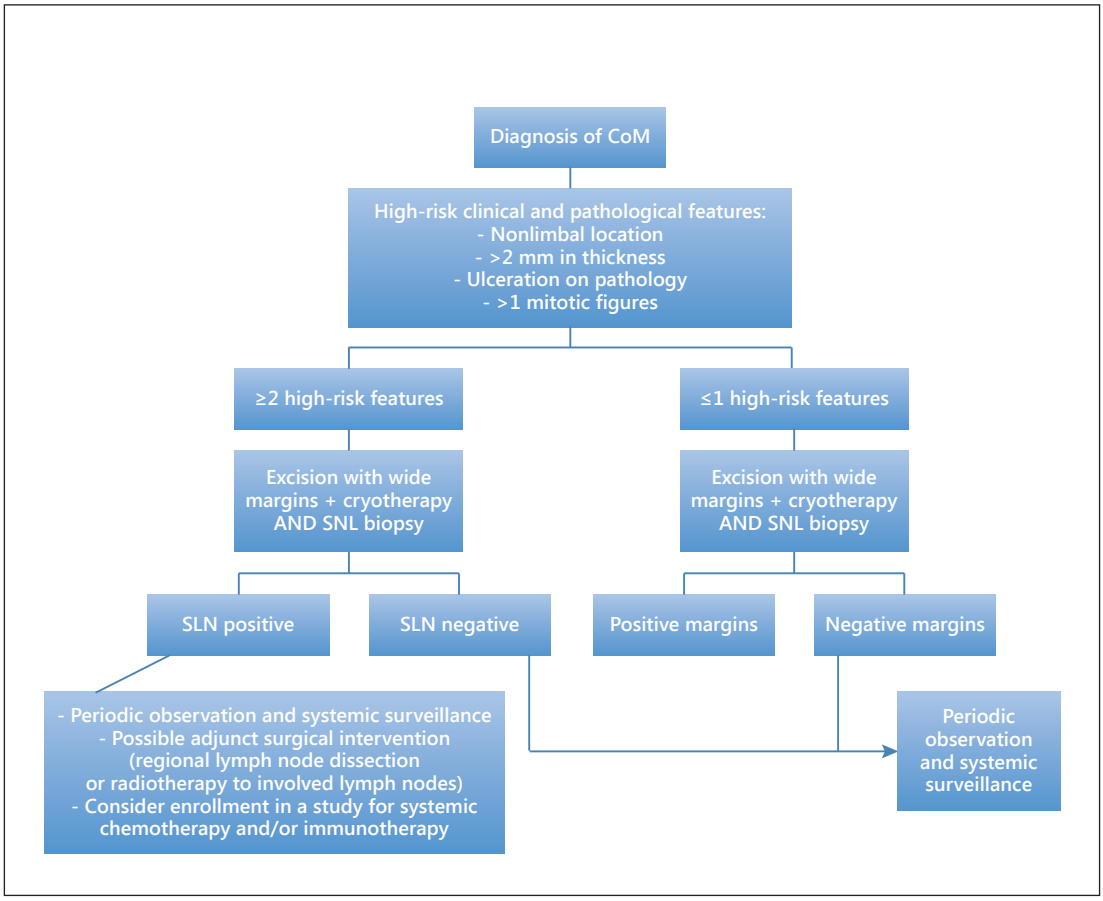

Fig. 2. An algorithm presenting a management plan for conjunctival melanoma based on high-risk clinical or pathological features.

should be educated about the disease and the signs as well as about the likelihood of recurrence based on the AJCC classification.

If the SLN were to be positive (in addition to the periodic ophthalmic observation), a referral to a medical oncologist with systemic surveillance is warranted. Further, adjunct surgical intervention including parotidectomy, neck dissection and possible postoperative radiotherapy to the regional lymph nodes should be considered. Enrollment in a study with systemic chemotherapy and/or immunotherapy should also be discussed with the patient. A conservative approach with PET scans can be performed every 6 months to evaluate for metastases. The algorithm is summarized in figure 2.

Conclusion

Patients that present with ≥2 high-risk features (clinical or pathological) should be considered for SLN biopsy. SLN is a low morbidity procedure that allows for the staging of CoM identifying patients that could benefit from additional local intervention or systemic adjuvant therapy. Multi-institutional prospective studies will be needed to validate the efficacy of SLN biopsy in the staging of conjunctival melanoma.

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