Ophthalmic Pathology Update

Conjunctival malignant melanoma: A rare variant and review of important diagnostic and therapeutic considerations

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Abstract

Malignant melanoma of the conjunctiva is a relatively infrequent neoplasm that can be associated with significant morbidity and cause diagnostic difficulty to both the ophthalmologist and pathologist. We herein describe the first reported case in North American and European databases of a rare variant—signet ring cell melanoma—arising in the background of primary acquired melanosis (PAM) and use this case as a review of important diagnostic and therapeutic considerations when faced with this condition.

Keywords: Conjunctival malignant melanoma, Signet ring cell, Primary acquired melanosis

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Introduction

Conjunctival malignant melanoma is an infrequent neoplasm of the ocular surface that usually occurs in the background of primary acquired melanosis (PAM) with atypia in persons of Caucasian ethnicity. Classically, it presents as a darkly pigmented mass of variable duration (often short) in the interpalpebral region of the bulbar surface that would cause little diagnostic difficulty for the ophthalmologist. On tissue examination, most ophthalmic pathologists (and general anatomical pathologists as well) would recognize the expansile nodule of epithelioid appearing pigmented malignant melanocytes in the substantia propria of the conjunctiva characteristic of malignant melanoma. However, malignant melanomas of other body sites are capable of protean presentations and pathology and the eye is no stranger to this territory.

This paper describes a rare signet ring cell variant of malignant melanoma of the conjunctiva arising in PAM, previously un-reported in the North American and European literature. A discussion of the diagnostic and therapeutic considerations when faced with ocular surface conditions simulating malignant melanoma will follow.

Case description

A Caucasian woman in her 6th decade of life presented with a pigmented lesion on the medial inferior bulbar conjunctiva of the left eye of unknown duration. The lesion was biopsied in mid-2007 at a peripheral hospital and due to difficulty with the pathologic interpretation it was referred for consultation. Ocular history was unremarkable. The remainder of the ocular examination was also unremarkable.

Histopathologic examination of the conjunctival lesion revealed a well-circumscribed nodule in the substantia propria (Fig. 1). In the conjunctival epithelium was a lentiginous proliferation of atypical, variably pigmented melanocytes along the basal layer that in places involved a little over half of the epithelial thickness (Fig. 2), consistent with primary acquired melanosis (PAM) with mild to moderate atypia. The nodule in the substantia propria consisted of a proliferation of signet ring type cells with hyperchromatic nuclei (some containing intranuclear vacuoles) displaced to the periphery of the cell by prominent amphophilic cytoplasm.

Immunohistochemical staining of the nodule revealed strong positivity for cytoplasmic vimentin, PanMel (Fig. 3)
and HMB-45; moderate positivity for S-100 protein; and negativity for mucin and cytokeratins. The PanMel stain also highlighted the extent of the PAM in the epithelium away from the tumor (Fig. 4).

Although the submitting pathologist favored a diagnosis of metastatic signet ring cell adenocarcinoma, a final diagnosis of signet ring cell melanoma of the conjunctiva in a background of primary acquired melanosis with mild to moderate atypia was rendered. Further evaluation of the patient revealed no evidence of other primary melanomas or metastasis. No further treatment was given.

The patient presented with recurrence of a pigmented lesion in the same site 8 months later, which was excised and treated with cryotherapy to the bed of the lesion. Histopathologic evaluation revealed the same signet ring cell morphology as shown in the initial biopsy. In consultation with the patient, oncologist and surgeon, it was decided to follow her clinically without resorting to more aggressive therapy.

Discussion

Signet ring cell melanoma is a very rare condition. It has been reported in skin,1-6 but usually as a metastatic lesion from a primary melanoma. An extensive search of the North American and European databases Medline and EmBase between 1946 and 2011 revealed that this condition has never been described in the conjunctiva.

Given that this lesion occurred in a background of primary acquired melanosis with moderate atypia, we feel this lesion is a primary malignant melanoma of the conjunctiva. This is supported as well by the evidence that this patient was screened and no other primary source was found. The initial difficulty in the diagnosis of this lesion was the unusual histomorphology, which initially led to a consideration of metastatic signet ring cell carcinoma. Immunohistochemical staining was vital in establishing the diagnosis. Pathologists should add this to the differential diagnosis of metastatic signet ring cell neoplasia to the conjunctiva.

This case serves as a useful introduction to a review of the lesions of the conjunctiva that may mimic conjunctival
melanomas. Neoplastic lesions of the conjunctiva can be classified in many ways; a useful paradigm involves dividing them into pigmented (melanotic) and non-pigmented (amelanotic) lesions. Differentiation between these conjunctival lesions can be challenging, hence the importance of an accurate diagnosis for the purpose of appropriate management and prognosis. Clinical examination with slit lamp biomicroscopy may be enough to establish a diagnosis in most of the cases with classical anterior segment features; nevertheless, the vital role of histopathology cannot be over emphasized for a definite diagnosis in cases that appear unusual.

It is occasionally difficult to decide when a biopsy of a conjunctival lesion is necessary. Proper history regarding lesion characteristics (appearance, duration, accompanying symptoms), medical and family history, ethnic background, and use of medications are extremely important. A proper clinical examination with slit lamp biomicroscopy that includes the size, color, focality, laterality, borders, elevation, feeder vessels, and location of the lesion with drawings for documentation is essential. In addition, a color photograph is useful in detecting progression of these lesions that may not be easily monitored with a simple drawing. When in doubt, a tissue biopsy is required for a definite diagnosis. A diagnostic biopsy is not usually necessary in cases of smaller tumors (<4 clock hours of limbal tumor or <15 mm basal dimension) that appear benign. If a small lesion appears suspicious, an excisional biopsy may suffice. However, if a larger lesion requires a biopsy, then an initial incisional biopsy may be appropriate and depending on the histopathologic diagnosis, more extensive surgery can be performed accordingly.7

Pigmented lesions of the conjunctiva may be melanocytic or non-melanocytic (see Table 1 for pigmented non-melanocytic lesions8—not discussed in this paper). Melanocytic lesions of the conjunctiva can be classified into nevi (congenital and acquired), melanosis (congenital and acquired), and malignant melanoma.9

In the above case, the differential diagnosis included pigmented lesions such as a conjunctival nevus and pigmented squamous carcinoma. If the lesion had been amelanotic, non-pigmented conjunctival lesions that may mimic amelanotic conjunctival melanomas, such as papillomas, pterygia, lymphoid hyperplasia, sebaceous gland carcinoma, and squamous carcinoma10 would be considered.

### Pigmented lesions

#### Malignant melanoma of the conjunctiva

Malignant melanoma of the conjunctiva presents as a raised, pigmented, or infrequently, a non-pigmented lesion. It may arise de novo; from a pre-existing nevus; but most commonly it arises from PAM.9 It represents a proliferation of atypical melanocytes that originates at some point in the conjunctival epithelium and by definition invades into the substantia propria (as opposed to malignant melanoma in situ, a non-invasive proliferation confined to the epithelium).

It can occur in all age groups, but most commonly in middle-aged adults and more commonly in fair-skinned individuals. It can occur in any part of the conjunctiva, but prefers the medial and temporal aspects.7 Malignant melanomas of the conjunctiva are quite rare (<2% of ocular malignancies), but are potentially lethal.7 It can spread through lymphatics and bloodstream or it can undergo direct extension to the globe and orbit. It most commonly metastasizes to the lung, liver, brain and bone.10 Ulceration and tumors greater than 2.0 mm in thickness are associated with a higher risk of distant metastasis.11 The amelanotic form of conjunctival melanoma is particularly aggressive and associated with a poor prognosis and risk of metastatic disease.12,13

Histopathologically, melanoma cells most often are epithelioid (like epithelial cells) in cytology and grow as irregular nests; or continuous or discontinuous single cells, that extend through all the layers of the conjunctival epithelium and into the substantia propria. An indication of epithelial malignancy is the irregular and scattered ascent of the atypical melanocytes to the surface of the conjunctival epithelium (so called pagetoid spread). These cells have large nuclei with chromatin clumping at the periphery of the nuclear membrane and distinct, usually large, eosinophilic nucleoli. Immunohistochemical staining with the melanocytic specific antibodies Melan-A (MART-1) and microphthalmia transcription factor (Mitf) are the most useful stains for identifying the proliferation as melanocytic, followed by the melanoma specific HMB-45 antibody.10 Although useful in other tissues, the S-100 antibody stain is not as sensitive and specific in conjunctival proliferations and its lack of significant staining may be misleading.

Ultrasound biomicroscopy (UBM) may serve as an additional diagnostic tool to estimate the tumor thickness prior to surgical resection of a conjunctival melanoma. Although infrequent, extra-scleral extension of a ciliary body melanoma can simulate a conjunctival melanoma and here UBM would prove very useful to confirm the location of the tumor.10 Management of conjunctival melanomas includes surgical resection with a wide margin excision (>3 mm), cryotherapy, and may also include topical mitomycin C (MMC) and/or alcohol epitheliecotomy,7 and topical interferon alfa-2b.14 If more extensive with orbital invasion, exenteration may be required. It is extremely important to examine the patient for metastasis in regional lymph nodes (pre-auricular and submandibular, as well as their draining basins), and consult the oncology service for a systemic metastatic workup.10

The role of sentinel lymph node biopsy in conjunctival melanoma is unclear and not a standard practice in many centers and therefore will not be discussed here.
Conjunctival nevus

Racial melanosis is a common congenital, bilateral condition characterized by flat pigmentation of the conjunctiva usually found in darkly pigmented individuals. Most common parts of the conjunctiva affected are the limbus (typically 3–4 mm from the limbus), and bulbar surfaces. Also not uncommonly they may be more intense around an Axenfeld loop or around an anterior ciliary vessel. The pigmentation is freely mobile over the sclera as the pigmentation is localized to the epithelial layer of the conjunctiva. It has essentially no risk of malignant transformation, although it can be mistaken for a pre-malignant condition (primary acquired melanosis – see below).

Conjunctival nevus

This is the most common melanocytic lesion of the conjunctiva. Most arise in the first decade or young adulthood, but can be present at all ages including the elderly; they are more common in Caucasians than other races and there is no gender predilection.

The most common regions of the conjunctiva affected are juxta-limbal, followed by caruncle, and finally, plica semilunaris. Clinically they can vary in size, ranging from very small to occupying over half the conjunctiva. They may contain cysts, and range in pigmentation from completely amelanotic to dark brown to black. They are usually freely mobile over the surface of the globe (except at the limbus), and this particular clinical feature is of importance because if a potential nevus is immobile (adherent to the globe), an underlying malignant melanoma should be suspected.

Nevi are classified histopathologically into junctional (basal epithelial in location), subepithelial (entirely within the substantia propria), compound (a combination of junctional and subepithelial), and other less common subtypes such as blue nevi and combined nevi (nevi with both a compound and blue component). These benign neoplasms are composed of nests of nevomelanocytes which are polyhedral to dark brown to black. They are usually freely mobile over the surface of the globe (except at the limbus), and this particular clinical feature is of importance because if a potential nevus is immobile (adherent to the globe), an underlying malignant melanoma should be suspected.

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Primary acquired melanosis (PAM)

This is an acquired, almost always unilateral, brown or tan colored flat patchy lesion of the conjunctiva that characteristically has a tendency to wax and wane over the lifetime of the individual. It affects middle-aged individuals typically of Caucasian ethnicity. It differs from a nevus historically as it is acquired in middle age, and clinically lacks a cystic component. It differs from ocular melanocytosis as the pigmentation is acquired, located within the conjunctiva, and is brown rather than gray. As for racial melanosis, PAM is different in terms of demographics as it is usually found in fair-skinned individuals and is unilateral.

Primary acquired melanosis is classified on the basis of histopathology into PAM without atypia (with no malignant potential), and PAM with atypia, which has a significant malignant potential (although in the past it was suggested that up to 45% evolved into melanoma, recent data suggest that this evolution is significantly lower at 8% at 5 years). The criteria defining atypia in PAM include architectural abnormalities (discontinuous lentiginous spread of atypical melanocytes; extension above the basal layer of the epithelium with intraepithelial nesting; full thickness epithelial disposition and pagetoid ascent), cytological features (epithelioid morphology and nuclear hyperchromasia and enlargement) and now should be supplemented with immuno-histochemical evidence of both the extent of the melanocytic proliferation (with the antibodies Melan-A (MART-1) and/or microphthalmia transcription factor) and increased cell proliferation (with increased Ki-67 (MIB-1) activity).

The management of PAM depends on the extent of involvement and the association with melanoma. It may range from observation of a small lesion (<3 clock hours) to an excisional biopsy with a wide margin along with cryotherapy. If the lesion is too large for complete excision or involves the fornices, selected incisional biopsies of any features that lead to suspicion of a malignant melanoma (nodular thickening in a previously flat area of pigmentation, increased vascularity, fixation of the conjunctiva to the underlying sclera, and ulceration), along with map biopsies of all four quadrants should be performed. If only epithelial disease is found,
Sebaceous gland carcinoma of the conjunctiva

This is a rare condition, with only a few reported cases in the literature.17–19 It is defined as squamous cell carcinoma of the conjunctiva with cytoplasmic pigment in the tumor, exactly the same histopathologically as conventional squamous cell carcinoma (SCC). Clinically it is almost impossible to distinguish this from conjunctival melanoma, which is more common and more lethal. Histopathology of the reported cases refers to both squamous cell carcinoma in situ (confined to the epithelium) and less commonly invasive squamous cell carcinoma in the substantia propria.17 Pigmentation is thought to arise from a neighboring melanocytic lesion, as most of the cases reported had racial melanosis, nevus, lentigo or pigmented solar keratosis juxtaposed to the tumor.17 Immunohistochemically, the neoplastic cells are strongly cytokeratin positive and are negative for melanocytic markers. Conjunctival PSCC appears to be slow growing, with little tendency for scleral invasion or distant metastasis.17–19 Management of this lesion is the same as for non-pigmented squamous cell carcinoma as discussed below.

Non-pigmented lesions

Not all conjunctival melanomas are pigmented; melanomas with little or no pigment can look like squamous and sebaceous gland carcinomas, papillomas, lymphoid hyperplasia, and even pterygia.10

Sebaceous gland carcinoma of the conjunctiva

Sebaceous carcinoma is a very rare malignant tumor with an incidence of 3.2% among malignant tumors and 0.8% of all eyelid tumors.20 It usually arises from the tarsal meibomian glands, or less commonly from Zeis glands of the eyelashes, or sebaceous glands of the caruncle and usually extends into the adjacent conjunctiva. It is extremely rare for this type of tumor to arise primarily from the conjunctiva. Only a few reported cases in the literature confirm this fact.20 Histopathologically, it is characterized by atypical basaloid appearing cells with foamy cytoplasm demonstrating pagetoid involvement of the epithelium and extending into the substantia propria as either a nested or diffused sheet-like infiltration. It has a marked tendency to metastasize early and is associated with a significant mortality.20

Lymphoproliferative disorders

These disorders can occur in the conjunctiva as isolated masses (primary disease) or may reflect a systemic condition (secondary disease). Typically, they present as a diffuse pink mass, slightly elevated, and most commonly located in the stroma of the fornical conjunctiva. The typical clinical appearance of the pinkish hue is referred to as a “salmon patch”. Only biopsy can determine the benign or malignant nature of this condition. Sheets of lymphocytes are found histopathologically, and are classified as reactive or atypical lymphoid hyperplasia, or malignant lymphoma. Most of the lymphomas are low grade B cell Non-Hodgkin’s lymphomas of the MALT (mucosa associated lymphoid tissue) subtype. Management includes chemotherapy and radiation therapy, depending on whether it is primary (confined to the conjunctiva) or secondary (associated with systemic lymphoma).7

Conjunctival papilloma

Squamous papilloma is a benign tumor, which is often associated with human papillomavirus (subtypes 6, 11, 16, and 18) infection of the conjunctiva. This lesion can occur in any age group, and is believed to be transmitted from mother’s vagina to child’s conjunctiva through the birth canal.7 Clinically, a papilloma appears as a pink mass with delicate, vascular fronds that may be pedunculated, usually located at the caruncle or in the inferior fornix, or sessile, usually located at the limbus. It can range from a small lesion to a quite extensive one covering the entire interpalpebral conjunctival and/or corneal surface simulating squamous cell carcinoma. Histopathologically it contains numerous vascularized papillary structures lined by acanthotic epithelium. Management can include observation (as some undergo

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Table 2. Adapted from Ref. 7.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anatomical location</th>
<th>Color</th>
<th>Depth</th>
<th>Borders</th>
<th>Laterality</th>
<th>Other features</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevus</td>
<td>Interpalpebral limbus</td>
<td>Brown/yellow</td>
<td>Stroma</td>
<td>Well defined</td>
<td>Unilaterial</td>
<td>Cysts</td>
<td>&lt;1% progress to conjunctival melanoma</td>
</tr>
<tr>
<td>Racial melanosis</td>
<td>Limbus, bulbar, palpebral</td>
<td>Brown</td>
<td>Epithelium</td>
<td>Ill defined</td>
<td>Bilateral</td>
<td>Flat, no cysts</td>
<td>Negligible progression to malignant melanoma</td>
</tr>
<tr>
<td>Ocular melanocytosis</td>
<td>Bulbar conjunctiva</td>
<td>Gray</td>
<td>Episcera</td>
<td>IIId defined</td>
<td>Unilateral</td>
<td>Congenital, usually 2 mm</td>
<td>&lt;1% progress to uveal melanoma (except in Caucasians: 1 in 400 risk of progression)</td>
</tr>
<tr>
<td>Primary acquired melanosis (PAM)</td>
<td>Anywhere, but usually bulbar</td>
<td>Brown</td>
<td>Epithelium</td>
<td>III defined</td>
<td>Unilaterial</td>
<td>Flat no cysts</td>
<td>Progress to conjunctival melanoma in cases that show atypia (see text above)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>Anywhere</td>
<td>Brown or pink</td>
<td>Stroma</td>
<td>Well defined</td>
<td>Unilaterial</td>
<td>Vascular nodules, feeder</td>
<td>32% develop distant metastasis by 15 years</td>
</tr>
</tbody>
</table>

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Table 2 summarizes the key differential diagnostic points of the pigmented melanocytic conjunctival lesions.7
spontaneous resolution), surgical excision, cryotherapy, topical interferon and mitomycin C, and oral cimetidine.7

Ocular surface squamous neoplasia (OSSN)

OSSN is a fleshy, sessile lesion that may be flat or slightly elevated, located most commonly at the limbus in the interpalpebral fissure. Secondary hyperkeratosis may lead to the appearance of leukoplakia. Histopathologically, the lesion shows partial thickness replacement of the surface epithelium with abnormal epithelial cells that lack normal maturation – a process referred to as dysplasia. Grading of dysplasia depends on the thickness of the involved epithelium ranging from mild (only 1/3 of the thickness) to full thickness of the epithelium, which is variably referred to as severe dysplasia or carcinoma in situ (CIS).7,16 Carcinoma in situ has a much higher risk of invasive carcinoma than the lower grades of dysplasia.

Squamous cell carcinoma of the conjunctiva (SCC)

Conjunctival SCC typically develops in either the limbal or bulbar conjunctiva as a fleshy pink, gelatinous, amelanotic, sometimes plaque-like mass. Pathologically, it represents an extension of in situ squamous carcinoma that has invaded through the epithelial basement membrane into the substantia propria where it gains access to the blood vessels and lymphatics with the ability for metastasizing, which unfortunately is uncommon. Important to note is the medical history of the patient. Patients who are HIV positive or are immuno-suppressed are more likely to develop this type of tumor and notably at a younger age (as young as 20–30 years, unlike the 50–70 years in typical SCC). And if so, are also at a higher risk for metastasis. Management includes partial lamellar sclerocconjunctivectomy with wide margins for the conjunctival component (and alcohol epitheliectomy for a corneal component if present) followed by cryotherapy. A thin lamella of underlying sclera should be removed where the tumor is adherent to the globe. Treatment may also include topical MMC, 5-fluorouracil, or interferon particularly in recurrent cases.7

 Conjunctival metastases

Finally, metastatic tumor to the conjunctiva, although a rare occurrence, should not be forgotten. Primary sites include breast, lung, cutaneous melanoma and larynx and may present as flesh colored and non-pigmented masses.21

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References