A RARE CONJUNCTIVAL MELANOMA CASE
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SUMMARY
Primary conjunctival melanomas (CM) are an exceedingly rare type of melanoma. They account for approximately five percent of all cases of ocular melanomas, with ocular melanomas representing only 3.7 percent of all melanoma cases.1-3 The majority of primary ocular melanomas occur in the uvea, but interestingly, CM and uveal melanomas bare little genetic similarity to one another. CM has far greater mutation commonality with mucosal and cutaneous melanoma.2,4-7

In this report, we describe a patient with a rare epitheloid cell type conjunctival malignant melanoma who was successfully treated with wide local excision.

CASE
A 72-year-old Caucasian male presented for routine outpatient dermatologic examination following excision of a nodular basal cell carcinoma (BCC) on his trunk in 2010 and a superficial and nodular BCC on his right leg treated with electrodesiccation and curettage in 2011. On examination, he was noted to have a 0.4cm firm, black pedunculated nodule (Figure 1) on the right medial canthal conjunctiva. The patient was previously unaware of the lesion. A conjunctival biopsy was performed due to suspicion of malignant melanoma. Of note on the biopsy, the lesion was not fixed to the sclera. Histopathology revealed an epitheloid cell type conjunctival malignant melanoma with a Breslow thickness of 2.2mm involving the deep and lateral margins (Figure 2). In addition, an in-situ melanoma involving the adjacent conjunctival epithelium was also identified. Immunohistochemistry of the tumor revealed positive staining with S100, melan-A, and HMB-45. PHH3 staining showed rare invasive tumor cells consistent with rare mitotic activity. The patient was referred for treatment including wide local excision with cryotherapy to the margins and subsequent sentinel node biopsy. The patient had negative sentinel lymph node biopsy and has been disease free for more than two years (Figure 3).

DISCUSSION
Primary conjunctival melanomas (CM) are an exceedingly rare type of melanoma. They account for approximately five percent of all cases of ocular melanomas, with ocular melanomas representing only 3.7 percent of all melanoma cases.1-3 The majority of primary ocular melanomas occur in the uvea, but interestingly, CM and uveal melanomas bare little genetic similarity to one another. CM has far greater mutation commonality with mucosal and cutaneous melanoma, and theoretically would lend itself to similar treatment modalities.2,4-7 CM is a disease mainly of 55- to 65-year-old Caucasians and lacks notable gender predilection. Rarely it has been reported in pediatric, Asian, and black populations.8,9 Clinical presentation typically consists of an enlarging fixed pigmented nodule in the peri-limbal area with the presence of feeder vessels. Less frequently involved locations include the palpebral conjunctiva, fornix, tarsus, or caruncle. Locations outside of the limbus...
portend a poorer prognosis. Other poor prognostic factors include tumor thickness greater than 2mm, de novo origin, ulcerated or nodular tumors, involvement of adjacent tissue structures, older age, nonwhite race, male gender, and local recurrence. Local recurrence is estimated to be 45 and 59 percent at five and 10 years, respectively.2,5,10-12

The conjunctiva consists of two or more layers of non-keratinized squamous or stratified columnar epithelium with interspersed goblet cells overlying the substantia propria. The substantia propria is the stromal component underlying the epithelium and is further divided into a superficial lymphoid and a deeper fibrous layer. Conjunctival melanocytes are located in the epithelium’s basal layer and substantia propria.13,14 The conjunctival lymphatics drain to the preauricular, parotid, submandibular, and deep cervical nodes.15

CMs are thought to arise de novo in 16-26 percent of cases. These lesions portend a poorer prognosis than CM arising from a precursor lesion.5,11,15 The risk factors for development of CM are largely unknown, but ultraviolet radiation is thought to play a role in pathogenesis, as the conjunctiva is the only mucosal surface with natural exposure to sunlight. Furthermore, NRAS (neuroblastoma RAS viral (v-ras) oncogene homologue) and BRAF (v-RAF murine sarcoma viral oncogene homologue B1) mutations may be found in CMs and are also found in sun exposure related cutaneous melanomas.4,6,7,15

Primary acquired melanosis (PAM) and conjunctival nevi are the two melanocytic precursor lesions that can give rise to CM, and an estimated five to eight percent of CMs arise in a combination lesion of PAM and nevus.11,13,16 PAM is the most common CM precursor and is reported in anywhere from 42-75 percent of newly diagnosed CMs.10,16 PAM most commonly presents unilaterally with a poorly circumscribed macular “dusting” of golden yellow or brown pigment located in any area of the bulbar or palpebral conjunctiva. It can also extend onto the surrounding cornea or eyelid skin. In rare cases, PAM can be non-pigmented. PAM is so named to differentiate it from secondary acquired melanosis and congenital melanocytic lesions. PAM lesions most commonly occur in middle-aged Caucasians due to a neoplastic proliferation of epithelial melanocytes. It has been proposed that PAM should be renamed conjunctival melanocytic intraepithelial neoplasia (C-MIN) or hypermelanosis for more accurate nomenclature. Histologic examination for atypia categorizes it into PAM with atypia (designated PAM+) and PAM without atypia (PAM-). PAM- theoretically portends no risk of malignant transformation. PAM+ is considered analogous to a cutaneous lentigo maligna in that it is a preinvasive intraepidermal lesion. It has been estimated that up to 46 percent of PAM+ lesions progresses to CM, and several factors affect the likelihood of malignant progression; epithelioid cytology, atypical melanocytes vertically invading the epithelium, pagetoid spread, and areas of pigmentation and thickening of the lesion. If multiple CM lesions are present, PAM+ is almost always the precursor lesion, but it remains more common for PAM+ to give rise to a singular CM.11,13,15,17 Due to the higher risk of progression to CM, PAM+ lesions occupying two to five clock hours should be excised with 4-5mm margins and cryotherapy to the edges, and PAM+ lesions occupying greater than five clock hours should have incisional map biopsies of all quadrants performed in addition to excision of the most thickened areas.3,10

Conjunctival nevi are the reported precursor lesion in two to 40 percent of CMs. Conjunctival nevi are usually unilateral, but in stark contrast to PAM, nevi are usually formed in childhood and are often well circumscribed light brown or initially non-pigmented papules containing cysts. These lesions are most commonly found on the palpebral conjunctiva or peri-limbal

Simulation Techniques Help Medical Students Empathize with Melanoma Patients

Simulation techniques can allow doctors to experience what it feels like to be a melanoma patient, according to a study, led by researchers from Queen’s University in Belfast in collaboration with colleagues from the University of Huddersfield and University College Dublin, and appearing in the British Journal of Dermatology.

As part of the study, medical students were encouraged to wear a highly realistic temporary tattoo of a malignant melanoma before listening to an audio account of a patient sharing their experience of what it was like to discover a melanoma.

“The experience had a profound and positive impact on our students. Beyond the clinical diagnosis it encouraged them to consider the person behind the illness, enabling them to develop greater empathy, which will stand them in good stead as future clinicians and healthcare providers,” says Dr. Gerry Gormley, lead researcher and senior lecturer at Queen’s University, in a news release.

“Experiential learning is important in training doctors to be fully prepared for future eventualities, an approach that could be rolled out wider to benefit doctors and patients alike.”

A medical student who took part in the study says, “It has been a really valuable experience to put myself in the place of a patient. I feel that I can better relate to patients who have received such a diagnosis. It has improved my empathy towards patients and has given me a much greater respect for what they have to deal with.”
area and usually present as a gradually darkening papule, with accelerations in pigmentation during puberty or pregnancy.

Conjunctival nevi are categorized identically to cutaneous nevi as being junctional, compound, or subepithelial. They are most commonly junctional, and CM has been reported to arise from both junctional and compound nevi. Nevus cell descent into the substantia propria can cause descent of surface epithelium and goblet cells, which is thought to explain the cyst formation that is characteristic of compound or subepithelial conjunctival nevi. These nevi should be monitored annually and have a slit-lamp photo taken at baseline for comparison. An increase in vascularity, color variegation, or enlargement warrants an excisional biopsy. Cryotherapy to the edges should be used for highly suspicious nevi or following histopathological evaluation, if warranted.13,17,18

Diagnosis of CM is made via histopathological evaluation showing sheets or nests of epithelioid, small polyhedral, spindle-shaped, balloon cells, or a combination of the aforementioned types of melanoma cells invading into the substantia propria from the epithelium. S-100, melan-A, and HMB-45 immuno-histochemical stains would be expected to be positive. It is important to exclude cutaneous melanoma metastasis to the conjunctiva or extraocular extension of a uveal melanoma. Differentiation can be made by microRNA expression profiling. CM has had 25 tumor specific microRNAs identified with eight of the 25 being unique to CM and not previously reported in cutaneous melanomas. None of the 25 isolated microRNAs have been reported in uveal melanomas. Another differentiating factor is the finding of BRAF and NRAS mutations in CM, which would be expected to be absent in the majority of uveal melanomas. Neither the 25 identified microRNAs nor BRAF mutation have been consistently shown to have significant impact on prognosis.2,6,11,15,19

Management of CM is debated, and consensus is lacking as to the optimal treatment strategy due to the scarcity of reported cases. Exenteration is no longer commonly recommended, except in extensive cases of orbital invasion.20,21

The most common treatment modality utilized is excision with 3-6mm of tumor free conjunctival margin with double freeze slow thaw cryotherapy to the margins. Excision with adjunctive topical 0.02 percent or 0.04 percent mitomycin C chemotherapy, brachytherapy, or interferon alfa-2b has also been reported. Epitheliectomy or sclerectomy is utilized when the tumor is adherent to the cornea or sclera, respectively. Excision without adjunctive therapy is discouraged and has been reported to result in higher rates of local recurrence and increased mortality. All cases of CM with tumor thickness greater than 2mm, histologic ulceration, or non-limbal location carry higher risk of regional metastasis, thus sentinel node biopsy is recommended in these cases.11,12,16,22-25

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