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CASE REPORT

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Malignant melanoma of the conjunctiva metastasizing to the submandibular gland: a case report and review of the literature

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Abstract

Background Conjunctival malignant melanoma is an aggressive tumor with the potential for metastasis and death. It is rare in the black population because of the protective effect of melanin. Metastases are usually to regional lymph nodes, most commonly the preauricular nodes, deep cervical lymph nodes, and the salivary gland.

Case presentation We described the case of a 41-year-old black African woman who presented to our ophthalmology clinic with a painless, right medial pigmented bulbar conjunctival swelling and right preauricular and submandibular swelling. Two years ago, she had similar swelling at the same location in the right eye. She subsequently underwent surgical excision under general anesthesia. Histology of both tissues showed proliferating malignant melanocytes that showed heavy pigmentation disposed of in solid nests, tongues, and sheets obscuring cellular details in these areas. Immunohistochemistry showed tumor cells to stain for HMB45 and Melan A. This led us to conclude that the tumor was a malignant melanoma. The patient died a year after making the diagnosis.

Conclusion Conjunctival melanoma is a rare ocular malignancy that should be considered in cases of pigmented lesions of the eye, especially in people with dark pigmentation. Primary acquired melanosis with atypia or a nevus are known as preexisting melanocytic lesions from which conjunctival melanomas might develop. Metastases are often to preauricular and cervical lymph nodes as well as to the salivary gland. This demonstrates the significance of early presentation, thorough history taking, physical examination, and surgical excision for histopathology.

Keywords Conjunctival melanoma, Ultraviolet radiation, Nevus, Melanin, Hyperpigmented, Salivary gland

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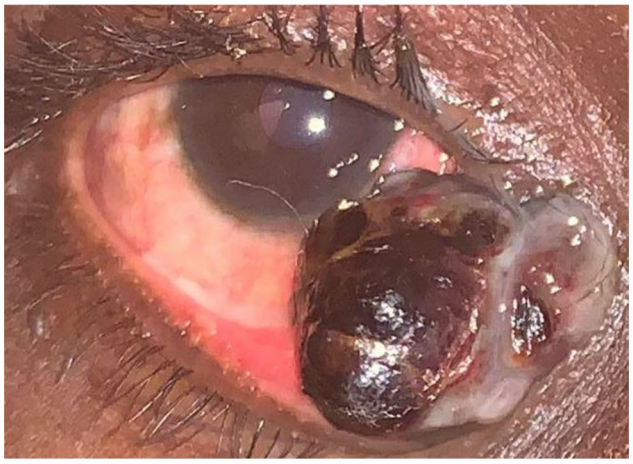

Fig. 1 Extensive conjunctival melanoma with involvement of the eye lids

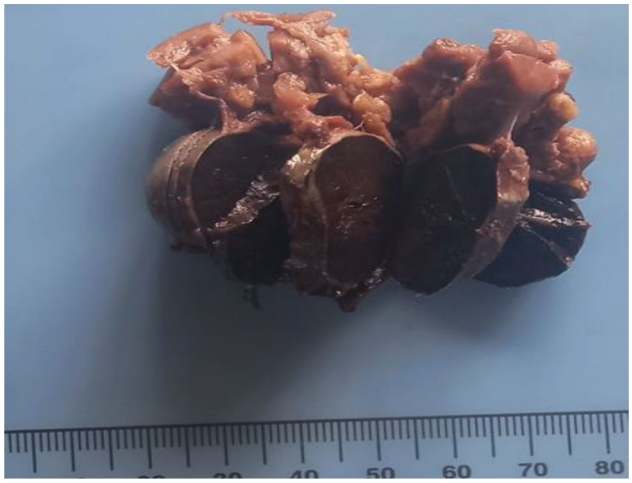

Fig. 2 A gross image of submandibular tissue

Introduction

Melanoma is a malignant neoplasm arising from melanocytes that originate from the neural crest and migrate to several tissues of the body during embryogenesis [1]. This neoplasm may be found in the skin (90%), uveal tract of the eye (5%), or mucosal membrane (1.3%).[2] Mucosal melanoma, which accounts for 1.3% of all melanomas, is an uncommon and aggressive form of melanoma that can develop in non-sun-exposed areas and can be found in all mucosal membranes [1, 2].

Conjunctival melanoma (CoM), which accounts for 5% of all ocular melanoma cases, is a rare and potentially devastating neoplasm characterized by neoplastic proliferation of atypical melanocytes in the basal layers of the conjunctiva and can develop from an area of primary acquired melanosis of the conjunctiva with atypia (PAM), in a nevus or de novo [3–6]. PAM with atypia, also referred to as 'conjunctival melanocytic intraepithelial neoplasia' or ''epithelial melanocytic proliferation', is responsible for approximately 60% of CoM, with a 13% chance of transformation. Conjunctival nevi, which precede CoM, can progress to melanomas in fewer than 7% of instances, whereas approximately 19% of CoM may arise "de novo" [6].

In this article, we report a rare case of conjunctiva melanoma metastasizing to the submandibular gland in a middle-aged black African woman.

Case report

A 41-year-old female trader presented to the ophthalmology clinic with painless, right medial pigmented bulbar conjunctival swelling and right preauricular and submandibular swelling. Conjunctival swelling initially about the size of a grain but progressively increased in size. There was a history of occasional contact bleeding from the mass and redness of the contralateral eyes. Two years ago, she had similar swelling at the same location in the right eye, which was excised at a private facility but was not sent for histopathological diagnosis. This index swelling reappeared four months after the first excision, necessitating her current presentation to the ophthalmologist.

Right jaw swelling in the submandibular area was noticed eight months prior. It progressively increased from the size of a nut to the present size of a tennis ball.

Examination findings from the right eye revealed an exophytic hyperpigmented and ulcerated mass on the medial bulbar conjunctiva extending into the upper and lower medial and palpebral conjunctiva with the involvement of the media canthus. The mass measured 2.0 × 2.2 cm (Fig. 1). It was firm, not tender, and associated with bloody discharge upon contact. The conjunctiva was hyperaemic and was associated with excessive hyperlacrimation. There were also matted, nontender preauricular, submandibular, and cervical lymph nodes measuring 5.0 × 4.0 × 1.0 cm, 5.0 × 4.0 × 3.0 cm, and 4.5 × 3.0 × 3.0 cm, respectively.

The right submandibular swelling measured 4.0 × 4.0 cm. It was firm, multinodular, not mobile, and not attached to the overlying skin (Fig. 2).

Examination of other systems was unremarkable. Her cranial and neck computed tomography scan revealed an irregular enhancing soft tissue pre-septal mass with nodular margins in the inferior-medial part of the eyeball. It measures 2.0 × 1.3 × 2.1 cm in LxAPxT. There was no orbital invasion, no attachment to the medial rectus, and no bony infiltration. The impression was that of an irregular right periocular pre-septal mass. Abdominopelvic ultrasound revealed mild hepatomegaly (16.3 cm), and there was no sonographic evidence of abdominal metastases. Other laboratory investigations, including her chest radiographs and liver function tests, were all within the normal range. The initial clinical impression was a medial conjunctiva melanoma with extension to the upper and lower palpebral conjunctiva and medial canthus of the right eye. She subsequently underwent wide surgical excision of the conjunctival mass and involved tissues, lid reconstruction, and

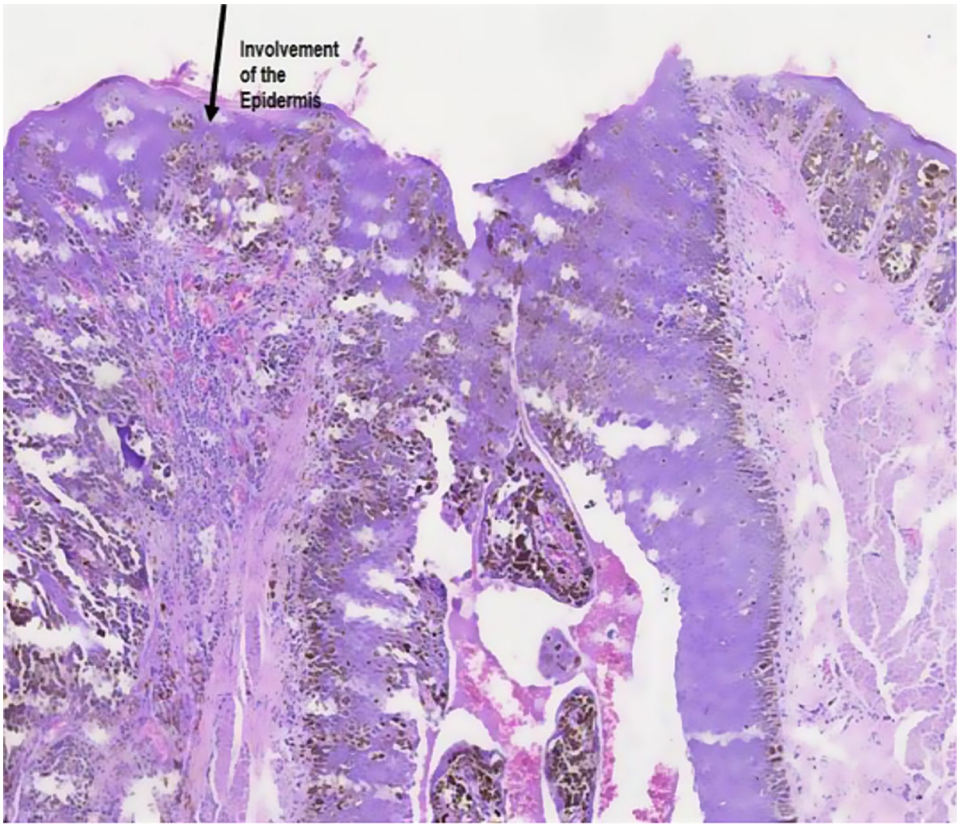

Fig. 3 Conjunctival melanoma ×10

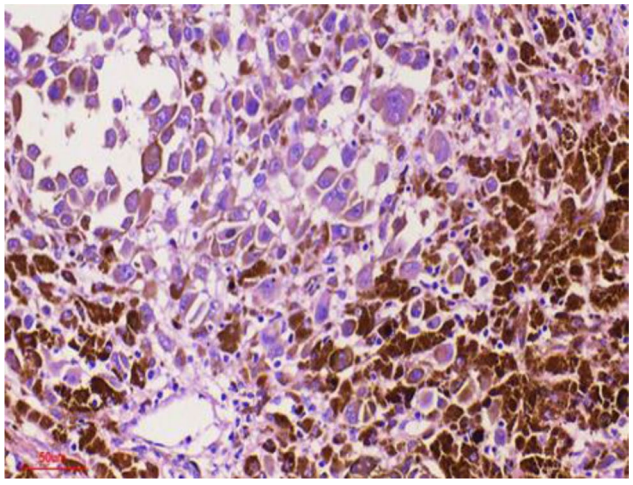

Fig. 4 Malignant melanocytes with heavy pigmentation ×40

neck dissection with an excision biopsy of the right submandibular gland and lymph node. The conjunctival mass was excised with a wide margin of 10 mm in the direction of the limbus. Her immediate postoperative period was uneventful. She was discharged on day 3 after surgery to come back after one week for a follow-up visit.

A specimen histopathology report from the excised tissues revealed a distorted architecture due to the presence of proliferating malignant melanocytes that showed heavy pigmentation, which obscured the cellular details in these areas. These cells formed nodular patterns and infiltrated the conjunctival stroma with reactive desmoplasia. The individual malignant cells were polygonal, with round to oval nuclei and prominent cherry red nucleoli. Mitosis is brisk with few atypical forms. The stroma shows dense lymphoplasmacytic infiltration. There was involvement of the conjunctival epithelia with focal ulceration. There was no perineural invasion or lymphovascular invasion. The margins were free of tumor deposits. The histology impression was that of a malignant melanoma Fig. 3 and 4). The Breslow thickness was 8 mm for the CoM. Pathologic TNM staging was pT1bNxM1. Further immunohistochemical studies for Melan A or MART1 and HMB45 revealed brown cytoplasmic staining of the tumor cells, which confirmed the diagnosis of nodular malignant melanoma Fig. 5 and 6). The lymph node tissue was not submitted for histopathology. She was then referred to the oncology clinic for possible commencement of immune checkpoint inhibitors. However, she was only able to receive a single dose of chemotherapy due to financial constraints before her death.

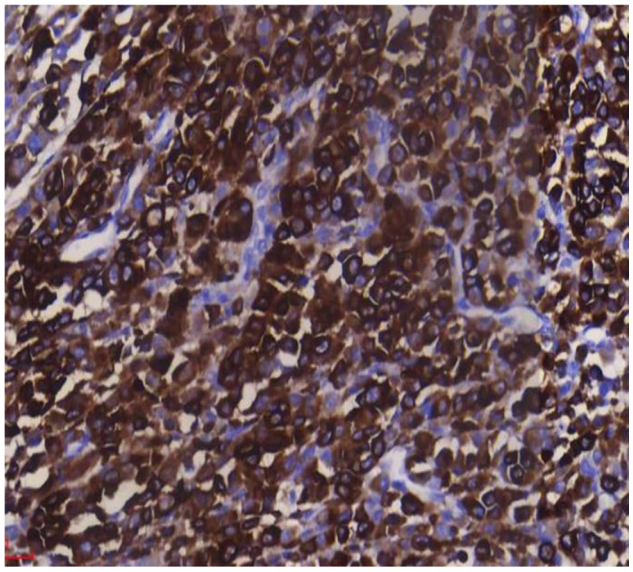

Fig. 5 Immunohistochemistry for HMB45

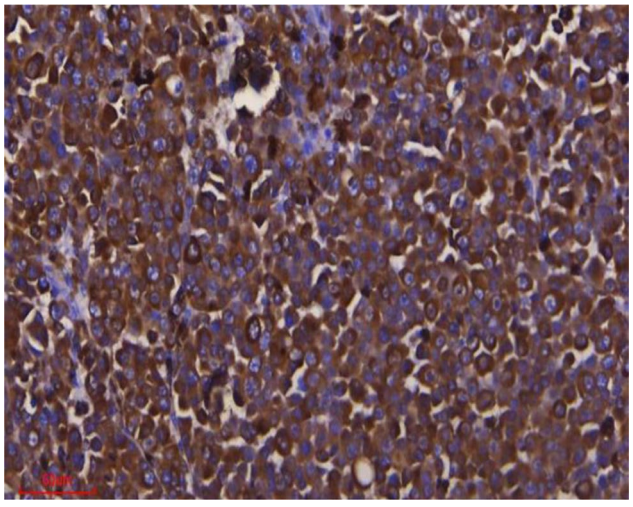

Fig. 6 Immunohistochemistry for Melan A

Discussion

Conjunctival melanoma rarely occurs in black individuals, which is partly attributed to the ability of deep pigmentation to shield nuclear DNA from ultraviolet radiation damage [7]. Only a few cases of CoM have been reported in black individuals, and there is no documented sex preference. A case series in Southwest Nigeria reported six cases of CoM in four females and two male individuals, with a mean age of 49.8 years (range of 25–75 years) [7]. Singh et al., reported two cases of CoM in a 64-year-old black man and a 57-year-old black woman [8]. Colby and Nagel reported a case of CoM arising from diffuse primary acquired melanosis in a young black woman [9].

CoM often manifests as pigmented lesions, which are most frequently found on the bulbar conjunctiva (92%) and impact the temporal quadrants in more than 60% of cases [6]. Our index patient presented with a right pigmented medial bulbar conjunctiva melanoma that extended onto the upper and lower medial and palpebral conjunctiva with involvement of the media canthus (Fig. 1).

CoM spreads either directly towards the orbit or through lymphatic and hematogenous routes. The greatest risk of metastatic spread is associated with tumors that exhibit a nodular growth pattern, recurring lesions, and "de novo" CoM [6]. It is well known that temporal conjunctival melanoma typically spreads locally to preauricular lymph nodes, where up to 41% of cases have been reported, followed by deep cervical lymph nodes and the submandibular gland [10]. Nasal conjunctival melanotic lesions often spread to the submandibular lymph nodes and from those nodes to the submandibular gland [11]. Distant metastasis often involves the skin, brain, adrenals, heart, lungs, peritoneum, pancreas, bowels, kidneys, bones, and spleen [6, 7]. The index patient presented late with metastases to the salivary gland giving her a poorer prognosis. However, metastases to the salivary gland are extremely rare, with only a few cases reported as case reports in the literature. Masaoudi et al., reported a case of CoM in a 10-year-old boy with metastases to the parotid gland [10].

Compared with other mucosal melanomas present in non-sun-exposed locations, CoM is the only mucosal melanoma that may develop from exposure to ultraviolet radiation (UVR) [2]. Although there is still controversy on this concept and there is insufficient evidence linking UVR, particularly ultraviolet-B (UVB) radiation, with direct damage to DNA bases as a risk factor for CoM [4, 7], the bulbar conjunctiva is directly exposed to UVR, which is different from other mucosal membranes, suggesting a role in the tumorigenesis of CoM [4, 7, 12]. Similar to cutaneous melanoma, CoM is much more common in white populations, although few cases have been reported in darker-pigmented people [13]. The protective properties of melanin, which can filter out twice as much ultraviolet-B radiation in pigmented individuals, may be responsible for the reduced prevalence of melanoma among black people [13].

Conjunctival melanoma presents clinically as an asymptomatic mass or an amelanotic to variably sized deeply pigmented plaque or macule. In addition, increasing tumor size, changes in tumor color, immobility to surrounding structures, and tumor extension onto the cornea have also been reported [14]. These findings were present in our index patient and the similar lesion she experienced two years ago could have been an atypical conjunctival nevus.

While more thorough treatments like orbital exenteration and adjuvant chemotherapy may be required

for widespread lesions on the ocular surface or palpebral conjunctiva, surgical excision and adjuvant therapy (such as cryotherapy, radiation, or topical chemotherapy) are typically used to treat localized disease. However, up to 66% of people with CoM may experience local recurrences despite treatment, and up to 38% will pass away from the illness within ten years of receiving initial care [4]. Our patient financial difficulty delayed the early commencement of adjuvant chemotherapy and she was only able to afford one cycle of chemotherapy before her death.

Like in cutaneous melanoma, BRAF mutations have been found in as many as 50% of primary and metastatic conjunctival melanomas. The V600E mutation (replacement of valine with glutamic acid at amino acid 600) accounts for approximately 80–90% of the mutations. The second most frequent mutation is V600K, which occurs at amino acid 600, where lysine is substituted for valine. In less than 6% of conjunctival melanomas, additional rare BRAF mutations are found [6]. Conjunctival melanomas with a BRAF mutation are more prevalent on the bulbar than on the extrabulbar conjunctiva. Given that the bulbar region of the eye, which is more exposed to sunlight, has an increased tendency for BRAF mutations, UVR exposure may be a risk factor for this condition [6].

Other mutations, in order of their frequency, include neurofibromin 1 (NF1), neuroblastoma RAS viral oncogene homologue (NRAS), Kirsten RAS oncogene homologue (KRAS), telomerase reverse transcriptase (TERT), tyrosine-protein kinase (c-KIT), TP53, BAP1 gene, or BRCA1-associated protein 1 gene, and patterns of CNVs resembling those of cutaneous and mucosal melanomas have all been implicated in the carcinogenesis of conjunctiva melanoma. There is a high tumor mutation burden, and TERT promoter mutations are associated with metastatic disease in CoM, thus limiting treatment options [4, 5, 12, 15].

The risk factors for metastasis and poor prognosis in conjunctival melanoma include a greater tumor thickness (thickness > 4 mm), non-bulbar location, low tumor pigmentation, histologic ulceration, brisk mitoses, and local invasion with involvement of palpebra conjunctiva [4, 16]. Similar to our index patient with poor prognosis which was worsened by her late presentation.

Conclusion

In conclusion, conjunctival malignant melanoma is a rare but aggressive tumor with the potential for metastasis and death. Although rare in black individuals, it is vital to recognize their precursor lesions early, including PAMs with atypia and an enlarging or atypical nevus. A wide excisional biopsy to confirm the diagnosis and determine the extent of tumor spread with a negative resection margin is often the best treatment approach. This approach is recommended, especially for preexisting lesions with worrisome clinical features, such as increasing tumor size, changes in pigmentation, immobility to surrounding structures, tumor extension onto the cornea, and diverse macroscopic appearances indicating a poor prognosis. This demonstrates the significance of early presentation, thorough history taking, and the worth of a well-organized local histopathology service.

Abbreviations

ENT	Ear nose and throat
TNM	Tumor Node and Metastases
Melan A	Melanoma Antigen
MART1	Melanoma antigen recognition by T cells 1
HMB45	Human melanoma black antibody
PAM	Primary acquired Melanosis
CT	Computed Tomography
UVR	Ultraviolet radiation
CNV	Copy number variation
NF1	Neurofibromin 1
NRAS	Neuroblastoma RAS Viral Oncogene Homologue
KRAS	Kirsten RAS oncogene homologue
TERT	Telomerase reverse transcriptase

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Author contributions

C.C.O. and A.I.S. reported the histologic findings. C.C.O, B.A.A., and S.O.A. did the clinical aspect. C.C.O did the final clinical report and the discussions. O.O.O and E.E.E did a thorough review of this write up. All authors contributed to the discussion and the final write up.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

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