

Oral medicine case book 61:

Oral malignant melanoma

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CASE REPORT

A 45-year old male patient presented at the Oral and Maxillo-facial Clinic, Tygerberg, with a pathological fracture of the left mandible following an extraction. The medical records of the patient revealed a history of multiple myeloma that was treated with Aredia (pamidronate disodium, an intravenous form of bisphosphonate), cyclophosphamide (an alkylating agent) and dexamethaxone (an anti-inflammatory and immunosuppressant drug). An orthopantomograph revealed osteonecrosis and pathological fracture of the left mandible, thought to be due to the earlier bisphosphonate administration. The patient received conservative management for the osteonecrosis and was stable at the time of the publication, (19 months after the initial presentation with the pathological fracture).

Clinical assessment during a routine follow-up visit, (31 months after treatment of multiple myeloma), revealed a flat, black pigmented lesion on the posterior part of the hard palate and involving the soft palate. The lesion had a slightly rough surface and measured 25 x 13mm in size (Figure 1). The patient had not noticed the lesion before and he had experienced neither pain nor discomfort in the area. Apart from a small polypoid lesion on the right buccal mucosa, no other oral or cutaneous lesions were present. An incisional biopsy of the palatal lesion was performed and the buccal polypoid lesion was removed at the same time.

Both tissue samples were fixed in 10% buffered formalin and submitted to the National Health Laboratory Service (NHLS) for histological evaluation. Histopathological assessment of the lesion on the buccal mucosa disclosed a squamous papilloma whilst the incisional biopsy from the pigmented lesion showed a malignant melanoma *in situ* (Figure 2). The patient was subsequently referred for complete removal of

ACRONYM

OMM: Oral mucosal melanoma

the palatal lesion. Histopathological assessment of the excised specimen showed an invasive malignant melanoma with a prominent *in situ* component (see Figure 3-5). Invasive melanoma involved the anterior margin of the biopsy. However, anatomical constraints prevented more extensive removal of the melanoma and therefore the patient was scheduled for postoperative radiotherapy. Regular follow-up assessments of the patient revealed absence of recurrent melanoma or metastases 10 months postoperatively.



Figure 1: A black pigmented lesion involves the posterior part of the hard palate and extends onto the soft palate. The ligatures seen on the premolars had been used for stabilising the pathological fracture of the left mandible.

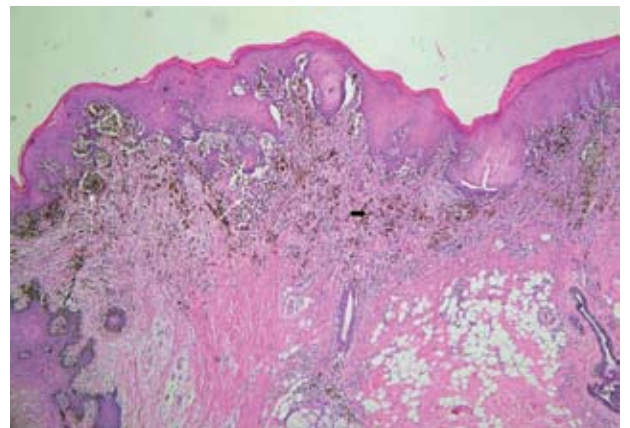


Figure 2: Histopathological assessment of the palatal lesion at low power magnification shows nests of atypical melanocytes at the epithelial connective tissue interface (white arrows). Melanophages are also seen in the superficial connective tissue (black arrow). (Haematoxylin and eosin stain)

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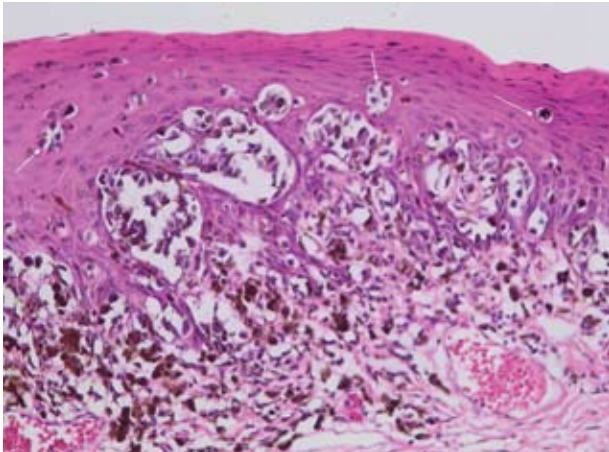


Figure 3: Malignant melanocytes extend into the epithelial layer in the form of nests and single cells, a feature known as intraepithelial pagetoid spread (arrows). Melanophages are present in the superficial connective tissue (H&E stain, original magnification x200).

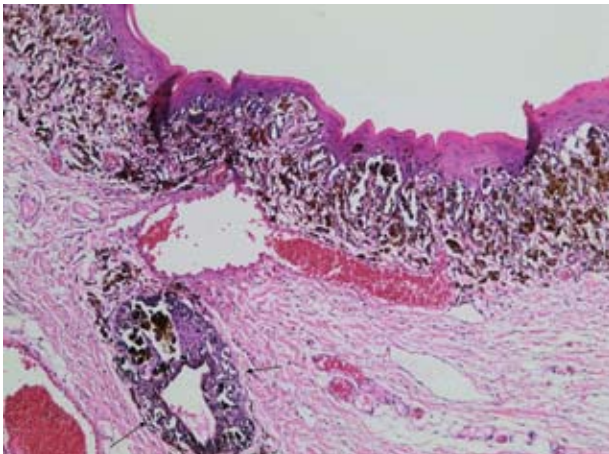


Figure 4: Malignant melanoma *in situ* extends into the underlying salivary gland ducts (arrows) (H&E stain, original magnification x100).

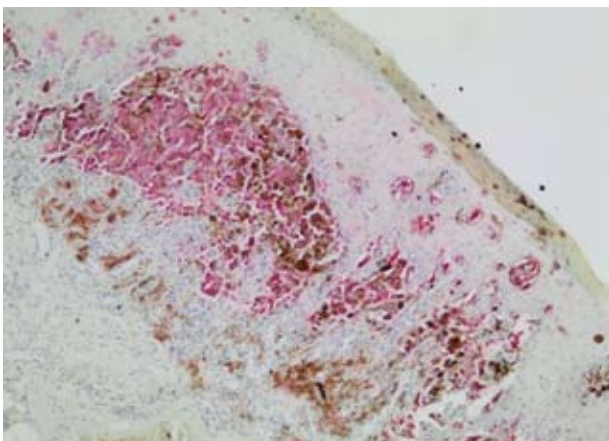


Figure 5: Melan A immunohistochemical stain, a marker of melanocytic differentiation, highlights intraepithelial pagetoid spread as well as malignant melanocytes at the epithelial-connective tissue interface and in the superficial connective tissue (original magnification x100).

DISCUSSION

Introduction

Melanomas are malignant neoplasms of melanocytes that derive from the neuroectoderm. Although the majority of melanomas involve the skin they can occur in any tissue containing melanocytes including the mucosa of the oral cavity, nasopharynx, eye, genital tract and anorectum. Oral mucosal melanoma (OMM) is a rare neoplasm that accounts for less than 0.5% of all oral malignancies and 0.2- 8% of all melanomas.¹⁻¹² Whilst melanocytes in the skin offer a protective function against

ultraviolet light, their function in the oral mucosa is unknown and in the mucosal tissues they do not produce melanin under normal physiological states.^{1,2,5} Skin melanomas and OMM differ significantly in many respects. The mean age of onset of OMM is roughly a decade later than its cutaneous counterpart. The latter is a multi-factorial disease with evidence of genetic and ultraviolet light exposure as predisposing factors. As can be expected, mucosal melanomas are not influenced by sunlight and they also seem to have a different genetic background. For instance, cutaneous melanomas generally show alterations in the BRAF oncogene, (a gene that produces a protein that plays a role in regulating the signalling pathways for cell division and differentiation) whilst most OMM show an over-expression in c-KIT, a receptor tyrosine kinase that is a key regulator of growth, differentiation, migration and proliferation of melanocytes.^{7,10,13} In addition, patients with OMM more frequently present with a more advanced stage of disease than skin lesions, due to the lack of early symptoms and relative inaccessibility. OMM therefore shows a poorer prognosis and limited 5-year survival rate in comparison to cutaneous melanoma.

In the present case, the OMM occurred some time after the patient received treatment for multiple myeloma, raising the question: is there any association between multiple myeloma and malignant melanoma? A recent report from a health-based social website states that in a group of 56,677 persons with multiple myeloma, 146 (or 0.26%) reported also having malignant melanoma.¹⁴ This number comprises only 0.63% of the 23,123 persons with malignant melanoma reported on the same website and is probably not statistically significant. Although melanoma may occur more frequently in patients with preceding lymphoma, a similar association has not been established for myeloma.¹⁵ It is theoretically possible that treatment with drugs affecting the immune status of a patient may stimulate an existing malignancy. However, this is purely speculation and will have to await more definitive analysis. The association with myeloma, reported in this patient, should thus be considered as purely coincidental.

Clinical presentation

The most common site for OMM is the hard palate, which accounts for 40% of all melanomas of the oral cavity. The maxillary gingiva and the alveolar ridge are the second most common sites, however, other oral sites can also be involved but OMM only rarely involves the mandibular gingiva.^{2,5,11,12} The peak incidence is in the 5th to 7th decades of life with a predilection for males (M: F = 2:1).⁵ The lesion is usually asymptomatic and the diagnosis is thus often delayed except in patients who seek routine dental treatment or present for management of aesthetic problems.^{11,12} Clinically, OMM varies from a macule to a nodule to a large exophytic mass with variable pigmentation. The border is usually irregular but is often well demarcated from the surrounding mucosa whilst the surface of the lesion may be wrinkled.¹² The clinical differential diagnosis should at least include oral melanocytic naevi, melanoacanthoma and Kaposi sarcoma in addition to OMM.

The aetiological factors associated with OMMs are unknown and as may be expected, there is no association with sun exposure.^{2,4} A history of a previous pigmented lesion, prior to the appearance of OMM, has been reported and contradictory reports have been published about the association between oral melanosis associated with tobacco usage, and oral malignant melanoma.^{5,6,12} Tobacco and formaldehyde exposure have been proposed as possible aetiological factors for OMM.¹² Mucosal malignant melanoma is seen more frequently in some population groups from Asia, some parts of Africa and Japan.¹

Histopathological features

The histomorphology of mucosal melanoma is variable and this is further complicated by non-pigmented and pigmented patterns. In malignant melanoma *in situ*, atypical melanocytes are distributed in a nested arrangement at the epithelium/connective tissue junction and with intraepithelial pagetoid spread, as seen in Figures 1 and 2 in the present case. Invasive OMM is characterised by invasion of malignant melanocytes into the underlying connective tissue, referred to as vertical growth. The malignant cells can vary in shape from spindled, epithelioid and plasmacytoid cells to small round blue cells. Confirmation of the melanocytic nature of the lesion can be done using immunohistochemical markers such as HMB45, Melan A or S100.^{7,11,12}

OMM is a very aggressive disease usually presenting at an advanced stage. Usually no radial growth phase is observed in these lesions whilst a vertical (or nodular) growth phase occurs early thus leading to an advanced stage at presentation.^{2,4} Unlike dermal melanomas, oral melanomas are classified histologically as *in situ* melanoma, invasive melanoma or combined *in situ* and invasive melanoma. Lesions that have uncertain histomorphological features of malignancy are termed atypical melanocytic hyperplasia.²

Molecular features of OMM

The molecular features of OMM are not as well established as those of cutaneous malignant melanoma largely due to the relative rarity of the former. Recent genetic studies identified mutations in DNA repair mechanisms that may be involved in the pathogenesis of OMM. These pathways include alterations in cyclin dependant kinase (CDKN2A) and mitogen-activated protein kinase (MAPK) pathways.^{4, 6} The former pathway is important in cell cycle regulation and the latter in cell growth and survival.⁴ As mentioned earlier, mutations in c-KIT (tyrosine receptor kinase) have been observed in 88% of oral melanomas, thus suggesting that the use of tyrosine receptor kinase inhibitors could be of therapeutic value in the management of head and neck mucosal melanomas.^{7,10,13}

Management and prognosis

The prognosis of OMM is very poor and the 5-year survival rate of patients is in the order of 15% but this depends on the stage of the disease. Microstaging according to the guidelines for cutaneous melanoma, and in particular Clark levels and Breslow thickness, does not apply to OMM. The American Joint Committee on Cancer (AJCC) has a staging system for OMM which includes features of the primary tumour, lymph node status and metastases (TNM).¹⁶ Primary OMM confined to the mucosal epithelium is normally regarded as a T3 lesion to indicate its aggressive clinical course.^{2,7} The poor prognosis of OMM, compared with cutaneous melanoma, relates to an advanced stage of development at the time of the patient's initial presentation.⁹ It should be stressed, however, that OMM is potentially curable if the tumour is diagnosed at an early stage when the lesion is still in its *in situ* phase and amenable to total surgical removal.¹²

Several clinical and pathological indicators have been shown to be associated with a poor prognosis in cutaneous melanomas. These include old age, male gender, specific sites such as the back, neck and acral skin and lymph node involvement. Likewise, the Breslow thickness and the presence of surface ulceration are histological indicators of poor overall survival and distant metastasis.⁷ Other histological factors of poor prognosis are perineural invasion, lymphovascular invasion and increased mitotic activity. On the contrary, the presence of tumour-associated lymphocytes is linked with a more favourable prognosis.⁸ Such prognostic

factors, in cases of OMM and head and neck melanoma, are yet to be established and the cutaneous parameters for OMMs do not apply, largely due to the anatomic complexity of the head and neck region.⁸

OMM is treated by surgical excision, with clear mucosal margins, and the use of additional radiotherapy and chemotherapy in specific cases.¹¹

CONCLUSION

Due to a lack of symptoms in the early stages of OMM, patients usually present late and early detection is thus uncommon. The importance of early detection and diagnosis cannot be overemphasised as it dramatically improves the prognosis. A high index of suspicion is needed when evaluating pigmented lesions of the oral cavity particularly in high-risk areas such as the gingiva and the palate. Oral health care practitioners need to approach all oral pigmented lesions with circumspection with due regard for the variable morphology and asymptomatic nature of OMM, which may prevent early detection and diagnosis. Moreover, information on the aetiopathogenesis of and the risk factors associated with mucosal melanoma is still sketchy and is open for future investigation.

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