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Case Report

Primary Melanoma of the Oral Cavity: A Case Report with an Overview on Its Molecular Pathogenesis

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ABSTRACT

Primary melanoma of the oral cavity is an infrequent neoplasm of very aggressive characteristics; represents 0.2% to 8% of total cases of melanoma from other sites of the body. It occurs between 30 and 90 years of age, with higher incidence in the sixth decade, with a slight male predilection. The primary sites of occurrence in the oral cavity are the palate and maxillary gingiva. Since most melanotic lesions in the oral cavity are painless in their early stages, a delayed recognition and subsequent treatment result in worst prognosis. This article emphasizes how crucial it is to maintain a high index of suspicion for any pigmented lesion within the oral cavity. Here we present a case of melanoma that was present in the upper gingiva with distant metastasis and briefly reviews the relevant literature that explains the nature and molecular pathogenesis of this lesion.

Keywords: melanoma, gingiva, melanocytes, mucosa, pigmentation.

INTRODUCTION

Melanoma of the oral mucosa is a rare malignant disease, occurring much less frequently than their cutaneous counterparts. Mucosal melanoma is a malignant neoplasm of neural crest- derived melanocytes or of melanocyte precursors as defined by WHO. [(1)] Mucosal melanoma tends to present at an advanced stage with more aggressive vertical growth (nodular) phase of disease and intense vascularization that could influence the elevated incidence of metastasis. [(2)] So a dentist or physician must carefully examine the oral cavity and any pigmented lesion that may exhibit growth potential must be biopsied. This article presents a case of melanoma that was present in the gingiva with distant metastasis and briefly reviews the relevant literature that explains its molecular pathogenesis. A better understanding of the underlying mechanisms of melanoma development and progression helps to design an effective intervention for metastatic melanoma.

CASE REPORT

A 46-year-old man reported to government dental college, Kottayam, India with the complaint of painless nodular, darkened gum in relation to upper front teeth for 2 months. The lesion started as

patch, which later became more elevated and extended to the gingiva of the left upper back tooth region, associated with tooth mobility. Personal history revealed smoking cigarettes daily.

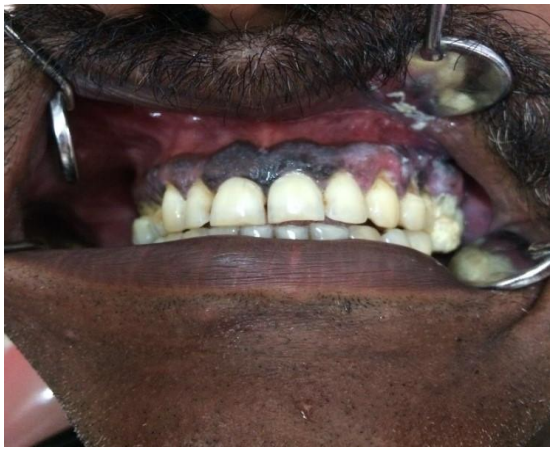

Figure 1:Intraoral photograph shows blackish discoloration of the upper gingiva.

On intra oral examination, an extensive, blackish-blue lesion of size 3x5 cm was present on the maxillary gingiva. The growth was extending from mesial surface of 12 to the mesial aspect of 22 and another isolated pigmented patch lesion extending from mesial aspect of 24 to distal aspect 26 having palatal and buccal vestibular extension with irregular borders. The surface of the lesion appeared wrinkled, and ulceration on the posterior aspect of the lesion showing bleeding on provocation (Figure 1). On palpation, the lesion was fibrotic, nodular and non-tender. The submandibular and upper cervical lymph nodes were palpable, fixed and tender. Intraoral periapical radiographs revealed bony erosion around 26. No other primary site of the lesion was found on examination. Correlating the clinical and radiographic finding, a provisional diagnosis of primary mucosal melanoma was made. Smoking associated melanosis, post-inflammatory pigmentation, medication induced melanosis, melanoacanthoma were also included in the differential diagnosis.

An incisional biopsy was performed; histopathology showed pigmented malignant cells infiltrating at the expense of stroma. Malignant melanocytes with melanin were seen proliferating in streaming pattern as well as in the form of small islands and cords. Tumor cells showed cellular pleomorphism with morphology ranging from spindle to epitheliod, hyperchromatic to vesiculated nuclei with prominent nucleoli, altered nuclear cytoplasmic ratio, increased mitosis and few abnormal mitotic figures. (Figure 2 &3). Tissue sections were positive for S-100 and Melan A molecular markers (Figure 4 &5). The histopathological features were in favor of melanoma. Patient was referred to a cancer center and further investigations disclosed distant metastasis to liver. However, we lost patient's further follow up.

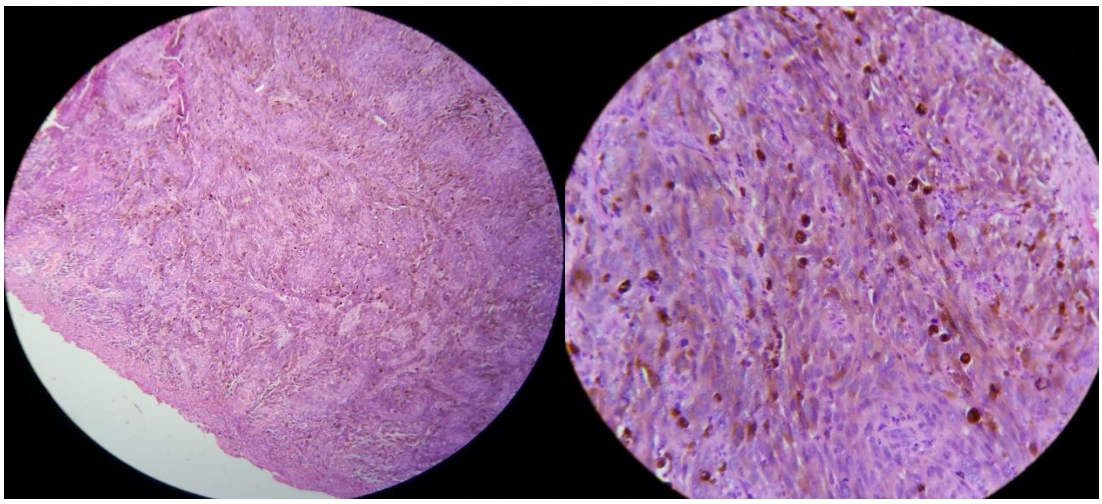

Figure 2: Photomicrograph (H&E 4x) shows malignant melanocytes with melanin proliferating in streaming pattern as well as in the form of small islands and cords.

Figure 3: Photomicrograph (H&E 40x) shows atypical melanocytes and melanin pigmentation interspersed within the connective tissue stroma.

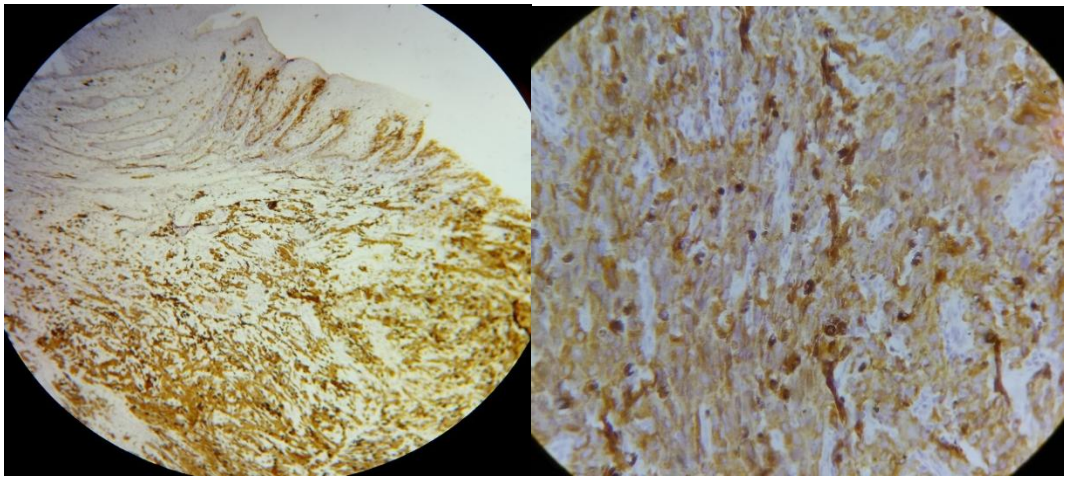

Figure 4: Photomicrograph (4x) reveals immunohistochemical staining with S-100 antibody showing cytoplasmic staining.
Figure 5: Photomicrograph (40x)reveals immunohistochemical staining with Melan -A antibody showing cytoplasmic staining.

DISCUSSION

Primary melanoma of the oral cavity (POM) is considered when the following criteria described by GREENE (1953) are fulfilled: demonstration of melanoma in the oral mucosa, presence of junctional activity and inability to demonstrate extraoral primary melanoma. [(2)]

The present case meets the clinicopathological criteria for the diagnosis of POM. It occurs between 30 and 90 years of age, with higher incidence in the sixth decade, with a slight male predilection. The primary sites of occurrence are the palate and maxillary gingiva but localization is more frequent in tongue, parotid, and tonsils when it is secondary or metastatic. The location, gender and age of the patient are consistent with the data given in the literature.[(2)] The POM remains asymptomatic for a long time, further delays the consultation, which is considered as one of the important reasons for an unfavorable prognosis. Ultraviolet-B light exposure and certain ethnic races play a major role in the development of cutaneous melanoma. Risk factors remain obscure for mucosal melanoma. The only known risk factor is the preexistence of melanin hyperpigmentation in mucosa. [(3)]

Even though there is no well-defined classification exists for oral melanoma, most authors use the classification of the Western Society of Teachers of Oral Pathology (WESTOP). They divide them according to its histopathological pattern into: (a) melanoma in situ, (b) invasive melanomas, and (c) melanomas with a combined pattern between invasive and in situ. They describe preceding lesions as atypical melanocytic hyperplasia, where there is hypercromatism and nuclei with infrequent mitotic activity. The presence of such lesions would indicate a high risk to develop mucosal melanoma. [(4)] PMO are more prone to develop distant metastasis than other head and neck melanomas. The most common metastatic sites are bone tissue, lung, liver and brain. [(3)] In the present case also patient had distant metastasis to liver.

On histologic evaluation, malignant cells of melanoma show a wide range of shapes, including spindle, plasmacytoid, clear cell, and epithelioid ones. The abundant production of melanin pigment may obscure the morphology of the tumour cells. Cells are arranged in loosely cohesive sheets, which in places can form alveolar clefts, nests or islands. Early invasive malignant melanoma and many in situ melanomas show a band like inflammatory infiltrate, often intermingled with melanophages, at the base of the tumor. [(5)] Many of these features were present in our case. These atypical features of melanocytes help to rule out other benign pigmented lesions which are mentioned in the differential diagnosis.

The immunohistochemical staining for NKI/C-3, S-100 protein, HMB-45, Mart-1 (Melan-A), vimentin, tyrosinase and microphthalmia transcription factor (MiTF) aid in the diagnosis. The HMB-45, Melan – A and MiTF is a much more specific marker than protein S-100. Melanoma and blue nevus are diffusely positive for HMB-45 but negative for desmoplastic melanoma. [(5,6)] Melan-A and S-100 are highly positive in our case.

The pathogenesis of melanocyte transformation remains incompletely understood. F. L. Meyskens Jr. and others propose that heavy metals and other chemicals play a cocarcinogenic role in melanoma pathogenesis. According to him, melanin (normally an antioxidant) is oxidized by reactive oxygen species generated by UV, normal metabolic processes, or inflammatory responses and causes increase in the pro-oxidant quinone-imine content which eventually leads to loss of control over melanosomal regulation and compartmentalization. [(7)]

Recent advances in molecular genetics and cancer stem cell biology have shed some light on the molecular basis of melanomagenesis. The BRAF and N-RAS mutations have been found in up to 50 % of cutaneous melanomas but are uncommon in mucosal melanoma. Mucosal melanoma often harbor mutations of KIT (CD117) that result in transcription factor MITF (Microphthalmia- associated transcription factor) phosphorylation which may contribute to melanomagenesis. MITF amplification is more prevalent in metastatic melanomas and is associated with resistance to chemotherapy. TP53 gene alterations in melanoma are rare compared to most other solid tumors. Another important mutation seen in the tumor suppressor gene PTEN which causes decreased apoptosis and increased mitogenic signaling. [(8-9)]

Some genetic variants with highly polymorphic Melanocortin 1 receptor (MC1R) gene are associated with reduced capacity for DNA repair or for apoptosis. Such variants may be at increased risk of malignant transformation. Abnormal downregulation of expression of E-cadherin molecules and upregulation of N-cadherin molecules that contribute to the invasive potential of melanoma cells. The process of melanin biosynthesis itself has some role in melanomagenesis. The loss of the integrity of melanosome membranes with leakage of toxic melanin particles and intermediates of melanogenesis into the cytoplasm and nucleoplasm of melanocytes, may cause DNA damage. This may be the one of the reason for 30% of all cases of oral mucosal melanoma arise within fields of benign or physiological melanin hyper-pigmentation. [(3)]

Oral mucosal melanomas (OMM) may be multifocal and new primary melanomas may arise at sites nearby the original primary melanoma. It is assumed that melanomas develop within epithelial fields harbouring multiple melanocytes that have undergone initial premalignant transformation. Upon acquisition of additional cytogenetic alterations, these precancerized melanocytes can acquire a malignant phenotype. [(4)] The present case also has multifocal origin.

Surgery remains the preferred treatment along with chemotherapy, radiotherapy, and immunotherapy. In cases where metastasis has already occurred, it is considered as classically incurable, surgery and other treatment modalities could be considered under the palliative care. [(9)] Melanoma in situ should have a 0.5 to 1.0 cm margin; thin melanomas (0.76 mm) should have a 1 to 2 cm margin; and intermediate and thick lesions should have a 2 to 3 cm margin clearance for surgery. The 5 year overall survival rate for mucosal melanoma ranges from 10 to 25% with a survival average of 2 years. [(10)]

CONCLUSION

OMMs are rare aggressive tumors, which presents with a variety of morphologic characteristics, and diagnosis generally at advanced stage of tumor in comparison with cutaneous melanomas. We

wish to emphasize how crucial it is to maintain a high index of suspicion for any pigmented lesion within the oral cavity. Review of published cases and recognition of new ones may guide in establishing definite classification and proposing clinical features that would facilitate its early diagnosis, apt treatment and better prognosis of this rare pathology.

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