Melanoma of the Maxillary Anterior Gingiva
Mark Eugene Peacock, Ilanit Stern, Cynthia S Ditslear, Mark R Stevens, Rafik A Abdelsayed

Abstract
Intraoral melanomas are extremely rare and exhibit a poor prognosis. These lesions have the tendency to metastasize, even more so than melanomas of the skin. Most cases (> 80%) occur on keratinized tissue of the maxilla, palate and gingiva. The clinical presentation can be diverse, demonstrating multiple shapes, sizes, and coloration patterns. Early on, smaller melanomas are usually asymptomatic, but can become painful if they expand. Clinicians should be suspicious of changing pigmentations, even though a significant percentage of oral mucosal melanomas are amelanotic. This case report is of an oral melanoma, primary site being the anterior maxilla. The patient did not seek care until the lesion was grossly enlarged and became symptomatic. The primary treatment remains wide surgical excision. Early detection and diagnosis of this malignancy is vital in order to improve the prognosis of these patients.

Keywords: Amelanotic; Gingiva; Melanoma; Melanocytes; Metastasis; Oral; Pigmentations.

Introduction
Primary oral melanoma is a rare neoplasm arising from uncontrolled growth of melanocytes found in the basal layers of oral mucosal epithelium. Melanocytes are derived from neural crest cells and migrate to several sites, including skin and mucous membrane. The reported prevalence rate of oral melanoma ranges from 0.2 to 8%.1,2 This disease accounts for approximately 1% of all oral cancer.1 The high risk sites for intraoral melanoma are the palate and maxillary gingiva accounting for 80-90% of the cases, but any mucosal site may be affected.3-7 Some of the other reported sites include the labial and buccal mucosa, tongue, and floor of the mouth.8,9 There are four main clinicopathologic subtypes of cutaneous melanoma: superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanoma, and nodular melanoma.10,11 In the first three subtypes a radial growth pattern starts where the malignant cells spread from the basal layer but remain confined within the epidermis before they invade the connective tissue and spread vertically. Nodular melanoma has a tendency to spread vertically and therefore is more aggressive. This classification is not applied to oral melanomas. Oral melanomas are generally similar to acral lentiginous melanomas, but in some cases akin to nodular melanomas.9 Most cases are discovered at an advanced stage when histopathological features are heterogeneous.12 A simple histological subclassification of oral melanoma was suggested at the WESTOP Banff workshop, where oral melanomas are classified into in situ and invasive types and invasive melanomas with an in situ component.9

Most studies on melanoma reveal a higher incidence in older males. Oral melanoma is seen rarely in children.3,13,14 The mean ages of occurrence are between the fifth and seventh decades.1,12 A review by Aguas et al showed the mean age was 59.2 years with a range of 16 to 91 years.15 Ages above 60 at time of diagnosis were linked to an increase in mortality.16 Oral melanomas arise more frequently in Caucasians17 and Asians, with highest incidence found in the Japanese.18 The white to black ratio is 2:1 for mucosal melanomas,17,19 however the frequency for blacks of African descent appears to be higher than average.13,20

The clinical presentation of oral melanoma may range in color: black, brown, gray purple, and red. However, lighter and near normal tissue color (amelanotic) can occur20-23 and up to a third of oral mucosal melanomas may be amelanotic.20,24 Oral melanoma can present as an unevenly shaped macule, plaque or mass, well circumscribed or diffused. Since the clinical manifestation varies and there is no distinct appearance to oral melanoma, the differential diagnosis is extensive. It can
include focally pigmented lesions such as melanotic macule, melanocytic nevi, multifocal continuous or noncontinuous pigmentation (some tumors have mixed melanotic and amelanotic areas), as well as vascular lesions such as Kaposi’s sarcoma. Initially, oral melanomas are typically asymptomatic, however, they can become painful with growth and expansion. Ulceration, bleeding, paresthesia, and ill-fitting prostheses are common complaints of patients presenting with late stage disease.\textsuperscript{5,15,24,25}

The prognosis of oral melanoma is poor. The 5-year survival rate is between 15 and 38\textsuperscript{\%}.\textsuperscript{16,26} Gingival melanomas generally have better 5-year survival rates than palatal lesions.\textsuperscript{27} A high degree of suspicion for melanoma is warranted for any expanding pigmented lesion. A heterogenous or an irregular macule at a high risk site may signify the development of an in situ melanoma, whereas an ulcerated or nodular architecture may represent invasive melanoma.\textsuperscript{11} This case presents a melanoma originating from the maxillary anterior gingiva in a 60 year-old man.

**Case report**

A 60 year-old white male presented to a dental clinic with chief complaint of “bleeding under the denture.” He first noticed that his denture did not fit the arch over a several week period. Past medical history included hypertension, hyperlipidemia, coronary artery disease, and a 40 pack-year smoking history. The patient had cardiac catheterization with stent placement almost a year prior to presentation without complications. The patient was on medications including aspirin, doxazosin, indomethacin, atorvastatin, metoprolol, nitroglycerin, and clopidogrel. Clinical examination revealed approximately 3 x 3 x 2.5 cm brownish-black lobulated exophytic soft tissue mass of the right maxillary anterior gingiva/palate (Fig 1a). There was no active bleeding observed at time of exam. CT scan with contrast showed bone destruction in the anterior maxillary alveolar ridge (Fig 1b). Other CT images of the spine showed lesions at L3 and C7 of the spine, which were consistent with a metastatic disease. An incisonal biopsy was performed under local anesthesia, and formalin-fixed specimen was submitted.

**Figure 1:** Clinically a lobulated exophytic brown-black tumor at edentulous maxillary anterior gingiva along with palate extension (a) and Axial CT scan showing anterior maxillary bone destruction (b).

Histologic examination of the hematoxylin and eosin-stained sections revealed fragments of parakeratinized oral mucosa supporting a poorly demarcated neoplastic cellular proliferation within the lamina propria which exhibited an organoid pattern (Fig 2a). The neoplastic proliferation is composed of nests, sheets and cords of polygonal and spindle-shaped cells separated in some areas by thin fibrovascular septa. The cells, morphologically consistent with melanocytes, exhibited prominent enlarged hyperchromatic nuclei with prominent nucleoli surrounded by lightly basophilic cytoplasm (Fig 2b). Cellular pleomorphism and atypical mitotic figures were noted. Neoplastic cells associated with melanin deposits were observed focally (Fig 2c). Immunohistochemistry using antibodies for S-100 and HMB-45 were positive in neoplastic cells. A final diagnosis of melanoma was made.

The patient underwent aggressive radiation therapy (stereotactic radiosurgery) for control of the primary lesion prior to planned wide surgical excision of the maxillary lesion and surrounding involved structures. The patient decided against proceeding with the planned maxillectomy in light of the poor
prognosis and expectation of a poor quality of life following surgery. In the eight months following his decision to decline surgery, the patient developed severe hip and back pain confining him to a wheelchair. A repeat whole body fluorodeoxyglucose (FDG) PET scan was performed. Radiologic examination revealed extensive cervical lymph node metastasis, extensive metastatic bone disease, and hypermetabolic lung nodules, consistent with lung metastasis. The patient died three months later, 2.5 years after the initial diagnosis.

**Figure 2:** The hematoxylin and eosin stained photomicrograph at scanner view (4x) showing subepithelial lobular growth of neoplastic melanocytes exhibiting an organoid pattern (a), at low power view (10x) the neoplastic melanocytes exhibiting hyperchromatic and pleomorphic nuclei with prominent nucleoli and at high power view (40x) atypical mitotic figures are evident with melanin deposits.

**Discussion**

Melanomas, whether cutaneous or mucosal, originate from melanocytes. Unlike cutaneous melanoma, etiologic risk factors for mucosal melanoma have not been established. Exposure to sunlight would not seem to play a significant role in the etiology of oral melanoma. This patient had a long pack-year smoking history. Tobacco use has been implicated. Axell and Hedin reported a higher level of oral pigmentation in tobacco users. Chronic irritation from the improper fit of a prosthesis (denture) has also been implicated as a possible etiologic factor. In the current case, it cannot be determined whether the loose denture was a pre-existing condition or a consequence of the expanding tumor.

Our differential diagnosis in this case was melanoma, angiosarcoma, and Kaposi’s sarcoma. The CT scans and biopsy supported the final diagnosis of primary oral melanoma. Oral melanoma can usually be diagnosed with hematoxylin-eosin staining (H&E). The use of immunohistochemistry (IHC) S-100 and HMB-45 was used to confirm the final diagnosis. Amelanotic growths do not have melanin-pigmented tumor cells that vividly display H&E staining, in which cases IHC is fundamental in establishing the final diagnosis.
Greene et al proposed three useful criteria in the diagnosis of primary oral melanoma (Table 1). This patient presented with all three criteria. At the time of diagnosis, the staging was determined to be Stage IV (distant metastases). The poor prognosis in this case may be related to the vertical growth phase and metastatic lesions in the spine. Histopathologic parameters by the Clark and Breslow classifications (Tables 2 and 3) are routinely used for assessment of tumor prognosis in cutaneous melanoma. The Clark system measures the depth of the invasion, and the Breslow categorization analyzes the thickness of the tumor measured from the granular cell layer of the epidermis to the deepest point of invasion. The Clark and Breslow classifications have not been validated as prognostic predictors in oral melanoma due to architectural differences between oral mucosa and skin. The oral mucosa is thinner than skin and lacks microanatomic layers of tissue comparable to those of the skin, which are used in these classifications. However, it was recommended by the 1995 Westop Banff Workshop to evaluate these criteria for future retrospective studies on oral melanoma. Tumor depth of the primary lesion in this case was not pertinent as the growth had already penetrated the underlying bone and adjacent tissues. There was prevalent metastatic disease to cervical and submandibular lymph node chains. Median survival rate is drastically reduced from 46 months to 18 months with nodal involvement.

Table 1: Greene GW et al. criteria for primary oral melanoma.

| 1. | The presence of malignant melanoma in the oral mucosa. |
| 2. | The exclusion of primary melanoma extra orally. |
| 3. | The presence of junction activity. |

The 5-year survival rate for oral melanoma remains grim. The variation of life expectancy is multifactorial. The literature suggests that the stage of lesion at time of diagnosis, metastasis, and anatomic location are all important factors involved in calculating survival. The 5-year survival for gingival melanoma is slightly better (18%) than for palatal melanoma (11%). In contrast, Chan et al in a study of 35 patients over a 31-year period found the anatomic site of the tumor had no impact on survival. The rarity of oral melanoma continues to contribute to the lack of well-controlled studies on treatment protocols. Current treatment practices are derived from retrospective series or individual case reports without proven therapeutic guidelines.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Level I</td>
<td>Confined to the epidermis (in situ melanoma)</td>
</tr>
<tr>
<td>Level II</td>
<td>Invasion of the papillary dermis but does not extend to the papillary-reticular dermal interface</td>
</tr>
<tr>
<td>Level III</td>
<td>Invasion fills and expands the papillary dermis but does not penetrate the reticular dermis</td>
</tr>
<tr>
<td>Level IV</td>
<td>Invasion into the reticular dermis but not into the subcutaneous tissue</td>
</tr>
<tr>
<td>Level V</td>
<td>Invasion through the reticular dermis into the subcutaneous tissue</td>
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Table 2: Clark Classification (Level of Invasion)

<table>
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<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Less or equal to 0.75mm</td>
</tr>
<tr>
<td>Stage II</td>
<td>0.75 mm - 1.5mm</td>
</tr>
<tr>
<td>Stage III</td>
<td>1.51 mm - 2.25mm</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2.25 mm - 3.0mm</td>
</tr>
<tr>
<td>Stage V</td>
<td>Greater than 3.0 mm</td>
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Table 3: Breslow Thickness

Surgical resection when feasible remains the treatment of choice for oral melanomas. Adjunctive therapy (immuno/chemo/radio) is often also advocated. However, the literature reports no improvement with adjunctive therapies as it pertains to the overall survival rate. Recent reports supporting the use of biochemotherapy (combination of chemotherapy + interleukin 2/interferon) have been encouraging. Sun et al found a significantly higher 5 year survival rate in patients treated with surgery + biochemotherapy when compared to those treated with surgery, chemotherapy, surgery + chemotherapy, or surgery + radiotherapy (58.4% versus 20.7%). The patient in this article did experience a response to the radiotherapy consisting of pain control and tumor shrinkage.

Early recognition and biopsy of oral pigmented lesions is crucial in detection of oral melanoma. Surgery remains the best prospect for long-term survival based on complete resection of the lesion before metastasis and aggressive proliferation has occurred. Although complete resection is recommended, it is not always feasible due
to anatomical structures that make it unmanageable. Inadequate removal of all cancer mass contributes to the poor prognosis and possibly to metastasis. \(^{34}\) Targeted immunotherapy may have promise as future treatment regimens are developed.

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**References**


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