Oral melanoma: review of the literature

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Abstract
Oral melanoma (OM) is an uncommon malignant tumor originated from the proliferation of melanocytes cells. This tumor can be present at any location in the oral cavity, however, it affects more frequently the hard palate and the maxillary alveolar mucosa. There seem to have a predilection for males, elderly and Japanese people. OM is usually asymptomatic in the early stages and it presents normally as a pigmented patch or mass with a rapid growth rate. In advanced stages, can show ulceration, swelling, bleeding, rapid enlargement and loosening of teeth. Diagnosis is based on the histological features, which are characterized by atypical melanocytes initially at the epithelial-connective tissue junction and later, invading the subepithelial connective tissue. The treatment of choice is a radical surgical excision. Additional treatments such as radiotherapy and chemotherapy have also been used to improve the prognosis. The main complications are the metastasis which can occur to any organ with a predilection for the cervical lymph nodes. The prognosis is extremely poor especially in advanced stages.

Key Words:
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Introduction
Melanomas are malignant neoplasms arising from uncontrolled growth of melanocytes, which are pigmented cells found in the basal layer of the epidermis and mucous membrane. Melanomas of the oral mucosa were first described by Weber in 1859. These lesions are much more uncommon than their skin counterparts and are considered one of the most deadly human neoplasms. This tumor affects more often the hard palate and the gingiva. Because of its aggressive behavior and extremely poor prognosis, early diagnosis and treatment should be performed as soon as possible.

Epidemiology
Malignant melanoma (MM) is a rare tumor representing 3 to 5% of all cutaneous malignancies, being the third most common malignant tumor of skin. Regarding involvement of the oral cavity, it is much more unusual comprising 2 to 8% of all melanomas. Although all races can be affected by MM, Africans and Japanese have a higher incidence than people of the western countries. Takagi et al. reported an oral occurrence of 7.5% of all melanomas in Japan. In this country, the higher percentage of oral melanoma may be explained by the low number of cutaneous melanoma found in this area.

About the gender, OM is more commonly found in males. On the contrary, skin tumor is more frequent in females. Some investigators say that the proportion male to female for OM is 2 to 1. Others say that there is just a slight predilection for males or no gender predilection at all. Based on previous observation, Trodahl and Sprague related that the course of OM is less aggressive in women. Onset is usually between 40 to 70 years of age with an average of 55 years and it is rare before 20 years. The main sites are the hard palate followed by the maxillary gingiva comprising 80% of all OM. Less common location in order of decreasing incidence includes buccal mucosa, mandibular gingiva, lips, tongue and floor of mouth. Although very uncommon, a case of intraosseous melanoma in the maxillary alveolus was described by Lombardi et al.

Etiology
In spite of the existence of OM has been known for a long time, the etiology of this neoplasm is still obscure. Although cutaneous melanoma has been associated to solar irradiation, it is well established that sun exposure does not play a role in the development of oral lesions. Some authors have suggested that mechanical trauma as well as ill-fitting dentures may induce melanoma in the hard palate. The use of betel nuts and nitrosamine exposure by Japanese people may also contribute with the high number of oral cases in Japan. Tobacco and formaldehyde exposure have also been suggested by Holmstrom and Lund to induce OM. However, there is no evidence that denture trauma, tobacco or any other known factor can induce the development of the disease.

OM arising from areas of previous pigmentation is still not well established. Literature has reported previous melanosis of several years of duration, being a predisposing factor for the development of these lesions in up to 50% of the cases. Takagi et al. reported that this percentage corresponds to 30 to 73% of the melanoma cases arising from a pigmented lesion. Although these are significant numbers, in India, where the number of OM cases is higher than usual, the incidence of melanotic precursor lesions is low. Other authors suggested that proliferation from prior pigmented lesions represents only exceptions. Another explanation is that these areas of hyperpigmentation may represent the radial growth phase of the melanoma persisting for months or years before the invasion or the vertical growth phase.

The fact that nasal cavity and hard palate, the two most common sites for head, neck and oral melanoma are anatomically associated, may indicate the involvement of an embryologic factor. These two sites are constantly being exposed to the air we breathe, therefore, irritants and carcinogenic agents present in the air possibly contribute for the disease development.

Clinical Features
OM are initially asymptomatic, and usually not noticed by the patients, which contributes for the delay of the diagnosis. Although OM often present as short history of rapid development mass, eventually it may develop as a slowly growing mass in amelanotic area present for months or years. The color varies from bluish-black to tan-brown or the lesion can be present as an amelanotic form. Some authors say that blue or white areas may represent partially pigmented lesions. There are a variety of forms such as pigmented macule or nodule, large pigmented exophytic lesion or amelanotic variant of any of these three forms. Manifestation normally can be noticed by ulceration, swelling, bleeding, nodular mass, rapid enlargement or loosening of teeth. When these signs are present, patients seek for treatment, however at this time, prognosis is already extremely poor. Therefore, all authors agree that any unexplained focal pigmentation in oral cavity not consistent with other lesions, or that are suspected of future change in their clinical appearance should be perform a biopsy without delay. It is very important to establish the differential diagnosis for pigmented lesions of the oral mucosa, which includes amalgam tattoo, physiologic pigmentation (racial and post inflammatory), melanotic pigmentation induced by drugs, oral melanotic macule, nevi melanoacanthoma and other benign melanocytic lesions such as lentigo simplex. There are also
some systemic diseases associated with intra and extraoral pigmentation including neurofibromatosis, polyostotic fibrous dysplasia, Addison disease, Peutz-Jeghers syndrome and multiple endocrine neoplasia syndrome. Clark et al. have described three predominant types of skin melanoma according to their clinical features: nodular melanoma (NM), superficial spreading melanoma (SSM) and lentigo maligna melanoma (LMM). NM is usually an elevated lesion with vertical growth only, thus it metastasize early and shows very poor prognosis. SSM is the most usual type commonly found as a slight elevated pigmented patch lesion with regular outline. LMM, also denominated melanoma in situ, is frequently present in sun exposed areas of elderly. Its radial growth phase can be present for up to 25 years, having the best prognosis of the three types. Classification for OM has not yet been determined. Many OM have a histological similarity with LMM in its radial growth phase. But once invasion begins, oral lesions are very aggressive and can metastasize, similar to the vertical growth phase of SSM. Some investigators reported that OM should be classified along palmar, planar and subungal melanomas, which are aggressive types of skin melanomas, as acral lentigo melanoma (ALM). Other, in the recent literature, recommended classifying OM separately from cutaneous lesions basically because of the poorer prognosis of the first one. Rapini et al., after a review of 177 of OM cases, concluded that the distinction between ALM, SSM and LLM could not contribute for the prognosis of oral lesions. In addition, because of the controversy among OM classification, these lesions should be referred simply as “oral malignant melanoma with radial growth phase”

**Histological features**

The diagnosis of OM is performed according to the histological features, which are identical to those of skin melanoma. Atypical melanocytes are initially present at the epithelial-connective tissue junction and proliferate toward the surface and laterally along the basal cell layer. Melanocytes show variation in nuclear size, shape and staining characteristics. Brown pigmentation consistent with melanin intra and extracellular can also be present. Lesional cells can be found in the early stages as individual cells among the basal epithelial cells or clustered as nests within the basal cell layer. When the vertical growth begins, atypical melanocytes invading subepithelial connective tissue can be seen isolated or like cords of cells. Malignant cells in the invasion phase present spindle-shaped or epithelioid.

However, the tumor has an ability to imitate a variety of other malignancies, specially the amelanotic type melanoma. Immunohistochemical analysis using S-100 protein, melan-A or HMB-45 monoclonal antibodies are useful for the diagnosis of this type of OM and to distinguish it from other malignancies.

Regarding the depth of tumor invasion, it is general agreement that is directly related to the prognosis of skin melanoma. There are two systems of histological classification. Clark et al. have developed five levels of invasiveness based on the histological measurement. Level I is considered melanoma in situ because all the tumor cells are found above the basement membrane. In level II, the tumor cells have broken through the basement membrane invading the papillary zone of the dermis. In level III, the cells at the base of the tumor form a line at the interface between the papillary and reticular dermis. When the malignant cells invade the reticular layer and are found between the bundles of collagen, level IV is reached. In the last stage, level V, there is invasion of the subcutaneous tissue and survival rate is very poor.

The other classification made by Breslow uses a microscopic optical micrometer. According to this measurement, primary cutaneous tumors with less than 0.75mm have nearly 100% of survival rate. Tumors between 0.75 to 1.5mm have 90% and prognosis for melanomas between 1.5 to 3.5mm is 40%. The combined use of the two systems of classification is useful to indicate the prognosis of skin malignant melanoma. However, the differences in anatomy between oral and skin make is considered inappropriate to directly categorize oral mucous membrane specimens into one of these levels.

**Treatment**

There is a consensus that the treatment of choice for OM is radical surgical excision. Even when the lesion is small, it is still treated with more than 1cm of clinically normal mucosa margin. Underlying bone must be removed and hemimaxillectomy is commonly required for palatal lesions. Because anatomic limitations present in the oral cavity may difficult the surgical excision, eletrodissection and cryosurgery have been used in some cases. Radiation therapy can be used as an additional treatment after surgery when adequate margins cannot be achieved or as primary treatment in patients that can not undergo surgical procedure, which occur particularly in elderly or medically compromised patients. Preoperative chemotherapy is occasionally used to reduce the tumor size. Other therapies, including laser needs more studies to be used as a treatment.

Regional lymph node dissection is normally performed when lymph node involvement is observed. However, there is still no consensus regarding the practice of regional lymph node dissection in patients with clinically negative nodes. Some authors say that the prophylactic dissection of normal nodes has not been proved to significantly decrease recurrence and improve prognosis of OM. According to Bartkowski et al., dissection should be done in all cases with lesions greater than 3mm of thickness, even with clinically negative nodes.
Prognosis

The prognosis of OM is much poorer than skin melanoma. A 5 year survival rate for OM is between 4.5 to 29% with a median survival rate of 18.5 months after initial diagnosis\(^{6,9,10,14,16,32,38,39,55}\). For the dermal type, survival varies from 35 to 45%\(^{56-57}\). The better prognosis for OM may be associated to small lesions cases, early diagnosis and treatment, and the worse prognosis to greater lesion and the presence of regional or distant spread.

OM has a predilection for lymph nodes metastasis. Followed by distant spread. Lesions of OM can metastasize to any organ\(^ {10,12,17,32,39}\). The organs that are most commonly affected are lungs, brain, liver and bones, but malignant melanomas may metastasize to any organ\(^ {10,12,17,32,39}\). The presence of lymphatic metastasis at the time of diagnosis seems to decrease the survival rates. Prognosis may be improved with lesion limited to a single metastatic site, a nonvisceral location rather than a visceral site and a remission duration of 12 months or more\(^ 8\).

Many reasons to explain the poor prognosis have been proposed such as delay in diagnosis, difficult anatomy, increased in vascularity of oral mucosa and more aggressive biologic behavior of the oral form\(^ {6,12,17,55}\). The old age of the patients may be relevant too\(^ {44}\). Dermal melanoma survival rate is negatively associated to the depth of invasion and the establishment of a vertical growth phase\(^ {6,9,38,40}\), what is suspected to happen in oral cavity too. Irregularity of the borders, color and tumor diameter are relevant for cutaneous\(^ {29}\) but not for oral lesions. There seems to be no consensus between investigators about results of depth of invasion and prognosis for OM. Shah et al.\(^ {59}\) reported survival rate of 30% in lesions smaller than 5mm in depth, 18% for invasion greater than 5mm and 10% for patients with tumor thicker than 1cm.

Regardless the presence of lymphatic metastasis at the time of diagnosis, the same author\(^ {59}\) reported a 5 year survival rate of 25% for node negative patients against 19% for node positive ones. Despite the survival numbers in the literature, the prognosis of each case should depend upon the extent of the tumor spread, on a correct clinico-pathological staging of the primary lesion and on the presence of regional or distant spread\(^ {8}\).

In summary, there is a need for separating prospective studies of OM because of its singular biological behavior when compared to cutaneous melanoma. Future studies should attempt to establish etiology, clinical and histological classification, prognosis and other controversial issues related to oral melanoma.

References
