LITERATURE REVIEW

ORAL MELANOMA: WHAT DOES THE DENTIST NEED TO KNOW?

MELANOMA ORAL: O QUE O DENTISTA PRECISA SABER?

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ABSTRACT

Oral melanoma is a malignant neoplasm of melanocytes, characterized by aggressive behavior and an extremely poor prognosis. Melanomas in the oral cavity are rare and are usually diagnosed at an advanced stage, reducing patient survival. The aim of this narrative literature review is to compile the essential aspects of oral melanoma and other pigmentations to guide early diagnosis by the dentist. Comprehensive searches were conducted in the PubMed, Embase, Lilacs, and Cochrane databases. Oral melanoma typically presents as a macule or nodule, brown or black in color, and may show variations in color and even depigmentation. It has a predilection for the palate and maxillary gingiva, is usually asymptomatic, and affects slightly more males, especially between the 4th and 7th decades of life. Although they share similar clinical characteristics with cutaneous melanoma, they are considered distinct variants. Dentists must be aware of the main clinical characteristics of oral melanoma and other pigmentations of the oral cavity to make an early diagnosis of the neoplasm and manage the case appropriately.

Keywords: Melanoma; Neoplasms; Pathology, Oral; Diagnosis.

RESUMO

O melanoma oral é uma neoplasia maligna de melanócitos, caracterizada por um comportamento agressivo e prognóstico extremamente reservado. Melanomas na cavidade oral são raros e geralmente são diagnosticados em estágio avançado, reduzindo a sobrevida dos pacientes. O objetivo desta revisão narrativa de literatura é compilar os aspectos essenciais do melanoma oral e demais pigmentações para orientar o diagnóstico precoce pelo cirurgião-dentista. Realizou-se uma pesquisa nas bases de dados Pubmed, Embase, Lilacs e Cochrane. O melanoma oral apresenta-se como uma mácula ou nódulo, de coloração castanha ou preta, podendo demonstrar variações na cor e até mesmo despigmentações. Ele tem predileção pelo palato e pela gengiva maxilar, usualmente é assintomático, e aparenta acometer ligeiramente mais o sexo masculino, especialmente entre a 4ª e 7ª décadas de vida. Apesar de possuir características clínicas similares com o melanoma cutâneo, são consideradas variantes distintas. O cirurgião-dentista deve conhecer as principais características clínicas do melanoma oral e demais pigmentações da cavidade oral a fim de realizar o diagnóstico precoce da neoplasia e conduzir o caso adequadamente.

Palavras-chave: Melanoma; Neoplasias; Patologia Bucal; Diagnóstico.

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INTRODUCTION

Melanoma is a malignant tumor of melanocytes, which are melanin-producing cells found in the basal layer of the epidermis. This neoplasm is characterized by very aggressive behavior, and it can occur in the skin, uvea, and mucous membranes (1,3). Oral melanoma (OM) is extremely rare, accounting for 0.5% of all oral malignant tumors (1,4). However, it is more invasive than cutaneous melanoma (CM), as well as being associated with a higher likelihood of spreading to other parts of the body, and higher recurrence rates after treatment (5), presenting an extremely reserved prognosis (6).

Usually, the OM does not present symptoms, which delays the search for specialized care (7). Furthermore, as there are several benign entities with a clinical appearance similar to early-stage melanoma – such as nevus, melanocytic macule, and melanoacanthoma – the lesion may be misdiagnosed (8). Considering that the dentist plays a central role in the early identification of OM, this narrative literature review aims to compile the clinical, differential, histological, and management aspects of this malignant neoplasm.

LITERATURE REVIEW

Methodology

A search strategy was developed by combining the mesh term "Melanoma" with its respective entry terms "Melanomas" OR "Malignant Melanoma" OR "Melanoma, Malignant"; the mesh term "Mouth" with its entry terms "Oral Cavity" OR "Cavity, Oral"; and the mesh term "Neoplasms" with its entry terms "Tumor" OR "Neoplasm" OR "Cancer." The free terms "pigmented lesions" OR "diagnosis" OR "nevus" OR "biopsy" were added to the search strategy, which was adapted for the different databases Pubmed, Embase, Lilacs, and Cochrane. The inclusion criteria were observational studies, clinical studies, narrative and systematic reviews; articles in English, Portuguese, or Spanish; and published in the last twenty years. The exclusion criteria consisted of animal studies, letters, conference abstracts, and theses. Additional searches were conducted in the reference lists of the included articles. The clinical, differential, histological, and management characteristics of the OM were extracted from the selected references.

Classification

Melanoma is responsible for about 1.7% of global cancer diagnoses and for more than 80% of skin cancer deaths (2). Melanomas are classified as *cutaneous*, which account for 90% of cases; and as *non-cutaneous*, which include uveal melanoma and mucosal melanoma (3). The mucous type (1%), first described in 1859 (9), affects various body surfaces, and, being more aggressive, has a worse prognosis compared to CM (3). In addition to the oral cavity, it can develop in the nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, and larynx (10), as summarized in Figure 1.

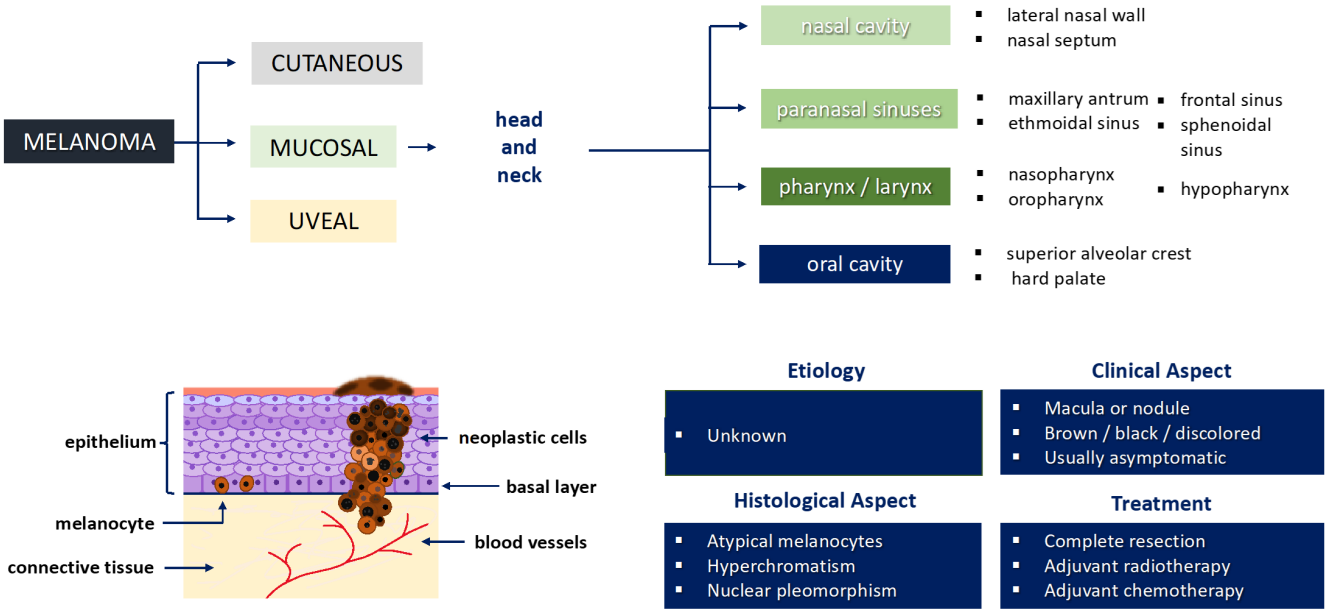

Figure 1: Classification of melanoma types and reported locations in the head and neck with their respective most affected sites (above); Diagram of the histological aspect of OM and summary of the main points on etiology, clinical aspect, histological and treatment of the lesion (below).

Pathogenesis and risk factors

Melanoma is characterized by proliferation of melanocytes. In the skin, melanin is transferred to keratinocytes and acts as a barrier against solar ultraviolet radiation, the main risk factor associated with CM (1,11). In the oral cavity, solar radiation does not influence the pathogenesis of melanoma, for which no clear risk factor has been identified (10,12). Notwithstanding, smoking, alcohol, chronic irritations caused by dental prostheses, and exposure to formaldehyde have been proposed in the etiopathogenesis of the lesion, while viral association with papillomavirus, herpes, and polyomavirus seems unlikely (8,13). Genetic factors are involved (7), and the Asian population is more affected, for reasons still unknown (14). Most cases of OM recur in normal mucosa, while approximately 30 to 37% arise from pre-existing pigmentation for several months or even years (7).

Clinical Aspect

The OM has a predilection for the palate and the upper gingiva, where it is described as a macule or nodule, with brown or black coloring, with irregular margins (1,15). It can show color variation, with black, brown, gray, purple, and red shades (7), as well as adjacent satellite lesions can be seen (10). The amelanotic form of melanoma has little pigmentation and occurs in 30% of cases, being characterized as a flat or nodular and erythematous lesion (16). Other possible locations of OM are the lower gingiva, the buccal mucosa, and the floor of the mouth (17). The OM is usually an asymptomatic lesion, especially in the early stage, in which it is very similar to a nevus or melanocytic macule; however, as the OM grows, it presents ulceration, bleeding, and pain may be the last manifestation (10,17). Men seem to be slightly more affected than women (1,7,15), especially between the fourth and seventh decades of life, with an average age of 60 years (7).

Differential Diagnosis

The oral cavity may present pigmented lesions of completely different nature, which can be disseminated or focal, as summarized in Figure 2.

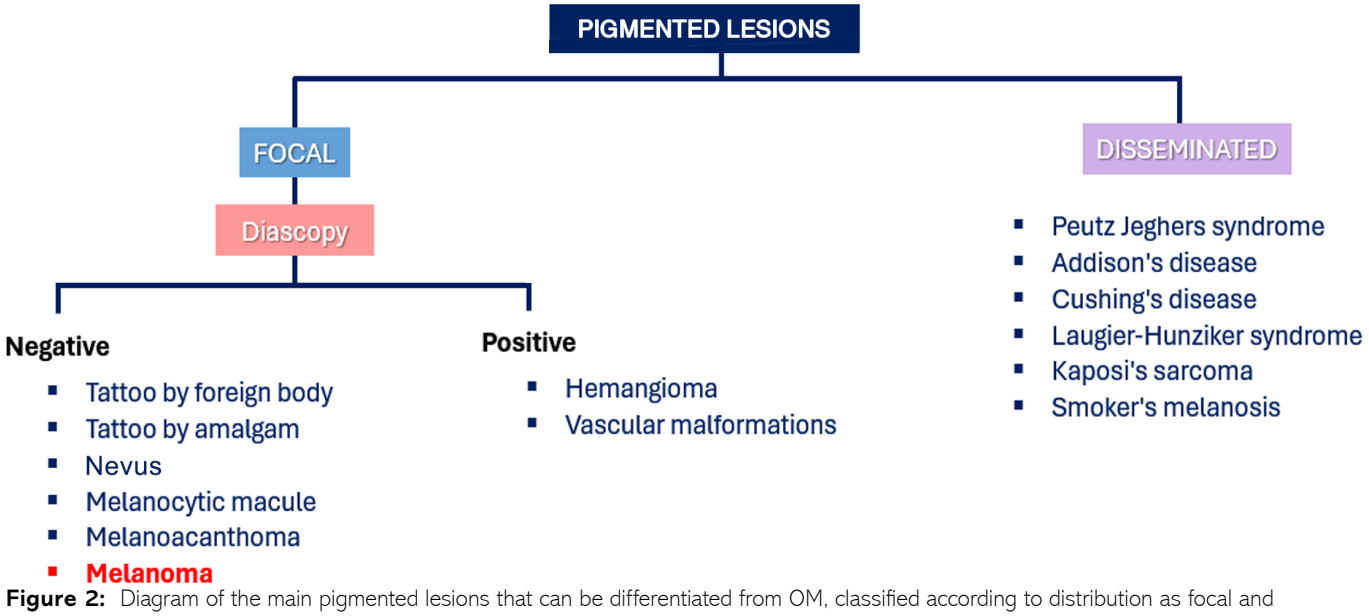

Figure 2: Diagram of the main pigmented lesions that can be differentiated from OM, classified according to distribution as focal and disseminated, and in relation to the diascopy as negative or positive.

Focal pigmentations make a differential diagnosis with melanoma in its early stages (18). On the other hand, disseminated pigmentations may be associated with physiological pigmentation or systemic conditions that manifest from childhood or in adulthood. Peutz-Jeghers Syndrome, for example, is a rare genetic disease linked to mutations in the STK11 tumor suppressor gene that manifests early in childhood. Brown or black pigmentations are noticeable in the perioral region, also affecting the oral mucosa and the skin of the hands. In Addison's Disease, there is destruction of the adrenal cortex leading to insufficient corticosteroid hormones, resulting in diffuse macular pigmentation mainly on the buccal mucosa, palate, lips, and gingiva. Tests evaluating plasma levels of ACTH (adrenocorticotropic hormone) and serum levels of cortisol are useful in diagnosing this disease (19).

Pigmentations in Addison's Disease are similar to those in Cushing's Disease (18), which is caused

by a pathological pituitary activation that raises serum corticosteroid levels (20). Kaposi's sarcoma in its early stage is a vascular endothelial neoplasm associated with HHV-8 (human herpesvirus 8) most frequently found in patients with AIDS and its oral lesions are flat or slightly raised, with a color ranging from brown to purple, usually bilateral (21). Furthermore, it is important to recognize smoker's melanosis, an excessive production of melanin in response to the toxic substances of tobacco smoke, which primarily affects the anterior lower gingiva, but also the oral mucosa, the lip, the hard palate, and the tongue (19). Focal pigmentations, contrastingly, can be differentiated during diascopy examination being either positive or negative. The diascopy technique, or vitropression, consists of applying pressure with a glass slide on the lesion and, if ischemia is observed at the site, there is an indication of a vascular origin. Positive diascopy is observed in cases of hemangioma, a benign proliferation of blood vessels associated with childhood; and in vascular malformations, which are defects of vascular morphogenesis. The clinical aspect of these two pathologies is similar and consists of macules, papules, or nodules that vary from red to purple, with a smooth or lobulated surface (22).

Lesions that are negative for diascopy include foreign body tattoos, such as amalgam and graphite, and melanocytic lesions, such as nevus, melanocytic macule, and melanoacanthoma (20). Nevi are proliferations of small, ovoid nevus cells, common on the skin but rare in the oral cavity, where they mainly affect the palate (19). The nevus variant called Spitz nevus, or benign juvenile melanoma, is a lesion that shares some histopathological aspects with melanoma but is not malignant, with a higher occurrence in childhood (22). The melanocytic macule, or focal melanosis, is a lesion resulting from increased melanin production with occasional elevation in the number of melanocytes, where there is a predilection for women and the most affected site is the vermilion of the lower lip. In turn, melanoacanthoma is a proliferation of dendritic melanocytes with a predilection for black women in the third and fourth decades of life, with the buccal mucosa being the most affected region (19,21).

Considering that the clinical aspect of melanocytic lesions can be indistinguishable from early-stage melanoma, biopsy is essential. Large lesions should undergo incisional biopsy at their thickest portion, while smaller lesions can be addressed by excisional biopsy, if the appearance does not suggest malignancy (23). Sometimes, the OM may be widespread, and its staging follows the TNM classification (tumor, node, metastasis) (10), with the aid of ultrasound or computed tomography of the head, neck, and thoracoabdominal regions for diagnostic definition (23).

Histopathological Aspect

The OM is a neoplasm with varied histological characteristics (24). Epithelioid, spindle-shaped, or plasmacytoid melanocytes with large vesicular nuclei and prominent nucleoli are observed in the epithelium and at the junction with the connective tissue (25). Most melanomas contain melanin, with hyperpigmentation of the basal layer, and few cases are amelanotic. The microscopic pattern of pagetoid spread is usually observed in any type of melanoma, in which isolated melanocytes or in groups infiltrate the layers above the basal cells of the epithelium (27). The immunohistochemical exam is a complementary diagnostic technique that employs three main biomarkers most of the time, with the S-100 protein demonstrating reactivity in 97% of cases, the HMB-45 in 71%, and the MART-1 (Melan-A) in 74% (26).

Treatment and Prognosis

OM is treated with wide surgical resection of the tumor (28), performed without considering the Breslow index, which is the thickness of the lesion, from the most superficial layer to the deepest reached by tumor cells (4). Dissection of cervical lymph nodes is performed in patients with clinically evident regional metastases (4). Local or distant recurrences are common and lead many patients to death, being associated with tumor size, vascular invasion, and non-radical resections of the lesion (28). The most prevalent sites of metastases are the lungs, liver, brain, bones, and lymph nodes (16). Radiotherapy can assist in local disease control, especially when surgery does not achieve negative margins. Compared to adjuvant chemotherapy and radiochemotherapy, the three modalities demonstrate a similar 5-year survival rate. However, the prognosis of OM is generally poor, regardless of the type of treatment used (29).

DISCUSSION

Melanoma is a neoplasm with aggressive behavior, and its incidence is expected to increase in the coming decades (2). The OM, which accounts for 2 to 8% of all melanomas (12), represents a challenge in terms of diagnosis and management for the dental surgeon. The OM and the CM are currently considered distinct variants from each other, both molecularly (28) and in behavior (7), since the OM is more invasive than the skin variant (5,8), in addition to being rarer (1). Besides, it is established in the literature that the pathogenesis of CM is strongly associated with solar

radiation, being modulated by genetic factors (2). On the other hand, the development mechanism of the oral variant is still unknown (10); the recent systematic review by Thuaire *et al*. (4) did not identify any defined risk factor for MO. Herein, the need for future research is highlighted in order to fill this gap in understanding the etiopathogenesis of OM.

The diagnosis of OM is complex considering that its clinical appearance, especially in the early stages, can be similar to other benign focal pigmented lesions, such as nevus, melanocytic macule, and melanoacanthoma. Moreover, OM is usually asymptomatic and progresses unnoticed by the patient, delaying its diagnosis (7,15,30). Particularly, the clinical recognition of the amelanotic form of OM is challenging due to the lack of pigmentation (16). It worth to highlight that in face of a pigmented oral lesion, the dentist should initially rule out the possibility of any systemic disease or syndrome that could cause oral pigmentation. For this, in addition to the multiple injury framework, complementary laboratory tests may be necessary, such as measurement of corticosteroid hormones or identification of infectious agents.

Once disseminated lesions are ruled out, the next step in the diagnostic reasoning is to check for a possible vascular origin of the focal pigmentation through the diascopy, in which the hypotheses of hemangioma and vascular malformation can be excluded if the result is negative. When there is suspicion of amalgam tattoo, radiographic exams can be useful in demonstrating metallic fragments in the mucosa. The ABCDE system is traditionally used to differentiate CM from benign pigmentations, with each letter representing a characteristic associated with the malignant lesion: A, Asymmetry; B, irregular Borders; C, heterogeneous Coloring, with shades of red, white, and blue; D, Diameter greater than 6 mm, and E, Evolution over time, that is, changes in size, shape, coloring, or symptoms (17,31). Despite its usefulness in the early detection of CM, it does not correlate as well with OM, but it can serve as a basis for its evaluation, considering that many of the characteristics of CM have already been observed in the oral lesion (31). In the same way, the Clark and Breslow classification for CM also has no reliable correlation for OM (16). In cases where the origin of focal pigmentation cannot be determined, a biopsy should be performed to exclude the possibility of OM, especially when the lesion is located on the palate or maxillary gingiva, the areas of greatest predilection for the disease.

The management of patients with melanoma requires a multidisciplinary approach (17), with the basis of OM treatment being the complete resection of the tumor (32). The major difficulty, however, lies in obtaining wide and defined excision margins (16). The use of radiotherapy after surgery is associated with a reduction in the possibility of local recurrence, but this issue is still controversial and a subject of debate. In CM, genetic mutations are known, including BRAF V600E, NRAS mutations, and TERT promoter mutations (4,34,35). The knowledge of these mutations allowed the creation of adjuvant systemic therapies for CM: immunotherapy is indicated for patients with a high risk of tumor recurrence and employs anti-CTLA-4 and anti-PD-1 antibodies, being applied alone or combined with targeted therapy, which uses BRAF and MEK inhibitors. However, the rarity of OM makes it difficult to conduct research with a high level of evidence and to develop specific systemic therapies as is the case for CM (28).

Even with progress in melanoma treatment, the 5-year survival rate for advanced cases remains low (36), a fact that underscores the importance of rigorous investigation of any pigmented lesion for early diagnosis of OM. The dentist should regularly inspect the oral cavity for changes, inform and encourage the patient's self-examination (7).

CONCLUSION

Melanoma in the oral cavity is a rare disease with a poor prognosis. Considering that the lesion is generally asymptomatic until advanced stages, and can be clinically similar to benign pigmented entities, early diagnosis by the dental surgeon is essential for reducing mortality. In this sense, any unexplained pigmentation in the oral cavity should be evaluated with rigor and precision.

The authors declare no conflict of interest.

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