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Primary Oral Mucosal Melanoma: a Short Review

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Abstract

Primary Oral Mucosal Melanoma (POMM) is a very rare entity and it develops from malignant transformation of melanocytes from mucosal epithelium. POMM has a very poor prognosis and aggressive behavior. It represents only 0.5% of all oral malignancies, accounting 0.2 to 8% of all melanomas, with an incidence of 1.2 cases per 10 million per year. POMM is asymptomatic in its early stages and usually not noticed by the patients, resulting in the delay in diagnosis. Immunoreactivity of melanoma cells to antibodies against: S-100 protein; Melan-A (MART-1) and HMB-45 (gp100) can be very useful to distinguish POMM from other malignancies. Others markers may indicate variations in its biologic behavior and prognosis, such as Ki-67; P53 and P16, and maybe useful for prognostic prediction.

Keywords: Oral; Mucosal; Melanoma; Immunohistochemistry

Introduction

Primary Oral Mucosal Melanoma (POMM) is a very rare entity and it develops from malignant transformation of melanocytes from the mucosal epithelium. POMM usually unravels with poor prognosis and it may show a more aggressive behavior than its cutaneous counterpart [1-5].

Epidemiology

Primary oral mucosal melanoma represents 0.5% of all oral malignancies, accounting for only 0.2 to 8% of all melanomas, with an incidence of 1.2 cases per 10 million per year [1,5-14]. POMM shows a variable peak of incidence (between 30 to 90 years-old), but it is usually diagnosed in patients older than 60 years old [1,2,5,7-11,13-15]. In a recent work our group reported patients ranging from 9 to 91 years and average age at the time of diagnosis was 61 years [9].

Generally POMM does not show gender preference, [9,10,15,16] however some authors refer that incidence is slightly higher among males than females; i.e. 2:1 male/female ratio [2,7,8,11,13].

The POMM has a higher incidence in Asians, Africans, Hispanics and Asian Indians, probably due to the more frequent findings of melanin pigmentation in oral mucosa of these races [1,8,10,13-17].

Clinical and Histological Features

POMM is asymptomatic in its early stages and it is usually not noticed, resulting in the delay in diagnosis [1,12,16]. The prognosis of POMM is extremely poor with a reported 5-year overall survival rate of 8%.[5] Differential diagnosis of POMM includes: melanosis; melanotic macule; oral nevi; racial pigmentation; smoking-associated melanosis; melanoplakia; postinflammatory pigmentation; amalgam tattoo; medication melanosis; melanoacanthoma; Peutz-Jehgers syndrome; Cushing's syndrome; Addison's disease and Kaposis's sarcoma [1,10,14].

The lesions are asymmetric, irregular in outline and occasionally multiple[13] and the surface can be macular to nodular, and it can assume white, brown, gray, black, dark blue, purple and red shades, sometimes with erythema or ulceration present [1,2,8,10-13,16]. The preferential location of melanoma in the head and neck is the nasal cavity, maybe it explain why POMM is more common in the hard palate (up to 80%), considering the proximity and embryological origin [8,9,15-17]. But it also develops in other sites: upper and lower gingiva, buccal mucosa, tongue and floor of the mouth, lips and uvula [11,14,16].

Histologically POMM is similar to Lentigo Maligna Melanoma in its radial growth phase. However, once invasion begins, it is very aggressive and can metastasize similar to the vertical growth phase of Spreading Melanoma. Some authors classified POMM as Acral Lentiginous Melanoma. It is characterized by the proliferation of atypical melanocytes that vary in shape, including: epithelioid, spindle, plasmacytoid tumor cells, clear cells arranged in sheet-like, organoid, alveolar, neurotropic or desmoplastic configuration, and located along the junction between epithelial and the connective tissue, also invading the connective tissue [6,11,16] (Figure 1).

The Clark and Breslow classifications are the most frequently used assessment system for the prognosis evaluation of cutaneous melanoma [17], but are less used for the primary oral mucosal melanomas due to the histological peculiarities of oral structures. Thus, in 1995 the Western Society of Teachers of Oral Pathology agreed that the POMM should be considered separately from the cutaneous counterparts [8,16]. In 2004, Prasad et al. [18] classified POMM in three histological stage: stage 1 (primary site); stage 2 (with lymph node metastasis); stage 3 (with distant metastasis). Yet, they established a three-level microstage system: Level 1 (*in situ* melanoma with no evidence of invasion or with the presence of individual or agglomerated invasive melanocyte with fewer than 10 atypical melanocytes near the subepithelial junction); level 2 (melanoma cells limited to the lamina propria); level 3 (invasion of the deep conjunctive tissue, including skeletal, muscle, bone or cartilage) [11,16,17].

Etiopathogenesis

Sun exposure appears to play a major role in the cutaneous

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melanoma's development [1]. On the other hand, mucosal melanoma of the oral cavity has no association with sun exposure, but certain factors (ethnicity; family history, syndrome and preexisting lesions) can influence the development of POMM [16].

Immunohistochemical Features

Immunoreactivity of melanoma cells to antibodies against: S-100 protein; Melan-A (MART-1), HMB-45 (gp100) and Tyrosinase can be very useful to distinguish POMM from other malignancies [13,19]. Others markers lead to variations in its biologic behavior and prognosis, such as Ki-67; P53,P16 and MITF [4,19,20] (Figures 1 and 2).

In 2001, Prasad et al. reported the expression of melanocytic differentiation markers in a serie of Malignant Melanoma of the Oral and Sinonasal Mucosa (including: primary, recurrent and metastatic tumors), and they observed imunostaining for S100 (97%); Tyrosinase (94%); Melan-A (85%) and HMB-45 (71%) in Oral Mucosal Melanomas. Garzino-Demo et al. [7] showed S-100 protein and homotropine methylbromide (HMB-45/gp100) in 80% of all cases. In a series of primary oral and nasal melanomas, positivity for HMB-45 and S-100 protein was observed in 94% and 88% of cases, respectively [21]. Recently de-Andrade et al. [12] reported HMB-45 immunostaining in all cases of melanoma, whilst Melan-A stained 86,36% and only 50% of the cases were S100 positive.

The proliferation marker Ki-67 has been considered to be the most useful tool to assess neoplastic cell proliferation in melanomas, with some studies recognizing its prognostic value. The mean and standard deviation of Ki-67 labeling index in POMM was 15.88 ± 22.09 [4], however it was previously described by de-Andrade et al., [22] as 31.7% (range 10.3 – 52.7%).

P53 is known as a tumor suppressor gene and it can be found in half of human cancers. The mutated P53 cannot perform its natural role of protecting cell genome, consequently cell with damage DNA proliferate, resulting in the development of malignant neoplasms [4]. Hicks and Flaitz [6] found 11/17 cases expressing P53 in oral mucosal melanomas; on the other hand Tanaka et al. [23], found P53 expression in only 2/13. Ahn et al. [24] demonstrated P53 expression

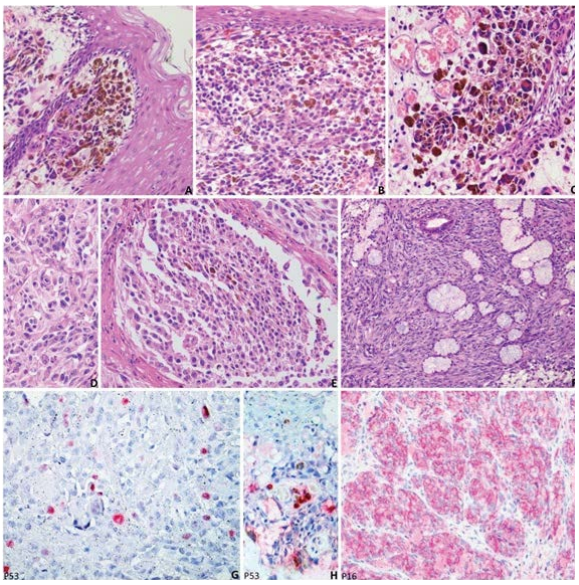

Figure 1: Histological features and P53 and P16 immunostaining: Primary Oral Mucosal Melanoma.

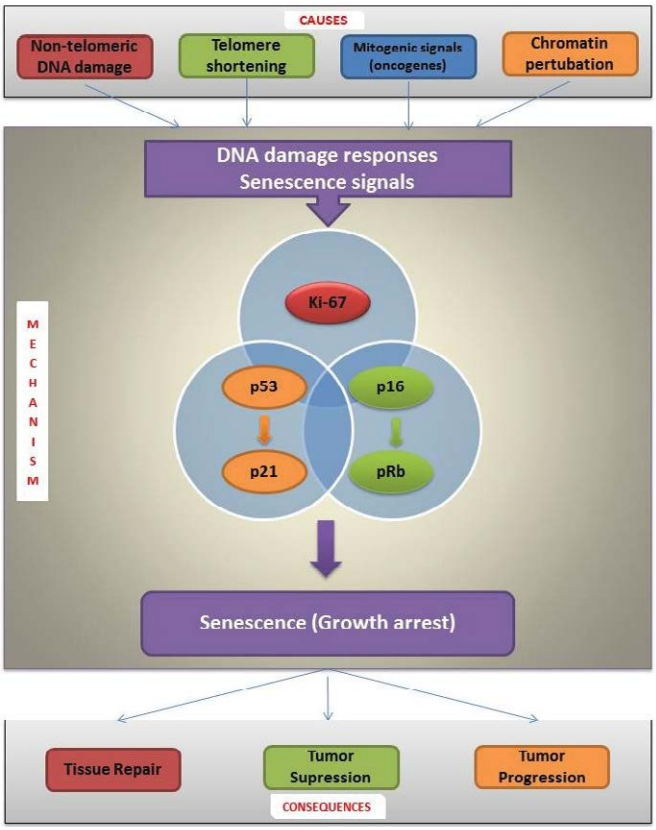

Figure 2: Tumor progression and tumor supressor.

in 6/24 In a series of mucosal melanoma of the head and neck; later in a similar study, other group observed that P53 expression occurs in about 21% of mucosal melanomas [25]. Recently a study comparing immunohistochemical profile of oral mucosal and head and neck cutaneous melanoma, P53 was evaluated and its expression did not show a significant difference between the two locations. The exact status of the P53 gene and protein in melanoma is still unclear. Moreover data regarding its biologic; prognostic; etiologic role in this tumor are controversial, especially at mucosal sites [4].

P16 is a member of cyclin-dependent kinase (CDK/Cyclin) inhibitor protein family encode by multiple tumor suppressor gene 1 (MTS-1), thus loss of P16 expression has also been reported in a small number of oral mucosal melanomas [25]. Positive staining for P16 was found 7/13 cases of malignant melanoma of oral mucosa [23]. In 2012, p16 protein was expressed in 35% of neoplasic cell in only one case out of 13 primary oral mucosal melanoma [20], on the other hand, in our experience we observed that 50% of 35 cases were positive for P16 protein expression [26]. Lost of P16 expression was observed in 75% cases of mucosal melanoma of head and neck [25].

MITF plays a critical role in the regulatory network of transcription factors and signaling pathways that control the survival, prolifaration and differentiation of melanoblasts and melanocytes, and as well as melanogenesis [27,28]. Prasad et al. [19] observed immonostaining for MITF in 27/35 Melanoma of Oral Mucosa, however, recently Alaeddini and Etemad-Moghadam [29] found MITF protein expression in 5/19 cases of Oral Mucosal Melanoma.

Conclusion

Primary Oral Mucosal Melanoma is very rare and it has a poor

prognostic. The POMM's etiopathogenesis is still unclear, however immunohistochemical markers help their diagnosis. According to the literature and our experience, the first choice as a POMM marker is S100, however Melan-A, HMB-45, P53, P16, MITF or Ki-67 are good markers, thus their combination with S100 can support and validate POMM final diagnosis. Further studies, including genetic assays, are needed to draw a better understanding of this peculiar neoplasm.

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