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Primary melanoma of the oral cavity: Ten cases and review of 177 cases from literature

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Abstract

Oral melanoma is an infrequent but aggressive neoplasm. In contrast to cutaneous melanoma, it does not have a defined set of clinical and pathologic classification criteria. We present 10 cases of primary melanoma of the oral mucosa, and review 177 cases published in the international literature. Patients and methods: We compiled a database of patients seen at our department between years 1990 and 2004. A retrospective study of this data was performed. Age, sex, localization and histopathology were all considered. Tobacco consumption and the presence of traumatic factors in the oral cavity were also compared. We compiled another database with 177 cases reported in the international literature during the same time period. Primary and metastatic cases were included. Age, sex and localization were among the factors taken into account. Results: Of the total of 23,685 patients seen at our department in this period, 399 (1.68%) were diagnosed with cancer, 10 (2.5%) of whom were diagnosed with primary oral melanoma. The gender distribution was 1:1, and ages ranged from 30 to 88 years old, with a mean of 67.5 years old. In 80% of the cases, the oral melanoma was localized in the maxillary, and in 20% of the cases, it was localized in the mandible. No connection was found with tobacco consumption. In 60% of the cases, we believe there was a link with prosthetic microtrauma. Of the 177 cases described in the literature, 89% were primary and 11% secondary. The gender distribution was 46.9% female and 53.1% male. Ages ranged from 16 to 91 years old, with a mean of 59.2 years old. Localization: 68.36% maxillary, 11.30% mandible and 20.34% in various oral localizations.

Key words: Oral melanoma, melanic pigmentation, oral nevus.

Introduction

Primary melanoma of the oral cavity (POM) is an infrequent neoplasia of very aggressive characteristics originated from the malignant transformation of the melanocytes of the mucosa.

It represents 0.2% to 8% of the total cases of melanoma from the other localizations of the body (1-6) and 0,5% of all oral neoplasia (7,8). It occurs between 30 and 90 year of age, with higher incidence in the 6th decade (7,9,10). In general it doesn't have gender preference (3,4,11) though some authors refer that incidence is slightly higher in males (1,7) and others in females (12). 80% of the cases are localized in the maxillary with prevalence of the hard palate or combined with gingiva or alveolar ridge (5,9,13,14). The POM has a higher incidence in yellow, black races and in the Indian of Asia (1,12,15). This is attributed partially to the frequent finding of melanic pigmentation in the oral mucosa of these races. The appearance of primary melanoma located in the oral cavity is rare, even more exceptional is the secondary form (metastasis in the oral cavity of primitive distant melanomas) (16).

When it is secondary or metastatic the localization is more frequent in tongue, parotid and tonsils (2,5).

It is considered primary POM when the following criteria described by GREENE (1953) are fulfilled:

- Demonstration of melanoma in the oral mucosa.
- Presence of junctional activity.
- Inability to demonstrate extraoral primary melanoma. (16).

The POM is distinguished clinically by presenting asymmetric lesions of irregular outline; the color may be uniform, though generally has a mixed coloring (17) that varies from light brown to dark brown and from black to blue, red when non-melanotic which can simulate a vascular tumor or a salivary gland tumor (1,5). For the POM there are no geographic differences as occur with its cutaneous homologue, since there is no evidence of the influence of UV radiation in the development (13). The POM is very aggressive (11) and as in its beginning it may poses a stable clinical aspect, differential diagnosis with other entities such as Addison's disease (13,16) Peutz Jeghers's syndrome (16) or Kaposi's sarcoma must be performed (13,17). Also, with melanic pigmentations, both from racial or irritative causes, with melanocytic nevi (8,16,17) and with other pigmentations of exogen cause, such as amalgam tattoo (8,11,13,16,17). According to the literature, differential diagnosis with melanoacantoma should be considered as well (8,16). Delgado Azañero et al. (7) presented a practical and technically simple method for the clinical diagnosis of POM, which allows differentiating this neoplasia from other pigmented lesions. The clinical test consists in rubbing the surface of the lesion with gauze with the objective of verifying if it stains black

due to the presence of melanin pigment on its surface. The authors refer that a positive result was obtained in 84,6% of the cases, that the method possesses an elevated sensibility to anticipate diagnosis and that a negative result does not exclude the possibility of this neoplasia, since there are cases in which the malignant cells have not invaded the superficial layers of the epithelium. The Melanoma that involves the mucosa of the region of the head and neck is more aggressive when it is presented clinically as nodular, with a vertical growth that invades the sub mucosa (8). The prognosis is poor (8,9,10,15) it is based on the histological type, the depth at microscopic level of the tumor's invasion and its localization. The literature points out that in the oral cavity it is observed with greater frequency in the mucosa that covers the bone tissue, such as that of the hard palate and gingiva. These localizations would play a significant role in the early invasion of the adjacent bone (18) being an additional reason for the poor prognosis presented by this pathology (9).

The precursors are not well identified,(18) some authors point out an atypical melanocytic hyperplasia (increase in the cell number) (8,12) that proliferates in a previous stage to the apparition of the neoplasia (1), others refer to a preexisting melanosis (increase of the melanogenesis) when these precursors would be the initial stage of a prolonged evolution of horizontal growth, before entering in the invasive stage of vertical growth (6,9,13). Other authors consider also as precursors the melanocytic nevi (8) and qualify as interesting the coincidence that in the oral activity, these are localized with higher frequency in the hard palate as the melanoma (1). Weber described POM for the first time in 1859 and clear classification criteria haven't been incorporated as they exist for the cutaneous melanomas. Many classifications have been established to study it but none have been universally accepted (7,9,17,18). Regarding the classification and prognosis, the criteria developed by Clark and Breslow are not useful in the oral cavity because of the histological peculiarity it presents (9). In 1995 the Western Society of Teachers of Oral Pathology (Westop) agreed that the lesions of the POM should be considered separately from the cutaneous forms (17). And in response to the revision of several factors associated with primary oral melanomas collected in different Department of Maxillofacial Pathology, they proposed to classify them according to their histological pattern that divides them in: melanoma in situ, invasive and combined. The nomenclature employed is simple; they describe preceding lesions as atypical melanocytic hyperplasia, where there is hyperchromatism and nuclei with infrequent mitotic activity. The presence of such lesions would indicate a high risk to develop mucosal melanoma (8). Cebrián Carretero et al. (9) point out that maybe the most useful classification to establish prog-

nosis is the one which distinguishes three stages:
 I) Tumor limited to the oral cavity
 II) tumor with lymphatic dissemination
 III) tumor with distant metastasis
 Prasad et al. (19) in their series of melanomas of the mucosa of the head and neck found that the majority of these cases (71%- 97%) were diagnosed at stage I and proposes to divide it into 3 levels, where the relevance of thickness of each of them is pointed out as a prognostic factor, specially because of the possibility of survival. This rate after 5 years is, in general, lower than 20% (1, 2,6-9,14).

Unfortunately the POM remains asymptomatic for a long time and is frequently detected when there is presence of hemorrhage (14-16) being diagnosed in late stages of the disease when there is invasion of the underlying tissue (7). This diagnosis is often reached too late because the absence of symptoms delays the consultation in the adequate time (6,13,16). The former is considered one of the most important reasons for an unfavorable prognosis (14). The diagnosis of non-melanotic melanomas is more difficult than the one for the pigmented type (20-22) and the prognosis tends to be poorer (20). Early detection and opportune treatment constitute the primary weapons to improve the prognosis (7,12).

Objective: the presentation of 10 cases of Primary Oral Melanoma and the review of other 177 cases referred by different authors, which have been published in international literature in the 1990- 2004 period.

Material and Methods

A data base was compiled from the medical history file of the patients seen at the Oral Medicine Chair of the School of Dentistry of the University of Buenos Aires (FOUBA) Argentina, during 1990-2004. A retrospective study was performed. Age, sex, location and histopathology were considered (Fig.1,2,3,4) in relation to

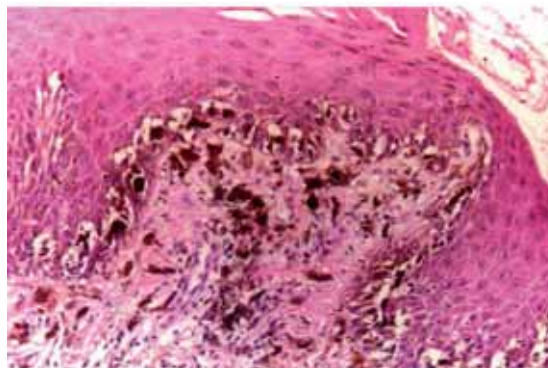


Fig. 2 Clinical Case 1
 Biopsy of the palate exhibiting in situ melanocytic growth with pigmentary loss to fibrosed estroma. HyEx25



Fig. 3. Clinical Case 4
 Clinical description: tumor in hard palate, left side, towards the back vegetant appearance, color black, secil base, 14 by 22 by 3 mm solid nitid borders; non-ulcerated surface, towards the front another elevated lesion smaller size and dark, presence of brown stains and others to the front of the palatine wrinkles of a blueish color. Several smaller lesions cover diverse extensions of the palate and gingiva, all of which are asintomatic.

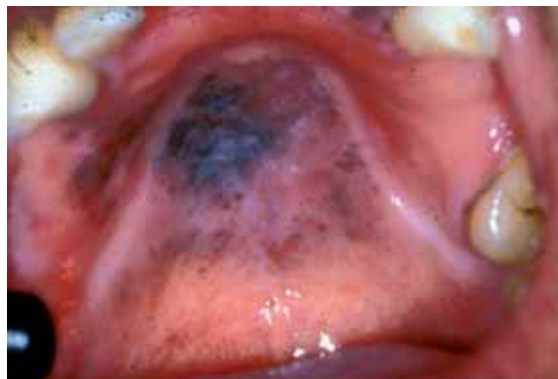


Fig. 1. Clinical Case 1
 Clinical description: on the hard palate, left side and central region, a brown-blue stain with dark borders can be seen. Around the lesion there is a dotted melanosis towards the left side and a more accentuated and darker melanosis towards the right side.

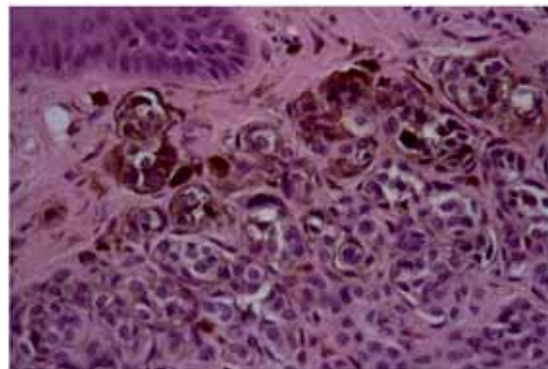


Fig. 4. Clinical Case 4
 Histopathology: Infiltrating Melanoma. Atypical melanocytes that form bundles of tumoral infiltration may be observed. Detail of melanic pigment can be observed. HyEx40

Table 1. Presentation of 10 cases of primary oral melanoma.

Case	Gender	Age	PS	State	Denture	Tobacco	Location	Treatment	Clinical Aspect	Histologic pattern	Follow-up
1	Male	50	NO	I	YES	NO	Hard palate Maxillary gingiva (FIGURE 1)	Surgery Radiation	Macular	In situ (FIGURE 2)	Alive without disease x 6 years
2	Male	88	NO	II	YES	NO	Hard palate Maxillary gingiva	None	Macular	Combined Invasive with in situ	Died of disease 30 months after diagnosis
3	Female	30	NO	I	NO	YES	Mandibular gingiva	None	Macular	Invasive	Alive without disease x 5 years
4	Male	75	NO	I	YES	NO	Hard palate Maxillary gingiva (FIGURE 3)	Surgery Radiation Chemotherapy	Nodular	Invasive (FIGURE 4)	Died of disease 8 years after diagnosis
5	Female	65	NO	I	YES	NO	Hard palate Maxillary gingiva	Surgery	Macular	Combined Invasive with in situ	Information not available
6	Female	85	YES	I	YES	NO	Mandibular gingiva	Surgery	Nodular	Invasive	Information not available
7	Male	62	NO	I	NO	NO	Maxillary gingiva	Surgery	Nodular	Invasive	Information not available
8	Female	85	NO	I	YES	NO	Hard palate Maxillary gingiva	Surgery	Nodular	Invasive	Died of disease 3 years after diagnosis
9	Male	55	NO	I	NO	NO	Hard palate Maxillary gingiva	Surgery	Nodular	Invasive	Died of disease 2 years after diagnosis
10	Female	80	YES	I	NO	NO	Hard palate Maxillary gingiva	Surgery	Nodular	Invasive	Died of disease 08 months after diagnosis

Reference: Ps:Painful symptoms

Table 2. Oral melanoma. Location by region of total cases.

AUTHOR	N° of cases	LOCALIZACION									
		PALATE	MAXILLARY		MANDIBULAR GINGIVA / ALVEOLAR RIDGE	TONGUE	LIP	BUCCAL MUCOSA	TONSILS	PAROTIC GLAND	OTHERS SITES
Patton (1994) ²	15	1	2	3	4	5	6	7	8	9	10
van der Waal (1994) ¹³	8	6			2	5	2	3		3	
Umeda (2002) ¹⁸	15	5	8		1						1
Tanaka (1994) ³	20	6	10	2	1						1
Manganaro (1995) ¹⁶	4	1	2	2	1						
Lombardi (1995) ²⁴	1		1								1
Oribe (1998) ⁴	1										
Strauss (1994) ⁵	1	1									
Yoshida (1994) ²³	2	1		1							
Albertos Castro (1998) ¹¹	1	1									
Santamaria (1997) ³⁰	1				1						
Westop Banff workshop (Barker BF)(1997) ¹⁷	50	19	7	9	8	1	4	2			
Tanaka (1998) ²⁸	3	1	1				1				
Colella (1998) ²⁵	1	1									
Gorsky, Epstein(1998) ¹⁰	6	3		1					2		
Dimitrakopoulos(1998) ²⁶	1			1							
Pechitt-Wood (1990) ²⁷	1		1								
Smyth (1993) ⁶	5	3			1					1	
Lopez Graniel (1999) ²⁹	15	11		1		1		2			
Notani(2002) ²⁰	3	1		1							
Delgado Azañero-Mosqueda Taylor (2003) ⁷	13	4	3	1	2		2				1
Garzino-Demo (2004) ¹⁵	10		3	3	2	1					1
Total bibliographical cases	177	64	33	23	20	9	9	8	2	4	5
	100%		67,79%		11,30%	5,09%	5,09%	4,52%	1,13%	2,26%	2,82%
All cases presented FOUBA	10	4 40%	3 30%	1 10%	2						
	100%		80%		20%						

tobacco use and the presence of oral traumatic factors in all the studied patients. Another data base was compiled with the cases of oral melanoma studied by different authors in the international literature. 177 cases studied in 22 articles, published in the 1990-2004 period were included, these are referenced in (Table 2) by author and number of cases presented by each of them. Age, sex and location were considered, as well as primary and secondary or metastatic melanomas of the oral mucosa. Absolute frequency, relative frequency, range and mean were determined.

Results

Over a total of 23685 patients treated for different pathologies of the oral mucosa, 399 were diagnosed with cancer (1,68%) including leukemia and lymphoma. Resulted 10 primary melanoma of the oral cavity 2,5% of the total neoplasia diagnosed in this period (Table 1). The distribution by sex was 1:1. The age range 30 to 88 years old with a mean of 67.5 years. Of the 80% situated in the maxillary 40% corresponded to the palate, 30% combining palate and alveolar ridge and 10% in the upper gingiva. The 20% corresponding to the mandible was localized in the gingiva (Table 2). Micro trauma by denture was found in 60% of the patients and there was no relationship found with tobacco use (Table 1). In the 177 cases from the literature the distribution by sex was female 46,9% and male 53,1%. The age range 16 to 91 years with a mean of 59,2. 89% were primary and the remaining 11% metastatic (Fig.5). 67,79% were situated in the maxillary and 11,30% in the mandible. The remaining percentage in the following locations: tongue 5,09%, mucosa of the lip 5,09%, buccal mucosa 4,52%, parotid gland 2,26%, tonsils 1,13% and combined or mixed between the soft palate and the buccal or lip mucosa or maxillary sinus 2,82% (Table 2).

Discussion

The oral melanoma is an extremely rare entity and given the low survival of these patients, we consider that all contributions to its knowledge, early detection and early treatment are very important. The etiology is unknown (9,11,13). The pathologic findings referred to melanic stains in the mouth preceding melanoma are extremely important.

In the oral cavity there is no influence of the UV radiation, as occurs in cutaneous melanomas and therefore their discovery is delayed in relation to the latter. Evolution is usually ignored because of the scarce symptoms it presents, often omitted for a long time (14-16). In general, the patients delay consultation (6-13) to when the tumor doesn't allow them the correct use of their dentures or when it ulcerates (10-12) hemorrhage is the most frequent symptom (14-16). Another symptom is dental mobility (11) and in some occasions pain

and paresthesia. In our casuistic patients didn't refer painful symptoms, except the patient from case n° 10 where pain was the motive for consultation and in case n° 6 where the lesion in the alveolar ridge prevented her from using the denture correctly and caused her pain.

In accordance with the different authors from the literature 80% of the POM presented it was localized in the maxillary (5,9,13,14). In the cases from the literature it turned out to be the most frequent localization between the primary ones (68%). In our casuistic there were no metastatic oral melanoma, whereas in the cases from the literature 11% were metastatic, in different locations (Table 2). It must be taken into account what some authors say about metastatic melanomas and that the most frequent location is the tongue and the parotid gland, followed by the tonsil (2,5). This tendency is notable in the results (Fig.5).

There is no relevant proof that the trauma of the dentures stimulates or influences the development of the POM (1,13) there is only reference to the mechanic irritation caused by maxillary denture in the palate, especially in edentulous patients (13). They also refer that the dentures easily ulcerate the lesions causing bleeding (6). We found that 60% of our patients were denture wearers that caused micro trauma on the lesions, corroborating the possibility that the trauma could represent a role in the evolution of this tumor. Although the majority of the POM appear in the sixth decade of life, (7,9,10) in our casuistic study the highest incidence was in the eight decade. In the literature the highest was the fifth decade followed by the sixth decade. The distribution by sex in our casuistic was the same for both sexes which coincided with some authors from the literature (3,4,11). On the contrary in the literature it was higher in males in agreement with other authors (1,7). Hematic and lymphatic dissemination is possible (9) that may be followed by metastatic adenopathy (11) especially in the tumors with vertical growth. The profuse vascularization could influence in the elevated incidence of metastasis (14). Garzino Demo et al. (15) conclude their work pointing out that the PMO are more prone to develop distant metastasis than other head and neck melanomas. The proliferation may reach bone tissue, lung, liver and brain (5,23). At the moment of diagnosis, in our casuistic study, 90% of the cases were in stage I, following Prasad et al. (19) who suggest that in their series of cases of melanoma of the head and neck mucosa (71%-97%) at the moment of their appearance were in stage I. The diagnosis of melanoma can be confirmed by positive immunohistochemical for S-100, HMB-45, Melan A and vimentina, especially in non-melanotic melanomas for accurate diagnosis (6,11,12,18-24). The accepted therapy for this pathology is the total surgical elimination with a wide margin and bone resection (7,8,9,12,22-30). Cebrían Carretero et al. (9) consider that chemotherapy

and immunotherapy would have a poor contribution in the improvement of prognosis. Survival after 5 years mentioned in the literature is less than 20% (2,6,9,14,22,26). In the review by Rapini et al. (1) over 101 patients it was 13%. In the series by Lopez Graniel et al. (29) was 6,6% and both the average from the series of y Delgado Azañero et al. (7) as that of Hicks et al. (8) was 15%. In our study we verified that in case N° 1 (Fig.1) which diagnosis was melanoma in situ (Fig.2), the prognosis was more favorable and the patient continues alive to date, with a survival rate greater than 5 years.

Conclusion

With the purpose of reducing the diagnostic delays, it is necessary to learn about the possible presentations and the most frequent localizations of the oral melanoma, especially of those lesions that appear in regions of the oral cavity used as support of dentures and that because of their lack of adaptation could cause micro trauma. In all these cases we suggest the extirpation as a prophylactic measure and histopathology.

Considering that it is an extremely rare disease, the majority of the information is obtained from a small series of cases. We believe in the importance of the analysis of previously published cases and the divulgation of the new ones, to help establish a definite classification and propose clinical features that would facilitate early diagnosis, indispensable for treatment and prognosis of this pathology, since to date it is the only resource to improve the survival of these patients.

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