Original Article

Oral malignant melanoma: History of malignant degeneration of a pigmented lesion

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(Received: 22 November 2018, accepted: 22 January 2019)

Keywords:
melanoma /
pigmentation /
neoplasms

Abstract – Introduction: Oral malignant melanoma (OMM) is a rare malignant lesion of the oral mucosa. It accounts for 0.5% of oral cavity cancers and less than 1% of all melanomas. Most cases arise on the palate or gingiva. OMM is caused by unknown factors. Benign pigmentation may precede the neoplasm by several years. The malignant transformation of benign melanosis is poorly understood. **Observation:** The aim of this work is to present a new clinical case of oral malignant melanoma which appeared on benign melanosis with a brief review of the literature. A 37-year-old woman presented with a blackish pigmented plaque that covered the hard palate and vestibular maxillary gingiva and a soft, friable 2 cm nodule with ulcerated surface next to the 11, 12 and 13. Fifteen years ago, the patient underwent a biopsy that was in favor of benign melanosis. Unfortunately, the patient was followed for one year and then was lost. Recently, in front of the rapidity of the extension of the lesion, she came again. After biopsy, a final diagnosis of OMM is retained. **Commentaries:** OMM is often asymptomatic. It presents usually as a 1.5–4 cm, blackish grey, irregular, flat or nodular lesion. The neoplasm can appear on apparently normal oral mucosa and may be preceded by benign pigmented lesions. Few articles discussed malignant transformation of benign melanosis. OMM is characterized by its poor prognosis. The treatment of choice for OMM remains surgery with wide clear margins. **Conclusion:** Close monitoring is needed to detect signs of transformation and to early diagnose melanoma.

1 Introduction

Oral mucosal melanoma is a malignant neoplasm of melanocytes. It's a rare entity accounting for only 0.5% of melanomas. There is a slight male predominance, and the median age at diagnosis is 55–66 years. The most common oral cavity sites of melanoma are the palate and maxillary gingiva. Mucosal melanomas, which are biologically distinct from their cutaneous counterpart, are caused by unknown factors. They often emerge from pre-existing benign pigmented lesions [1–3]. The exact mechanism of malignant transformation is still unknown. Cutaneous premalignant melanocytic lesions have been well described [3]. But, clinical and histological features of "oral premalignant melanocytic lesions" are lacking. Several case reports are reported in the English language literature. The aim of this article is to report an additional clinical case of oral malignant melanoma with a history of benign melanosis and to analyze its clinical and histopathological features.

2 Case report

A 37-years old woman presented to our department of oral medicine and oral surgery at Monastir dental clinic with a 3 months history of swelling and bleeding in the right maxillary gingiva. A review of her medical history revealed cervical lymph node tuberculosis treated in 2005 by surgery and antibiotics. The patient had neither personal history of malignancies nor treatment with radiation or chemotherapy. Besides, 15 years earlier, at age of 22 years, she has had pigmented lesion on the hard palate and maxillary gingiva. The lesion was a large brown-black flat patch up to 4 cm in its greatest dimension. The lesion was asymptomatic and the patient was unable to remember how long it was present. An incisional biopsy was made. A final diagnosis of benign melanosis without any atypical melanocytes was rendered. Unfortunately, over the course of the next 15 years the patient was lost.

In 2017, due to the widening of the lesion and the appearance of a gingival mass in front of the right maxillary incisors and canine, the patient consulted again.

Intraoral examination showed multiple lesions in the same places of the old benign melanosis. The lesions were asymmetric, irregularly shaped and nonuniformly pigmented. Their color varied from light brown to black. The bigger patch

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Fig. 1. Clinical presentation: A. An extensive pigmented lesion with variegation was seen in the maxillary buccal gingiva and alveolar mucosa from tooth #16 extending to #27 with ulcerated soft and friable nodule of 2 cm long. B. Patchy dark pigmentations were also found in the whole palate.

Fig. 2. Computed tomography scan: A. Axial. B. Frontal slices: no bone spread was noted.

was spread over the hard palate crossing midline and measured approximately 5 cm. Satellite lesions surrounded it. On the buccal side, a black nodular component was in the center extending from the right central incisor to the right canine. It was ulcerated and bleeding at the slightest touch. The lesion was described as having soft consistency.

On close examination, a slightly elevated dark pigmented plaque component and a non-elevated light brown macular component reached alveolar mucosa. There were no palpable lymph nodes (Fig. 1).

An incisional biopsy was performed. Histological report concluded to malignant melanoma of the gingiva. The patient underwent pertinent imaging studies to assess the primary lesion and its bone invasion and to rule out metastatic lesion. Computed tomography (CT) scan of the head and neck revealed no bony invasion and showed 12 mm submandibular lymph node. Brain CT scan was negative. However thoraco-abdominal CT scan founded no signs of distant metastasis except 2 nonspecific lung micro nodules which have been assigned to tuberculosis (Fig. 2).

Subsequently, the patient was referred to the oncology department. She was considered as clinical stage II (T3N1M0) (Tab. 1). The best treatment would have been total maxillectomy associated to cervical dissection and postoperative

radiotherapy if surgical margins were proved positive. But extended lesion and proximity of vital structures declined this decision. So, only 70-gray palliative radiotherapy was performed. Oral mucositis developed later with radiotherapy and healing did not begin until the end of therapy (35 sessions). Xérostomia and radiation-induced dermatitis were the quite mandatory sequela after head and neck radiotherapy (Fig. 3).

At 10 months follow up, no new pigmented areas were noted. Local examination showed lesion's size decrease. But, the nodular component persisted (Fig. 4). Magnetic resonance imaging (MRI) will be programmed in 2 months to better evaluate local control and rule out distant metastasis.

3 Discussion

Head and neck mucosal melanoma constitute less than 1% of all melanomas and arise for the most part, in two primary sites: the sinonasal region and oral cavity. In the fourth edition of the World Health Organization Classification of Tumors of the Head and Neck, oral and sino-nasal mucosal melanomas are recognized as distinct entities. Oral malignant melanoma (OMM) is the second most common site of occurrence of mucosal melanoma in

Table 1. Clinical staging system for oral malignant melanoma with histopathologic microstaging for stage I (Prasad [20]).

Stage I	Primary tumor present only (Tany N0 M0) Level I: pure <i>in situ</i> melanoma without evidence of invasion or <i>in situ</i> melanoma with "microinvasion". Level II: invasion up to the lamina propria. Level III: deep skeletal tissue invasion into skeletal muscle, bone, or cartilage.
Stage II	Tumor metastatic to regional lymphnodes (Tany N1 M0)
Stage III	Tumor metastatic to distant sites (Tany Nany M1)

Fig. 3. Radiotherapy sequel: A. Xerostomia. B. Radiation induced oral mucositis. C. Radiation induced dermatitis. **Fig. 4.** Superposition of clinical aspects: A. Clinical presentation at diagnosis. B. 7-months follow up presentation. C. 10-months follow up presentation: decrease in the extent of the lesion.

the head and neck [4,5]. Primary OMM is rare. It represents 0.5% of all oral malignancies and 0.2 to 8% of all melanoma [2]. This prevalence seems to have been stable for 2 centuries. Melanoma is a tumor of the adult. It occurs mostly in the 4th to the 6th decade of life with a range from 4 to 92 years [1,2,4,6–8]. It is often said that there is a slight male predilection of 2:1 [1,2,4,6–8]. Whereas other studies showed no sex predilection, even more there was a female superiority [9,10]. OMM is known to occur more frequently in Japanese, African, and North American Indian populations than in European populations [2,11]. High risk sites are the palate and the maxillary gingiva. However, all oral mucosa sites can be affected by OMM [1,2,4,6–9].

Oral malignant melanoma is usually painless. It is often described as a uniformly pigmented black or brown lesion. But sometimes several shades co-exist: black, brown, gray, pink and red. 10% of oral melanomas are nonpigmented called amelanotic melanoma. The lesions are asymmetric and irregular in outline. Sometimes, they are multiple. The elemental lesion may be a flat macula, a low elevated plaque or a soft nodule. These clinical aspects can be present at the same time [1,2,4]. Tanaka tried to establish a clinical classification and defined 5 types [9]. Unfortunately, this classification has no prognostic value. Ulceration and bleeding are late signs. Unlike squamous cell carcinoma, there is no induration [1,2,4].

So far, the etiology of oral malignant melanoma is poorly understood, unlike cutaneous melanoma which has well-defined risk factors. Therefore, it is still difficult to recognize subjects at highest-risk for developing OMM [5]. Some authors suggest tobacco smoking, inhaled or aspirated environmental carcinogens and chronic irritation as possible risk factors [2].

It is true that most of these tumors appear to be *de novo*. Haïtami *et al.* reported three cases of melanoma that appeared on healthy mucosa after dental procedures [5]. However, it needs to be mentioned that about one-third of melanomas have had a history of benign pigmented lesions for months and even years before malignant transformation [1–3]. Unfortunately, the exact mechanism of malignant transformation is unknown. We will present here a non-exhaustive summary of literature cases about melanoma emerging from flat precursor lesions (Tab. 2). To the best of our knowledge, in addition to our clinical case, there are only 7 case reports in English literature which analyze well the clinical and histological features of progression from benign pigmentation to oral malignant melanoma (Tab. 2).

Several descriptive terms have been used to describe premalignant lesions: oral benign melanosis, pre-malignant melanosis, oral melanotic macule, melanocytic dysplasia, melanocytic hyperplasia, neoplastic melanocytic proliferation (Tab. 2) [3,6,12–17]. The average age at diagnosis was 44 years with an interval between 22 and 62 years. No sex predilection was noted. Precursor lesions were irregularly shaped flat, preferentially localized in keratinized tissues, at the same sites of melanomas. Lesions' size ranged from 0.5 to nearly 5 cm of major axis. Lesions have evolved for months and years and they were characterized by their tendency to recur after excision, persistence and enlargement [3]. It is accepted that clinical evaluation of cutaneous melanocytic lesions is guided by ABCDE criteria. The guidelines evaluate for asymmetry, border irregularity, color variegation, a lesion that exceeds a diameter of 6 mm, and lastly evolution, or change in the lesion over time [2]. Many authors claimed that these criteria do not sit well with oral pigmented lesions. However, most of premalignant lesions including our patient transgressed these criteria when progressing to oral malignant melanoma. According to the western society of teachers of oral pathology (WESTOP), both clinical and histological criteria should be used for the monitoring of pigmented lesions and recognition of potentially malignant ones [18].

Biopsy of oral pigmented lesion is still controversial. Umeda involved the biopsy as well as any procedures before the definitive intervention (such as teeth extraction, incision...), in the bad prognosis of OMM. In his case-control study, there was a statistically significant difference between 5-year survival rate with and without procedures before definitive surgical treatment ($p < 0.05$). Without biopsy, the 5-year survival rate was of 91.7%. However, it dropped to 25.9% for patients who underwent these procedures [8]. On the other hand, without histological analysis, we can never recognize the exact nature of an oral pigmented lesion. So no early treatment could be started. Until tangible evidence, it is not asserted that

biopsy increases the risk of local or distant spread of melanoma [2]. Moreover, when we find melanocytic hyperplasia or dysplasia in histological reports, the entire lesion should be completely excised with clear margins [3,18]. For our patient, the lesion covered the entire palate, and histo-pathological report reported no sign of dysplasia. In principle, incisional biopsy was sufficient. But close clinical follow up had to be maintained.

Histological features of potentially malignant pigmented lesions were multifarious. We can find hyperpigmentation in the basal layers, proliferation of dendritic melanocytes with or without atypia, proliferation of clear cell [3,13,15–17,19]. These data are found in Umeda's gradual enlarging pattern of oral malignant melanoma. Meticulous examination revealed that OMM went through three phases: a nodular phase usually affecting the centre, a slightly elevated, deep brownish-black pigmented plaque phase, and a flat light-brown macular phase [11]. In the macular phase, a simple hyperpigmentation in the basal layer is found. Lentiginous proliferation of dendritic melanocytes without apparent cellular atypia may be also noted. The pigmented plaque lesion contains atypical melanocytes nests or individually proliferating tumor cells in the lower epithelial layers. It's considered pre-invasive phase. Macular and plaque phases form radial growth pattern of OMM [3,11]. Overall, most of premalignant lesions histological findings appear to be consistent with features found in the macular and plaque phases of OMM [3]. Only the nodular phase corresponds to true invasive melanoma when vertical growth pattern begins with spindle-shaped or epithelioid tumor cells in the submucosa [3,11].

So, in OMM cellular morphology shows a wide range of features [1,2,4,8,9,20]. Since histological aspect is non-pathognomonic, and 10% of the melanomas are amelanotic, the diagnosis becomes a heavy task. Immunohistochemistry is strongly indicated. Melanocytes markers commonly used are protein S100, melan-A, tyrosinase, HMB45 [2,4,7,8,20].

OMM treatment is based on surgery with wide clear margins. For the palate, maxillectomy with 3–5 cm margins is recommended [2]. To meet this requirement, it is necessary to extend the excision to the soft palate, the tonsillar pillar, and into the pterygomaxillary space. But, the proximity of vital structures makes this objective difficult. No consensus exists so far. Recently, Umeda suggested excision of the lesion with an intraoral approach and involving at least 1.5 cm of healthy tissue, therapeutic radical neck dissection for stage II tumors and immune-chemotherapy [8]. Radiotherapy as first-line treatment does not exceed surgery. Tanaka reported that primary lesion was controlled in 92.3% of cases with surgery, whereas only 53% cases had controlled primary lesion in radiotherapy group [21]. Post-operative radiotherapy is beneficial in cases with positive surgical margins or a strong likelihood of local or regional recurrence [1,2,10]. It's the most effective treatment modality for palliation which was the case of our patient [2].

Despite improved treatments, OMM prognosis remains poor. The average 5-year overall survival rate varied from

Table 2. Summary of literature case reports: Demographic, clinical and histopathological findings, pathology diagnosis of premalignant melanocytic lesion and time to onset of oral malignant melanoma.

Author/ year	Age/race/ sexe	Location of pre-malignant lesion	Size (cm)	Clinical findings	Histological findings	Diagnosis of the pre-malignant lesion	Time to diagnosis of OMM	Reasons for consultation
Rapini [12]; 1985	9 years/ F	Lips	NP	NP	NP	NP	20 years	Enlarging/ pain
Rapini [12]; 1985	46 years/ white/M	Palate	NP	NP	NP	NP	6 years	Enlarging
Taylor [13]; 1990	22 years/ white/M	Mandibular gingiva	0.5	Pigmented lesion	Squamous epithelium with anastomosing and elongated rete ridges and “abundant pigmentation in the basilar” and scattered melanophages in the stroma	Benign gingival melanosis	5 years	Enlarging/ ulceration
Umeda [14]; 2002	58 years/ Asian/F	Palate	NP	Pigmented macule	Lentiginous proliferation of dendritic melanocytes and melanin products. Melanocytes formed small nests in the tip of rete ridges	Melanocytic dysplasia	3 years	Follow up visits
Kahn [15];2005	38 years/ white/F	Palate	1.2	Elongated bluish- black macule with an irregular brown periphery	1: Normal mucosa except “for increased melanin pigmentation in the basal layer” 2: Intense pigmentation and “large number of melanocytes” in the basal cell layer with “clear cell (melanocytic) proliferation” 3: HMB-45 was positive 4: NP (postirradiation change of salivary ductal epithelium) 6: Increased numbers of pigmented melanocytes at the dermalepidermal junction with prominent dendritic melanocytes hyperplasia + malignant melanoma <i>in situ</i> 6: Labial lentigo = hyperpigmented melanotic macule 7: Carcinoma <i>in situ</i> with focal areas of superficial invasion and melanocytic colonization + severe melanocytic dysplasia 8: Melanoacanthoma 9: Atypical melanocytic hyperplasia 10: Melanocytic hyperplasia with focal dendritic melanocytes	1: Oral melanotic macule 2: Oral melanotic macule OMM 3: Pigmented epithelial hyperplasia 4: Atypical melanocytic hyperplasia 5: Atypical melanocytic 7 years and 8 months	Increasing in size	

Table2. (continued).

Author/ year	Age/race/ sexe	Location of pre-malignant lesion	Size (cm)	Clinical findings	Histological findings	Diagnosis of the pre-malignant lesion	Time to diagnosis of OMM	Reasons for consultation
Kaehler [16]; 2008	57 years/ NP/M	Tongue	2.0 × 5.0	Bluish brown melanosis	Pronounced "basal hyperpigmentation" without elongation of rete ridges	Oral melanosis	9 years	Enlarging
Meleti [17]; 2010	50 years/ NP/M	Palate	1.5	Irregularly shaped flat, nonuniformly pigmented (predominantly brown-black), surrounded by minor brownish pigmentations	Limited amount of melanin pigment in the basal layer of epithelium and in the connective tissue. Mild signs of melanocytic atypia. In the underlying salivary glands, several pigmented epithelial cells in the interlobular and excretory ductal cells.	Possible neoplastic melanocytic proliferation with atypia and variable expression of melanin extending into the underlying salivary glands	4 years	Follow up visits
Shen [6];2011	60 years/ Asian/F	Palate	NP	NP	NP	Oral melanotic macule	1 month	NP
Patel [3];2017	41 years/ Asian/M	Maxillary gingiva	0.75	Bluish-black with slight variegation	Melanocytic hyperplasia with atypical melanocytes	Pre-malignant melanosis	12 years and 8 months	Bleeding and soreness
Patel [3];2017	62 years/ Asian/F	Maxillary gingiva	4.25	Bluish-black with color variation and an irregular border melanoacanthoma	Melanocytic hyperplasia with dendritic melanocytes migrating into spinous cell layer 11 months	Oral Reappearance and a salty taste associated with areas of the lesion		
Our case report	22 years/ Maghreb/F	Palate	4	Brown-black melanosis	Basal hyperpigmentation without any atypical melanocyte	Oral melanosis	15 years	Enlarging/ ulceration

Note: OMM: oral malignant melanoma; NP: not precised.

16.6 to 48% in various study [9,10,20]. Moreover, the median survival after diagnosis is estimated at 24 months [4]. Various prognostic factors have been investigated, but nowadays only clinical staging at presentation has been affirmed as the most important predictive factor determining outcome [2,4,9,10,20].

4 Conclusion

Oral malignant melanoma is a rare tumor of the oral cavity. It's renowned for its poor prognosis. Advanced disease at time of diagnosis is the only sure predictor of outcome. So, any suspected melanotic lesion should undergo histological analysis to diagnose OMM in its early stages or at best to rule out premalignant pigmented lesions. Close clinical follow-up of premalignant lesions is also emphasized up to a better understanding of cancerization phenomenon.

Conflicts of interests: The authors declare that they have no conflicts of interest in relation to this article.

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