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Oral melanoma and other pigmentations: when to biopsy?

Running head: Biopsy of Oral Pigmentations

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Abstract

Oral pigmentations (OPs) are often neglected, although a meticulous examination of the oral cavity is important not only in the diagnosis of oral melanoma, but also for the detection of important clinical findings that may indicate the presence of a systemic disease. OPs may be classified into two major groups on the basis of their clinical appearance: focal and diffuse pigmentations, even though this distinction may not appear so limpid in some cases. The former include amalgam tattoo, melanocytic nevi, melanoacanthoma, melanosis, while the latter include physiological/racial pigmentations, smoker's melanosis, drug induced hyperpigmentations, post-inflammatory hyperpigmentations, and OPs associated with systemic diseases.

We will discuss the most frequent OPs and the differential diagnosis with oral mucosal melanoma (OMM), underlining the most frequent lesions that need to undergo a bioptic examination and lesions that could be proposed for a sequential follow-up.

Oral pigmentations (OPs) are often neglected, although a meticulous examination of the oral cavity may detect important clinical findings in

systemic disease. OPs may be classified into two major groups on the basis of their clinical appearance: focal and diffuse pigmentations, even though this distinction may not appear so limpid in some cases. Oral malignant melanoma (OMM) is the most worrisome and life-threatening condition and should always be considered among the possible differential diagnoses.

We will discuss herein the most frequent OPs and the differential diagnosis with OMM, underlining the most frequent lesions that need to undergo a bioptic examination and lesions that could be proposed for a sequential follow-up.

Oral mucosal melanoma

OMM is uncommon in Caucasians (<1%), in comparison to the Japanese (7.5%)[1-4], developing mainly in the 4th-7th decades of life, median age 60 years.[4] Its frequency is estimated to range from 0.5-0.7% of all oral malignancies, representing a rate of frequency ranging from 25-40% among mucosal melanomas in the head and neck[3,5], slightly more prevalent in men.[3-5] Mucosal melanomas account for a frequency of 1.3-6.8% of total melanomas.[1,6] In contrast to cutaneous melanoma, OMM incidence has been stable over the last years.[3-5] The etiology of OMM remains unknown[3,5]: chronic inflammatory stimuli such as tobacco use and chronic mechanical irritation have been proposed among possible risk factors, though evidence and pathogenetic correlations are still lacking. Intrinsic genetic factors have been recently

described and OMM is now considered to be a distinct variant of melanoma, different from the cutaneous and ocular forms, with its own clinical behaviour.[5]

Most OMMs arise de novo from apparently normal mucosa, but about 30-37%[3,6] are preceded by oral pigmentations that last several months or even years. There are no reports in the literature regarding the malignant potential of oral melanocytic nevi or atypical melanocytic hyperplasias.[6] However, diagnosis is often delayed and prognosis is poor.[3,6] The lack of symptoms of OMM[5] is frequently emphasized and may justify the delay in seeking medical attention from patients.

On a clinical basis, OMM has been described as uniformly brown or black macules/patches or nodules often showing variation of colour, with black, brown, grey, purple, and red shades or depigmentations (fig. 1, table 2).[7] The hard palate or alveolus gingiva are most often affected.[3,5,6] Satellite foci within the oral mucosae surrounding the primary tumor have also been reported.[7] Moreover, similarly to their cutaneous counterpart, amelanotic melanomas presenting no pigmentation (33-50% of cases) have been reported.[3,5] OMM may be ulcerated in up to 1/3 of cases.[5] Some authors highlighted the usefulness of the cutaneous dermoscopic criteria (table 2) to rule out OMM[7], but limited data are available.[1] Despite the fact that dermoscopy may be considered a useful tool to support the diagnosis of OMM permitting an earlier diagnosis, the irregular oral mucosal surface and the complex anatomy represent technical limitations.

Olszewska et al.[1] reported that the typical dermoscopic patterns consist of irregular diffuse pigmentation and pseudo-network, together with regression structures and a blue-whitish veil. Other elements are the presence of different colours (blue, black, grey and brown), asymmetry of structures with irregular borders and sharp interruption of the reticular pattern. Atypical vessels together with irregularly distributed heterogeneous dots and globules may be observed.[1,8]

To date there is no consensus on OMM clinical diagnosis, or algorithms that indicate which is the best surgical approach to suspected lesions.

An early and prompt diagnosis of OMM could be important for the patient's prognosis, as OMMs show a more aggressive behavior and a worse prognosis than cutaneous MM.[3] In fact, almost 1/3 of patients presents lymph node metastases at the moment of the diagnosis of a primary OMM. The early development of metastases might be due to the high level of vascularization and anatomy of lymphatic drainage in this district.[3] Therefore, together with the clinical examination, imaging studies (ultrasound or CT scan) of the head and neck area are mandatory, as well as of the thoraco-abdominal district, for the correct tumoral staging.[3,5]

In contrast with cutaneous melanoma, OMMs display a very low BRAF V600E mutation rate (<6%), reducing the chances of therapeutic options with BRAF inhibitors, and no mutations are found in *NRAS* and *GNAQ/GNA11*.[5] Since the C-Kit mutations frequency seems to be higher (7-25%), therapy with Imatinib

may be considered an option, though recent studies report partial responses and the development of resistance to the treatment.[7] A recent study has shown the presence of BAP1 mutations and its correlation with the poor outcome in this tumor.[9]

Oral pigmentations in the differential diagnosis of OMM

FOCAL OPs DUE TO EXOGENOUS PIGMENT

- *Amalgam tattoo*

Metallic compounds and in particular amalgam, have been extensively used for the treatment of cavities in endodontic procedures. Patients usually come to our attention for the evaluation of blue to grey macules of the gingiva. No symptomatology is usually reported. These lesions are generally 0.1-2 cm in diamete[10], and are mainly located in the gingiva and alveolar mucosa, near the restored tooth. Other compounds such as graphite have been described as the cause of mucosal tattoos, mostly by accidental incisions and incorporation of the latter in the soft tissues.[11] Histology reveals amalgam particles along collagen fibers and around blood vessels.[10] Few lymphocytes and macrophages and sometimes foreign-body giant cells are detected.

Dermoscopy shows a grainy structureless homogenous bluish pattern (table 2).[1]

If an accurate anamnesis reveals a history of previously amalgam treatment[3], sequential clinical observations (every 3-6 months of follow-up) using global

oral photography (GOP) or dermoscopy, where possible for anatomic reasons, could be proposed.[6] Clinicians should pay particular attention to the location of gingival and hard palatal lesions, and a biopsy could be mandatory in case of clinical suspicion or minimal changes on follow-up, since these are the most common sites of oral nevi or/and OMM.[5]

FOCAL OPs DUE TO ENDOGENOUS PIGMENT

- *Melanoacanthoma*

Melanoacanthoma may also affect the oral mucosa after chronic traumas, most frequently in black women. On clinical observation this condition appears as a single, asymptomatic pigmented macule or plaque. A rapid increase in size has been reported and buccal mucosa is the most common site. Incisional biopsy and histological examination are required to rule out OMM.[6,12-14] Histology reveals dendritic melanocytes in an acanthotic epithelium with spongiosis, together with few lymphocytes and eosinophils.[11,14] An established dermoscopic pattern is lacking in the current literature.[2]

Self-healing after biopsy may occur and in long-lasting lesions topical steroids may represent a therapeutic option.[10,11] Sequential clinical observations (every 3-6 months of follow-up) using GOP and dermoscopy, where possible, could be proposed in order to monitor the lesion's evolution or treatment response.

- *Melanotic macules*

Melanotic macules, also known as melanosis, are benign OPs most frequently involving the lower lip and palate of women.[6] They present as single (less frequently multiple) brownish, well demarcated macules, less than 1 cm in diameter (fig.2, table 2). On histopathology these lesions are characterized by a normal number of melanocytes that show an increased melanin production and an increased basal cell pigmentation (fig. 3).[9,10,13] Three main dermoscopic patterns may be observed: reticular-like, parallel (fig.4a) and structureless (fig.4b). In the lower lip a parallel pattern with narrow linear or partly curved lines is most often detected, but a mixed parallel-structureless pattern may occur.[2] More recently, other authors described metaphorically other dermoscopic features of these lesions such as ring-like pattern, fish scale-like pattern and hyphal pattern.[15]

Sequential monitoring with GOP can be proposed in compliant patients if the lesions measure <0.5 cm.[4] Since the main differential diagnosis is OMM, a biopsy is required to rule out OMM in the case of size >0.5 cm and if different colours (such as brown/blue/grey/white) and/or irregular borders (frequently observed in these lesions) are present.

- *Melanocytic nevi*

Melanocytic nevi on the oral mucosa (OMN) are uncommonly observed. The reported incidence is 1:10000 and they generally arise in the second-fourth decades of life.[9,10,13] The most common locations are the hard palate, buccal mucosa and vermilion of the lip.[9,13] Clinically, these lesions appear as well demarcated dark black to brown or blue macules or papules (table 2). Dimensions are reported to range from 0.1 to, rarely, 3.0 cm and nevi measuring 0.5 cm are the most commonly observed.[6] On histopathology, the lesions mainly appear intramucosal (55%) and as blue nevi (36%).[3] Hematoma/hemangiomas and other vascular malformations should be ruled out on clinical inspection. Dermoscopy reveals symmetric homogeneous lesions and sometimes a regular pigmented network. A homogeneous bluish structure is observed in the case of blue nevus (table 2).[2]

Sequential monitoring (short follow-up every 3 months) could be proposed in patients younger than 20 years and for lesions of smaller diameter (< 0.5 mm). A biopsy is required in all other cases, or when lesions present minimal changes in sequential monitoring, in order to obtain the definitive diagnosis and rule out melanoma.[6]

DIFFUSE OPs

- *Physiological/racial pigmentations*

Physiological ethnic pigmentation usually occurs in non Caucasians, involving the gingiva symmetrically and sparing the mucogingival margin, due to increased melanin production (fig. 5). Clinically, diagnosis is easy and biopsy is not required.[3] Diffuse or patchy brownish pigmented areas are observed and no treatment is required (fig. 6, table 2).[16,17] In our series dermoscopy showed a parallel pattern (fig. 7a) and a homogeneous structureless pattern (fig. 7b). A transitory physiological OP may occur during pregnancy and may be associated with a concomitant skin pigmentation, also known as melasma affecting the nipple area and the genital mucosae. [16]

- *Smoker's melanosis*

Smoking-associated melanosis is a black-brown diffuse pigmentation determined by an increased melanin production in the basal layer, probably triggered by tobacco. Its occurrence and extension are both related to the number of cigarettes and the duration of smoking. Anterior gingiva, buccal mucosa but also the tongue and lip mucosa can be affected. No treatment is mandatory.[9,10,14]

Diagnosis is usually performed on a clinical basis and biopsy is not required. However, clinical monitoring is recommended (every 12 months), together with patient's self-inspection.

- *Drug induced hyperpigmenations*

OPs may be induced by a large number of drugs. A full medical history is mandatory when dealing with diffuse pigmentations and physiological causes are ruled out.[18] Drug-induced OPs may present as localized to multiple and diffuse brown-bluish-black areas.[16] Clinical monitoring, also on a regular basis (every 12 months), and patient's self-inspection every 3-4 months is recommended.

- *Post-inflammatory hyperpigmentations*

Post-inflammatory OPs develop after an underlying, usually long lasting inflammatory process.[14] Lichen planus and lichenoid reactions are most commonly involved.[19] Hyperpigmentation may persist after the resolution of the disease. Other possible conditions include chronic periodontal disease, pemphigus and pemphigoid.[10] A biopsy is recommended for single/isolated pigmented lesions, even if the diagnosis of an inflammatory disease is already acknowledged on anamnesis. Bowen disease with its pigmented variant, previously described in other mucosae, should be ruled out. Follow-up is

recommended for these patients, since the role of chronic inflammation in the pathogenesis of OMM is yet to be determined.[3,5]

Other systemic diseases

Systemic diseases associated with OPs may be due to multiple conditions, some life-threatening, including genetic (Peutz-Jeghers syndrome, Laugier-Hunziker disease, Leopard syndrome and Carney Complex syndrome) and endocrine diseases (McCune-Albright syndrome and adrenal gland diseases). The cutaneous and extra-cutaneous symptoms, together with the pathogenetic background, are summarized in Table 1.[20-26] Biopsy is necessary only for single lesions, isolated or occurring on a background of a diffuse pigmentation that evolves/changes over time upon clinical inspection.

OMM should be differentiated from a wide-ranging spectrum of affections, both benign and malignant, determined by endogenous and exogenous disorders that lead to pigmentations of the oral mucosae. The correct diagnosis of OPs is challenging for the physician for two reasons: firstly in order to rule out melanoma and secondly because OPs may represent an isolated finding or a manifestation of more complex systemic diseases.[17] Therefore, the oral cavity should be routinely investigated during dermatological examinations. To date there are no criteria that facilitate the clinical diagnosis in the oral cavity. Dermoscopy could represent a useful tool in the diagnostic differentiation from vascular abnormalities[27,28], although the compression may cause an alteration or

fading of diagnostic elements. The main observations could be red or pink homogeneous areas, with a slightly visible white collarette (not scaly as in the cutaneous dermoscopic observation) in pyogenic granulomas, or the typical red and dark lacunae in hemangiomas. OMM may feature vascular structures, though typically disarranged, but a careful examination of the perimeter of the mass should be made (where possible for anatomic reasons) in order to evaluate the presence of pigmented areas. In focal pigmentations (nevi, melanotic macules, melanoacantoma or amalgam tattoos), a biopsy is the diagnostic gold standard, especially for lesions with a diameter > 0.5 cm. Clinical morphologic changes on sequential monitoring should also require a biopsy. In the presence of diffuse oral pigmentations (in drug-induced manifestations, inflammatory diseases) a GOP is recommended and biopsy should be reserved for lesions that evolve during monitoring or/and present clinical similarities with OMM.[3] OPs due to systemic diseases should be followed up on a clinical basis.

In conclusion, considering the aggressive behavior and poor prognosis of OMM, oral cavity inspection should be regularly performed by clinicians and patients should be well informed and encouraged to carry out self-inspections.

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Figure and table legend:

Fig. 1: Clinical image of an oral melanoma of the soft palate, showing black, dark blue and grey colours in the periphery of the red and pink nodular tumor.

Fig. 2a,b Clinical images of labial melanosis showing a small diameter (2 mm), well-circumscribed brown macular lesion of the lower lip.

Fig. 3. Histopathologic image of an oral melanosis, showing the pigmentation of the basal layer of the epithelial mucosa, characterized by an increased production of melanin by basal melanocytes which are otherwise normal in number and distribution and an increased number of melanophages in the superficial chorion. H&E Original magnification 15 X.

Fig. 4. Dermoscopic images of labial melanosis showing a parallel pattern, with segments of accentuated pigmentation, reflecting the particular distribution of the dermal papillae in an arcuate semimucosa (a) and a homogeneous structureless pattern (b).

Fig. 5. High power image of a focal oral racial pigmentation highlighting the presence of melanophages in the chorion and the pigmentation of the basal layer. H& E Original magnification 25 X.

Fig. 6 (a) clinical image of a racial pigmentation of inferior gingiva in a black woman. (b) clinical image of a racial pigmentation of the lower lip in a black woman.

Fig. 7. Dermoscopic images of labial racial pigmentations showing a parallel pattern (a) and a homogeneous structureless pattern (b).

Table 1. Systemic diseases associated with oral and cutaneous pigmentations

Table 2. Clinical and dermoscopic features of OMM and main OPs.

Table 1. Systemic diseases associated with oral and cutaneous pigmentations

Systemic disease	**Oral and cutanous pigmentations**	**Systemic involvement**	**Genetic/immunologic background**
Peutz-Jeghers syndrome	Multiple brown macules on the lips, the perioral area, other areas (extremities).	Gastrointestinal hamartomatous polyposis; increased oncologic risk in other organs (breast, testicles, pancreas, thyroid)	Autosomal dominant disorder: mutation in the serine/threonine kinase STK11 gene on chromosome 19p13
Laugier-Hunziker Disease	Diffuse macular pigmentations (less than 5 mm in diameter) in the lips, perioral area and oral mucosae. Multiple melanosis in other areas such as genitalia, nail apparatus and conjunctiva may be observed	No malignant potential	Idiophatic acquired disorder
Leopard syndrome	Lentigines localized in the upper trunk, neck, extremities and	Electrocardiographic conduction abnormalities, ocular hypertelorism,	Genetic heterogeneous disorder

	genital region. The perioral area and lips are involved, sparing the oral cavity	pulmonar stenosi, abnormal genitalia, retardation of growth and sensorineural deafness	
Carney complex syndrome	Multiple and diffuse lentigines, endocrine disfunction and myxomatous tumors	Large-cell calcifying Sertoli cell tumor, osteochrondomyxoma, psammomatous melanotic schwannomas, growth hormone-secreting pituitary adenomas and breast ductal adenomas. Death usually occurs for cardiac myxomas.	Autosomal genetic disorder determined by an inactivation in the gene PRKAR1□ on chromosome 17 with an increase in protein kinase A activity
McCune-Albright syndrome	Oral pigmentations are rare. Unilateral and segmental skin pigmentation with an irregular profile (known as "coast of Maine-like"); may be congenital or developing few months after births	Monostotic/polyostotic fibrous dysplasia, endocrinopathies	Mutation in GNAS1 gene
Adrenal glands diseases	Diffuse skin and mucosal hyperpigmentation and bronzing. In the oral cavity blue-black-brown macules may be observed arranged in spots or streaks	Systemic findings (nausea, vomiting, loss of weight, hypotension) Neoplasms or infections (tubercolosis, fungal), hemocromatosis	An autoimmune destruction of adrenal cortex cells producing steroids, determining an increase of adrenocorticotropic hormone (ACTH) and subsequentially in melanocyte-stimulating homone (MSH)

Table 2. Clinical and dermoscopic elements of OMM and main OPs.

Focal pigmentation	Clinical features	Dermoscopic pattern
Oral melanoma	• brown or black macule/patch/nodule often showing variation of colour or depigmentation • 30-35% amelanotic • up to 1/3 of cases ulcerated	• irregular diffuse pigmentation and pseudo-network • regression structures and a blue-whitish veil • different colours (blue, black, grey and brown) • asymmetry of structures with irregular borders and sharp interruption of the reticular pattern • atypical vessels • irregularly distributed heterogeneous dots and globules
Amalgam tattoo	• blue to grey macules (0.1-2 cm in diameter)	• grainy structureless homogenous bluish pattern
Melanotic macules	• single (less frequently multiple) brownish, well demarcated macule (<1 cm in diameter)	• reticular-like • parallel (narrow linear or partly curved lines) • structureless • mixed parallel-structureless
Melanocytic nevi	• well demarcated dark black/brown/blue macule or papule (0.1-3.0 cm in diameter)	• symmetric homogeneous pattern • regular pigmented network • homogeneous bluish pattern (blue nevus)
Racial pigmentation	• Diffuse or patchy brownish pigmented areas	• Parallel pattern • Homogeneous structureless pattern