Pigmented lesions of the oral mucosa and perioral tissues: a flow-chart for the diagnosis and some recommendations for the management

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The term “pigmentation of the oral mucosa” is applied to a wide range of lesions or conditions featuring a change of color of oral tissues. Lesions not associated with an accumulation of pigment (e.g., Fordyce spots) are usually not classified as pigmented lesions. Two groups of pigmented lesions of the oral mucosa are recognized: 1) melanin-associated lesions, including racial pigmentations, melanotic macules, melanocytic nevi, and malignant melanoma; and 2) nonmelanin-associated lesions (e.g., blood-related pigmentations, metallic pigmentations). This paper presents a clinicopathologic review of the recent literature with emphasis on the main diagnostic features, including the use of immunohistochemical markers. A flow-chart is added that may help the clinician in the diagnosis and management of these lesions. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:606-16)

Human oral mucosa is not uniformly colored, and several degrees of chromatic variegation may be observed in physiologic and pathologic conditions.1-5 Oral subsites are characterized by different structural colors, depending on degree of keratinization, numbers and melanogenic activity of melanocytes, vascularization, and type of submucosal tissue (muscle, bone, cartilage). The physiologic color of the oral mucosa thus ranges from white to red-purple in light-skinned people, whereas an evenly black to brown color of gingiva and buccal mucosa and the lips are characteristic of dark-skinned people.1-5

In the present review, 2 groups of pigmented lesions are discussed: melanotic lesions and lesions caused by other pigments. After an overview of oral histology and physiologic of melanocytes, a flow-chart will be presented that may help the clinician in the diagnostic process (Fig. 1).

MELANIN-ASSOCIATED PIGMENTED LESIONS OF THE ORAL CAVITY

Oral mucosal melanocytes: histology and physiology

Melanocytes were first identified in the oral epithelium by Becker in 1927; a few years later they were isolated from samples of gingival tissue by Laidlaw and Cahn.7 During early intrauterine life, precursors of melanocytes, melanoblasts, migrate from the neural crest to the epidermis and the hair follicles, becoming differentiated dendritic cells.8-10 The head and neck region represents the first part of the body where melanocytes appear, after approximately 10 weeks of gestation.10

Melanocytes are located in the basal epithelial layer of squamous mucous membranes and do not contact each other. They are regularly interspersed between the basal keratinocytes. Melanocytic dendrites reach a number of keratinocytes in the close vicinity, and through these dendrites melanin is transported and transmitted to these epithelial cells.4,11-13 An age-related increase of oral melanocytes has been observed.14

The normal melanocytes of the oral mucosa have a
small round nucleus and a small amount of a clear cytoplasm, with slender dendrites extending between adjacent keratinocytes. Melanocytes are devoid of desmosomes or attachment plates. Melanin-containing electron-dense vesicles, so-called melanosomes, are formed within the cytoplasm and transported along the dendrites. The use of 3,4-dihydroxyphenylalanine, a substrate for tyrosinase, represents the most specific histochemical method for labeling melanocytes. Other methods include argentaffinic melanin-labeling techniques such as the Masson-Fontana staining. Inactive oral mucosal melanocytes, lacking melanin and melanin precursors, may not stain with this method.

Immunohistochemically, the S100 antigen is by far the most common marker used. The S100 staining appears to be stronger in melanocytes lacking pigment. Another commonly used marker is HMB-45, a monoclonal antibody directed against a melanosomal glycoprotein. It is not expressed by melanocytes that lack all melanogenic activity.

The main biochemical function of the mature melanocyte is a process called melanogenesis, through which the cell produces and delivers melanin pigment. Eumelanin (brown-black melanin) causes a brown-black color of the skin, hair, and eye, and pheomelanin has a reddish color. Neuromelanin, found in some nerve cells, is an unrelated substance.

Various stimuli, such as trauma, hormonal changes, medication, and radiation, may result in an increased production of melanin. Melanin functions include absorption of ultraviolet light and scavenging of some cytotoxic compounds.

Racial pigmentation (physiologic pigmentation)

No agreement exists in the literature on the definition of “race,” “racial group,” “ethnic group,” or “ethnicity.” Furthermore, it has been demonstrated that the strength of the relationship between skin color and ancestry is quite variable. As a matter of fact, the melanin content of the skin does not seem to be strictly related to ancestry,
genetically defined by the so-called “ancestry-informative markers.” On the basis of a multivariate evaluation, 3 categories of humans have been defined: whites, blacks, and intermediates. Factors considered include skin color in the medial part of the arm, color and texture of the hair, and shape of nose and lips.

Oral “racial” pigmentations (ORPs) are usually observed in dark-skinned populations. In a study of 1,300 children, ORPs were identified in 13.5%. Pigmentations are usually diffuse and bilateral, although a variety of patterns have been observed. Color ranges from light dark to brown. Gingiva, with the exclusion of the marginal border, and buccal mucosa are the most commonly involved sites (Fig. 2). Other sites include lips, palate, and tongue. Racial pigmentations are innocuous, and treatment is only for aesthetic reasons.

Melanotic macules of the oral cavity are relatively common lesions, caused by an increased production and deposition of melanin within the basal cell layer, the lamina propria, or both.

In the largest series from 1 source, Buchner et al. reported that melanotic macules of the lips and oral cavity represented 86.1% (665 cases) in a group of 773 cases of solitary melanocytic lesions, which represented 0.7% of a group of nearly 90,000 biopsies from oral cavity and perioral tissues. Of these, 207 were located on the lips and 458 involved various subsites of the oral mucosa. The vermilion border and the gingiva were the most commonly affected subsites (60%). In another review, Kaur gars et al. reported a prevalence of 0.4% among 86,202 biopsies from the oral cavity. Labial lesions almost exclusively affect the lower lip, whereas gingival melanotic macules are more frequently localized in the anterior part of the maxilla. Black patients are more likely to have involvement of the buccal mucosa. The female-to-male ratio is almost 2:1, and the highest incidence is reported during the fifth decade.

Controversy exists on the pathogenetic mechanism that leads to the development of melanotic macules, and it is not clear if they represent a physiologic or a reactive process. Some authors reported a positive family history, and a genetic predisposition has been hypothesized.

Melanotic macules are usually single well circumscribed blue or brown-to-black lesions homogeneously colored and less than 1 cm in diameter. Intraoral lesions tend to be larger than those located on the lips. Unlike ephelides, melanotic macules do not darken after exposure to sun radiation. Dermatoscopy may show a structureless pattern, characterized by a diffuse brown-black pigmentation, seldom irregularly distributed, without pigment network or globules and/or streaks. The diagnosis is usually made on clinical grounds alone.

From the histopathologic point of view, there is absence of rete ridge elongation and lack of prominent melanocytic activity. Pigmentation is usually most marked at the tips of the rete ridges, and melanophages can also be observed in the upper part of lamina propria. There is lack of atypia of melanocytes, and HMB-45 immunoreactivity is typically lacking. When melanin pigment is observed in the epithelium of a clinically nonpigmented lesion, the term “focal melanosis” has been used by some.

Lentigines and ephelides

The term lentigo (plural lentigines) indicates a well-defined hyperpigmented lesion of the skin with an increased number of melanocytes arranged as solitary units along the epithelial-mesenchymal junction without formation of nests. Lentigines are subdivided into simple lentigines and solar lentigines, the latter being associated with epithelial hyperplasia, which generally

Fig. 2. Racial pigmentation. Gingival involvement.

Fig. 3. Physiologic pigmentation on the tips of the fungiform papillae.
takes the form of rete ridge elongation. Melanocytic hyperplasia is minimal in solar lentigines.

Lentigo simplex is a lesion histologically characterized by more obvious melanocytic hyperplasia together with increased melanin formation. No clear data on epidemiology are available in White populations, whereas lentigo simplex has been reported to be the most frequent pigmented lesion in acral sites of darkly pigmented populations. Pathogenesis is most likely related to developmental or intrinsic defects in melanocytes homeostasis. Clinical features of lentigo simplex include light to dark brown pigmentation, usually sharply circumscribed. Lesions can be single or multiple, the latter situation being associated with a number of rare syndromes.

Different from lentigo simplex, solar lentigines (synonyms sun-induced freckles, lentigo senilis) are ultraviolet light–induced pigmented lesions. Epidemiology shows an increased incidence among the general population over 60 years of age.

Ephelides (freckles) are small (less than 1 cm) red or light to dark brown macules localized on sun-exposed areas of the body. They typically affect light-skinned individuals, are multiple, and are uniform in color and regular in outline, although confluence leads to irregularly shaped larger patches. Ephelides may appear at any age but most frequently occur in childhood. They wax and wane with the degree of solar exposure, being most conspicuous in the summer months.

No data exist on the prevalence of intraoral lentigines and ephelides; they mainly affect the vermilion border of the lips or the perioral tissues.

Melanocytic nevi

Oral melanocytic nevi (OMNs) are benign tumors of melanocytes. Approximately 500 cases have been reported in the English-language literature; no systematically assembled data on their frequency are available. A recent report from the Netherlands revealed an annual incidence of excised OMNs of 4.35 cases per 10 million population per year.

The etiology and pathogenesis of OMNs are poorly understood even though, as for their cutaneous counterpart, oncogenic mutations of genes coding for components of the RAS signaling pathways may play a role.

Regarding morphogenesis, the melanocytic proliferation can be divided into 3 phases: 1) proliferation of benign neoplastic melanocytes along the epithelial-mesenchymal junction (junctional nevus); 2) migration of these cells into the mesenchymal compartment (compound nevus); and 3) loss of the junctional component of the nevus, so that all remaining nevomelanocytes are located within the subepithelial compartment (subepithelial nevus) (Fig. 4). These steps correspond to the histologic variants of OMNs. Less common nevus subtypes include blue nevus (Figs. 5 and 6), combined nevus, and Spitz nevus.

In the histopathologic evaluation, the additional use of immunohistochemical stains may be required, such as the melanocytic markers Melan A, HMB45, and microphthalmia transcription factor. In melanin pigment–laden cells, additional markers, e.g. CD68, a marker for macrophages, may be helpful in identifying the nature of such cells. Such a procedure may be particularly helpful in arriving at a correct diagnosis of a blue nevus.

Congenital melanocytic nevi are present at birth, and those developing after birth are referred to as acquired nevi. Probably, most melanocytic nevi of the oral mucosa are acquired, even though some cases of congenital nevi have been reported. Sizes range from 0.1 to, rarely, 3.0 cm. The OMNs typically are well circumscribed round or oval macules or papules, but polypoid larger lesions have been reported as well. The OMNs have been reported to occur in a multiple fashion. Elevated acquired nevi are usually lightly pigmented, whereas flatter lesions tend to be more darkly pigmented. Colors vary: brown to blue, bluish gray, or black; generally an individual lesion has a similar color throughout. Rare nonpigmented nevi are on record. The hard palate, buccal mucosa, and gingiva are most commonly affected.

Despite a strong epidemiologic correlation between OMNs and OMMs with regard to age, gender predisposition, and oral subsites, there is no proof that nevi of the oral mucosa are markers of the development of malignant melanoma.
Melanoacanthoma

The term melanoacanthoma has been used to describe a rare benign mixed lesion of keratinocytes and pigment-laden dendritic melanocytes. Oral melanoacanthoma is thought to have a reactive nature and usually regresses spontaneously or after incomplete removal, such as incisional biopsy. Approximately 40 cases of oral melanoacanthoma have been reported. Differently from its cutaneous counterpart, oral lesions occur almost exclusively in Blacks, affect a much younger population, develop rapidly, and generally have a flat surface. The buccal mucosa is the most frequently affected subsite.

Tobacco-associated melanin pigmentation (smoker’s melanosis)

Smoking has been found to cause diffuse oral melanin pigmentation in European and Asian populations. Some authors have noticed a significant increase in gingival melanosis of children with parents who smoke. Smoker’s melanosis seems to be directly related to a stimulant effect of substances in smoke on melanocytes. In parallel to a model accepted for the skin, some authors hypothesized that melanin may play a role in detoxification of polycyclic amines nicotine and benzopyrene.

Subsites involved are mainly gingiva, hard palate, buccal and commissural mucosa, inferior surface of the tongue, and lip mucosa (Fig. 7). Smoker’s melanosis is usually black-brown.

From a histologic point of view, increased melanin is found in the basal layer of the epithelium and there may be melanophages in the subjacent connective tissue. No melanin is detected in the upper part of the epithelium. Smoker’s melanosis does not require treatment, and disappearance has been reported after cessation of the smoking habit.

Malignant melanoma

Oral malignant melanoma (OMM) is an aggressive tumor of melanocytes, accounting for 0.5% of all oral malignancies. The neoplasm is more common in Japan and Africa than in Western countries. The etiology of OMM is unknown. Tobacco use and chronic mechanical irritation resulting from ill-fitting dentures have been mentioned as possible risk factors. Most OMMs arise de novo from apparently normal mucosa, but about 30% are preceded by oral pigmentations for several months or even years.

The initial symptom and sign of OMM is the emergence of a mass lesion which is usually pigmented. The OMM may be uniformly brown or black or may show variation of color, with black, brown, gray, purple, and...
red shades, or depigmentations. Satellite foci occasionally surround the primary tumor. In amelanotic melanomas, pigmentation is absent \(^{55,56}\) (Fig. 8). The most frequently affected oral sites are the palate and the maxillary gingiva.\(^ {12,62}\)

The OMMs probably originate from junctional melanocytes; in their first phase of development, the cells are restricted to the epithelial compartment: in situ melanoma. Subsequently, melanoma cells invade the underlying tissues.\(^ {62}\) Melanoma cells show a wide range of shapes, including spindle, plasmacytoid, and epithelioid ones. Clear cell change is occasionally seen.\(^ {46,62,63}\)

The OMM is not subdivided into the classical cutaneous melanoma categories, which include superficial spreading melanoma, nodular melanoma (NM), and acral lentiginous melanoma (ALM). There is, however, often some similarity between ALM and NM.\(^ {12,59,62,64}\) The histologic microstaging system of Clark, used in cutaneous melanoma, can not be applied to oral mucosa, because of the lack of histologic landmarks analogous to papillary and reticular dermis.\(^ {12,62}\) Tumor thickness does not appear to be associated with prognosis.\(^ {63}\) The TNM clinical staging system for OMM recognizes three stages: stage I, primary tumor present only (T any N0 M0); stage II, tumor metastatic to regional lymph nodes (T any N1 M0); Stage III, tumor metastatic to distant sites (T any N any M1).\(^ {56}\)

In different series, the actuarial 5-year overall survival rate for head and neck mucosal melanoma ranges from 21% to 40%, and for OMM it is 15%, with a median survival of 25 months.\(^ {12,58}\) Gingival melanoma has a better 5-year survival rate than palatal, with a longer median survival period (46 months vs. 22 months, respectively).\(^ {12}\) Recurrent melanoma may manifest itself up to 10-15 years after primary therapy.\(^ {55}\) Distant metastases often affect the lungs, brain, liver, or bones.\(^ {66}\)

**SYSTEMIC DISORDERS ASSOCIATED WITH THE PRESENCE OF ORAL PIGMENTED MELANOCYTIC LESIONS**

**Peutz-Jeghers and other familial hamartoma syndromes**

The Peutz-Jeghers syndrome consists of mucocutaneous macules, intestinal hamartomatous polyposis, and increased risk of carcinomas of the gastrointestinal tract, pancreas, breast, and thyroid.\(^ {67,68}\) The disease is associated with germline mutations in the LKB1/STK11 gene located on the short arm of chromosome 19.\(^ {68,69}\)

Black-to-brown spots of less than 1 mm in size are typically localized on the lower lip and in the perioral area (Fig. 9). Intraoral, intranasal, conjunctival, and rectal pigmented lesions as well as spots localized on the acral surfaces may also be present.\(^ {1-3,68}\)

The oral lesions are benign and histologically characterized by an increase in melanin in the basal layer, without an obviously increased number of melanocytes.\(^ {1,2}\) A fading or a disappearance of the spots is usually observed in older age.\(^ {70}\) Interestingly, perioral lesions tend to persist.\(^ {1}\)

So-called “PTEN hamartoma tumor syndromes” (PHTS), characterized by mutations in the tumor suppressor gene PTEN (phosphatase and tensin homologue deleted on chromosome 10) include several rare diseases such as the Ruvalcaba-Myhre-Smith and Cowden syndromes.\(^ {68}\) Perioral lentigines have occasionally been reported in these.\(^ {2}\)

**Addison disease and other endocrine disorders**

Primary hypoadrenalism caused by autoimmune disease, infection, or malignancy, also referred to as Addison disease, is characterized by deficient production
of hormones of the adrenal cortex, leading to increased production of adrenocorticotropic hormone (ACTH). This may result in a diffuse dark pigmentation of the skin and the oral mucosa. Other signs and symptoms of Addison’s disease include anorexia, nausea, and postural hypotension.

Lips, gingival, buccal mucosa, hard palate, and tongue are usually involved (Fig. 10). Pigmented lesions may be diffuse or localized and usually precede skin manifestations.

Diffuse or discrete pigmentation of the lips and oral mucosa are sometimes observed in monostotic and polyostotic fibrous dysplasia (McCune-Albright syndrome), hyperthyroidism, and Nelson syndrome. Treatment of pigmented lesions of the oral mucosa associated with a systemic disorder is usually not required unless discomfort is present. The disappearance of oral lesions may follow the treatment of the underlying condition.

Other conditions

Oral melanocytic pigmentations have been reported in patients with Laugier-Hunziker syndrome (idiopathic lenticular mucocutaneous pigmentations) and with Carney complex (spotty skin pigmentations, myxomas, and endocrine overactivity). Human immunodeficiency virus infection has been associated with multiple usually well circumscribed melanotic macules localized on the buccal and palatal mucosa, gingiva, and lips. However, the association may be only coincidental. The histopathologic appearance is similar to classical melanotic macules. It remains unclear whether such pigmentations are caused by the virus, therapy, or other factors.

Chronic inflammatory conditions, such as oral lichen planus, pemphigus, pemphigoid, and chronic periodontal disease, are sometimes associated with deposition of melanin within the connective tissue, resulting in a darkening of the mucosal area. This phenomenon is mostly observed in dark-skinned individuals. Fixed drug reaction after administration with cotrimazole, tetracycline, colchicine, and ketoconazole also has been associated with postinflammatory hyperpigmentation. It is debatable if these reactions only depend on melanin.

The presence of lesions resembling melanotic macules of the palate in patients with lung diseases, including cancer, also has been reported, but there is lack of evidence of a true association. Melanin production and stimulation may also sometimes follow surgical procedures.

NONMELANIN-ASSOCIATED PIGMENTED LESIONS OF THE ORAL CAVITY

Lesions caused by endogenous pigments (blood-related pigmentations)

Extravasations of blood in hematomas, petechiae, purpurae, and ecchymoses may cause pigmentation as a result of accumulation and degradation of hemoglobin to bilirubin and biliverdin. Color of the lesions depend on length of time from trauma and may range from red to black. Typical traumatic events in the oral cavity possibly associated with blood extravasations and hyperpigmentation include biting, trauma with eating, and iatrogenic procedures.

Patients with hemochromatosis (“bronze diabetes”) frequently display bluish-gray pigmentation of the hard palate, gingiva, and buccal mucosa (Fig. 11). The pigmentation is caused by deposition of iron-containing pigments (ferritin and hemosiderin) within the skin and mucous membranes. Similarly, a diffuse black-brown pigmentation, most commonly in the junction between
the hard and soft palate, may be observed in patients with beta-thalassemia.1

Lesions caused by exogenous pigments (metallic pigmentation)

Amalgam pigmentation (amalgam tattoo). Accidental displacement of metal particles in oral soft tissues during restorative dental procedures using amalgam may result in amalgam pigmentation, the so-called “amalgam tattoo.”1-5 Terms such as focal argyrosis or oral localized argyria should be avoided, because not only silver, but also mercury and tin, are contained in the amalgam alloy.

Despite the high prevalence of these lesions among the general population, little information is available in the dental literature. Buchner and Hansen identified 268 (1.3%) amalgam tattoos among 20,731 specimens from the oral cavity.82

The cause of amalgam tattoos can be iatrogenic or traumatic. Metal particles may over time leach into the soft oral tissues, resulting in the discoloration. Buchner and Hansen82 and Owens et al.83 listed several iatrogenic and traumatic modalities through which amalgam may be introduced in the oral tissues: condensation of the material in abraded mucosa during routine amalgam restorative work, introduction of the material within the lacerated mucosa during removal of amalgam fillings or crowns and bridges, introduction of broken pieces into a socket or the periosteum during extraction of teeth, and introduction of metal particles in a surgical wound during root canal treatment with a retrograde amalgam filling.82,83

Amalgam tattoos usually range from 0.1 up to (rarely) 2 cm in size and can be solitary or multiple. Colors reported are blue, gray, or black with a spectrum of variegation depending on the depth of metal within tissues. Gingiva and alveolar mucosa are the subsites most frequently involved. In alveolar edentulous ridges, amalgam tattoos can also be associated with restored antagonistic teeth (Fig. 12). The diagnosis is based on clinical findings and the relationship with present or removed amalgam restorations.

Radiographic features may show localized radiopacities.1 Biopsy is indicated only when suspicion of OMM can not be ruled out on clinical grounds alone. Histopathologic investigation reveals amalgam particles dispersed in the connective tissue and sometimes in the walls of vessels. These particles may also line the basement membrane of the surface epithelium. Brownish granules within phagocytic cells and fibroblasts cytoplasm can also be observed.82,84 A spreading of these pigmented lesions mediated by local migration of phagocytic cells containing metal has also been described.1-3,82-84

Histopathologic examination of an amalgam tattoo is usually diagnostic because of the size and shape of the metal particles and the way they are spread in the tissue. However, in rare cases, one may need additional stains. The common melanin and iron stains are often not sufficient for differentiating between metal particles and melanin pigment. Instead, immunohistochemical markers such as HMB-45 and Melan A are more suitable for this purpose. When dealing with metal pigmentation, one may be able to identify the type of metal(s) by using electron-probe microanalysis.

There is no indication for complete removal of an amalgam tattoo.

Accidental or voluntary introduction of other foreign particles include graphite from pencil tips, tattoo inks, and chronic contact with charcoal toothpaste and vegetables such as Juglans regia, Cola nitida, and Catha edulis.1,2,86

Heavy metals. Systemically absorbed metals may induce discoloration of the oral mucosa, caused by peripheral metal accumulation. These conditions were frequent in the past as result of occupational exposures to certain drugs. Arsenic, lead, bismuth, mercury, silver, and gold are the metals most frequently involved.1-5

Bismuth was typically used for the treatment of syphilis, and its administration was associated with diffuse oral pigmentation and formation of a blue-black line at the marginal gingiva.1 A characteristic feature of plumbism (lead poisoning) is the so-called “burtonian line,” a gray linear area of discoloration below the gingival margin1,3,4 (Fig. 13). Silver (argyria) and gold (chryiasis) may produce slate-gray oral pigmentation and purple gingival discoloration, respectively.2

Heavy metal intoxication can be associated with a wide range of systemic signs and symptoms.1,3
DRUGS ASSOCIATED WITH PIGMENTED LESIONS OF THE ORAL CAVITY (EXCLUDING HEAVY METAL CONTAINING DRUGS)

Many nonheavy metal-containing drugs can induce discoloration of oral tissues. Direct deposition on oral surfaces, local accumulation after systemic absorption, stimulation of melanin-related pathways, and bacterial metabolism, alone or in combination, may result in oral pigmentations. The most commonly reported drugs are listed in Table I.

DISCUSSION AND PROPOSAL OF A FLOW-CHART

Diagnosis of pigmented lesions of the oral cavity and perioral tissues is challenging. Even though epidemiology may be of some help in orientating the clinician and even though some lesions may confidently be diagnosed on clinical grounds alone, such a diagnosis remains “provisional.” Definitive diagnosis usually requires histopathologic evaluation. Occasionally, immunohistochemical stains such as melanocyte marker HMB-45 and macrophage marker CD68 may be required to arrive at a correct diagnosis.

With the exception of OMM, all pigmented primary lesions in the oral cavity are benign, and treatment usually is required only when discomfort is present. No reliable criteria exist for the clinical differentiation between OMM and a number of other pigmented lesions, such as melanotic macules, oral melanocytic nevi, and amalgam tattoos.

The so-called ABCD checklist (asymmetry, border irregularities, color variegation, and diameter >6 mm) that is commonly used to aid in the identification of cutaneous melanoma may be of some help in the clinical diagnosis of oral melanoma. Rapidly growing pigmented lesions should always be biopsied.

Location on the palate increases the rate of suspicion of melanoma and usually requires a biopsy or long-term follow-up. When located on the gingiva, the main differential diagnosis is between amalgam tattoo and melanoma. In case of the slightest doubt a biopsy should be taken.

In Fig. 1 a flow-chart is depicted that may help the clinician in the diagnostic pathway of pigmented lesions of the oral cavity. When history allows classifying a lesion as melanocytic, a subclassification should be made according to the clinical suspicion of malignancy (ABCD checklist, recent history, age, and subsite involved). Lesions presenting no or low suspicion of malignancy may be confidently diagnosed on clinical grounds alone (e.g., oral manifestations of systemic diseases, physiologic pigmentations, or smoker’s melanosis) or may require histopathologic evaluation.

Some nonmelanocytic lesions, such as ethnic tattoos or pigmentations associated with heavy metal poisoning, are easily recognized on clinical grounds (e.g., burtonian line). In other cases, such as bluish discolorations not clearly related to amalgam restorations and/or not showing radiologic signs for the presence of metal particles, histopathologic evaluation is needed to reach a firm diagnosis.

A biopsy or referral to a specialist for further evaluation is indicated if the history does not allow distinguishing between melanocytic and nonmelanocytic lesion.

REFERENCES


Table I. Drugs potentially associated with oral pigmentations.

<table>
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<tr>
<th>Drug</th>
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<tr>
<td>Nicotine</td>
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<td>Phenothiazines</td>
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<td>Heroin</td>
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<td>Busulfan</td>
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<td>Doxorubicin</td>
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<td>Chlorhexidine</td>
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Fig. 13. Oral manifestation of lead poisoning ("burtonian line").


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