Oral soft tissue lesions: A guide to differential diagnosis
Part I: Introduction and changes in color

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Abstract

Oral soft tissues are affected by a multitude of pathologic conditions of variable etiology and significance, appropriate management of which relies on their accurate diagnosis. Considerable overlapping of signs and symptoms produced by diverse conditions poses significant problems for their diagnosis, which can be resolved only through a thorough knowledge of the clinicopathologic characteristics of each condition and a systematic approach to diagnosis. An essential component of the diagnostic process is the formulation of a differential diagnosis, which encompasses the possible diseases and conditions that could account for a specific constellation of oral signs and symptoms. To facilitate the challenging task of differential diagnosis, this review provides comprehensive lists of the various pathologic conditions that pertain to specific oral soft tissue changes. The latter are classified into three major categories: 1) changes in color, 2) surface alterations, and 3) masses or swellings. The first part of this review offers some general considerations for the differential diagnosis of oral mucosal and submucosal lesions and presents the range of pathologic conditions that result in color alterations of oral soft tissues. Lesions producing color changes of oral tissues are classified into 1) white, 2) red, 3) white and red, 4) yellow, and 5) pigmented, and are further subdivided on the basis of their etiology, pathogenesis, or tissue of origin. The fundamental characteristics of each disease category are discussed and correlated with the optimal diagnostic approaches and tests that will secure a definitive diagnosis.

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Introduction

The oral cavity is affected by a plethora of pathologic conditions that generally manifest as either soft or hard tissue lesions. The latter may or may not produce clinically detectable alterations and formulation of a differential diagnosis is mainly based on the corresponding radiographic changes. On the other hand, soft tissue lesions generally produce clinical alterations that are usually easily detectable by means of visual examination and palpation.

Accurate diagnosis of the various oral soft tissue lesions is a prerequisite for their successful management and treatment. However, the overlapping clinical and histopathologic features of the diverse diseases and conditions afflicting the oral soft tissues make accurate diagnosis a difficult and challenging task for general dentists and specialists alike. Thorough knowledge of the range of clinical and histopathologic manifestations of oral diseases is undoubtedly necessary for their diagnosis. At the same time, equally important is a systematic approach to diagnosis, the first step of which is the formulation of a comprehensive clinical differential diagnosis.

The clinical differential diagnosis of a lesion encompasses the list of the pathologic conditions that could account for the observed signs and symptoms. Although the list of possibilities for any specific sign or symptom can be quite long, assessment of a particular combination of signs and symptoms along with information obtained by a complete history should allow for the formulation of a relative narrow list of potential diagnoses. Nonetheless, only the knowledge of all possible conditions that may generate a particular change in the tissues will prevent omission of a possible pathologic entity from the differential diagnosis. Hence, classification of the various oral diseases into categories according to their corresponding specific tissue alterations represents an extremely useful tool for clinicians that can considerably facilitate the formulation of a complete and accurate differential diagnosis.

Oral soft tissue lesions result from histologic changes that affect either the mucosa or the underlying submucosa and can be separated into 3 large groups: 1) changes in color, 2) surface alterations, and 3) masses or swellings. Although a single pathologic condition may manifest a number of changes, altering the normal color, surface, and/or volume characteristics of the affected soft tissues simultaneously or successively, it usually produces only one or few specific types of mucosal or submucosal lesions.

In this review, the various diseases and conditions that account for oral mucosal and submucosal soft tissue lesions are summarized. The scope of this work is not to provide an all-inclusive analysis of these diseases (which would require one or more textbooks), but rather to classify them into categories according to their clinical presentations. Comprehensive tables are presented, which will aid clinicians to quickly review all diseases that may generate a particular type of clinical appearance and select those that are most likely responsible for a given lesion for further investigation. Moreover, conditions that result in a particular clinical alteration are classified on the basis of their etiology, pathogenesis, or tissue of origin, to facilitate their memorization and to provide an understanding of their cause and mechanism of development, which will help determine the diagnostic tests used and the therapy employed. Basic information is also provided on the correlation between specific disease types, and the appropriate diagnostic approaches and tests that will secure a definitive diagnosis.

Changes in color

A number of local and systemic conditions are responsible for alterations in the normal color of oral mucous membranes. Although various discolorations and variations in hue are seen clinically, the basic color changes can be classified into 5 main categories: 1) white lesions, 2) red lesions, 3) white and red lesions, 4) yellow lesions, and 5) pigmented lesions. Although the term “pigmented” could literally apply to various color changes including white, red, and yellow lesions, in the context of oral pathology it is conventionally used to describe color alterations that are predominantly either a) blue/purple, or b) brown/gray/black Pigmented lesions can be further divided according to their distribution into focal and diffuse. Finally, petechial and ecchymotic lesions may present as red or pigmented (blue/purple) lesions and are described separately.

B1 - White, red, and white/red lesions

There are numerous pathologic conditions that account for white, red or combined white/red lesions in the oral cavity, which are presented in Tables 1, 2, and 3, classified according to their etiology and/or pathogenesis. In general, the white color of a lesion is due to 1) a thickening of the epithelium (which may be the result of hyperkeratosis, acanthosis, or edema of the epithelial cells), 2) a whitish pseudomembane composed of surface debris or fungal colonies covering the epithelium, or 3) decreased vascularity or various deposits affecting the underlying connective tissue. It should be noted that ulcers or erosions, described in the section of surface alterations, may also appear as white lesions when covered by a fibrinous pseudomembrane. On the other hand, the red color of a lesion is usually indicative of 1) an inflammatory lesion of variable etiology (e.g. reactive, allergic, or infectious) accompanied by hyperemia, 2) an atrophy of the epithelium allowing easier visualization of the vascular component of the underlying connective tissue, or 3) a lesion

featuring proliferation of blood vessels. Ulcerative, erosive or vesiculobullous lesions may also manifest an erythematous component in their periphery; however, these lesions will be presented separately. Finally, certain diseases and conditions may simultaneously affect the epithelium and the connective tissue in more than one ways, presenting as a combination of white and red lesions.

Table 1 – White lesions

- **Physical and Chemical Injuries**
  - Linea Alba
  - Morsicatio
  - Frictional Keratosis
  - Sloughing traumatic lesions
  - Thermal burn
  - Chemical Burn
  - Nicotine stomatitis
- **Allergies**
  - Reaction to systemic drugs
    - lichenoid and lupus-like eruptions
  - Contact stomatitis
    - reaction to toothpaste, mouthwash, cinnamon, amalgam
- **Infections**
  - Candidiasis
    - Pseudomembranous
    - Hyperplastic
  - Syphilis
    - Secondary (mucous patches)
    - Tertiary (syphilitic glossitis)
  - Hairy leukoplakia
  - Diptheria
  - Koplik spots of Measles
  - Scarlet fever
- **Immunologically-mediated diseases**
  - Lichen planus
  - Lupus erythematosus
- **Premalignant Lesions**
  - Idiopathic leukoplakia
  - Actinic cheilitis
  - Tobacco pouch keratosis
  - Submucous fibrosis
- **Genokeratoses**
  - Leukoedema
  - White sponge nevus
  - Hereditary benign intraepithelial dyskeratosis
  - Pachyonychia congenita
  - Dyskeratosis congenita
  - Follicular keratosis (Darier's disease)
  - Incontinentia pigmenti
- **Systemic Diseases**
  - Uremic Stomatitis
- **Miscellaneous**
  - White coated tongue
  - White hairy tongue
  - Skin graft
  - Fordyce's granules
  - Palatal and gingival cysts of the newborn
  - Erythema migrans
  - Verruciform xanthoma

Table 2 – Red lesions

- **Physical and Chemical Injuries**
  - Irritational mucositis
  - Thermal burn
  - Chemical Burn
  - Radiation mucositis
  - Chemotherapy mucositis
  - Xerostomic mucositis
  - Nicotine stomatitis
- **Allergies**
  - Reaction to systemic drugs
    - Anaphylactic stomatits and intraoral fixed drug eruptions
  - Contact stomatitis
    - Plasma cell gingivitis
- **Infections**
  - Gingivitis - Periodontitis
  - Candididiasis
    - Erythematous
    - Denture sore mouth
    - Angular cheilitis
    - Median rhomboid glossitis
  - Pharyngitis
  - Lymphonodular pharyngitis
  - Scarlet fever
- **Immunologically-mediated diseases**
  - Lichen planus
  - Lupus erythematosus
  - Vesiculobullous/erosive diseases
- **Premalignant Lesions**
  - Erythroplakia
  - Actinic cheilitis
- **Vascular Lesions**
  - Petechial and ecchymotic lesions[1]
  - Hematoma
  - Hemangioma
  - Sturge-Weber angiomatosis
  - Telangiectatic lesions
    - Hereditary hemorrhagic telangiectasia
    - CREST syndrome
  - Pyogenic granuloma
  - Kaposi's sarcoma
- **Systemic Diseases**
  - Anemia
    - Iron deficiency anemia
    - Pernicious anemia
  - Vitamin B Deficiency
  - Psoriasis
- **Miscellaneous**
  - Erythema migrans
  - Verruciform xanthoma

(Footnotes)
[1] See Table 6

Table 3 – White and Red lesions

- **Physical and Chemical Injuries**
  - Thermal burn
  - Chemical Burn
  - Nicotine stomatitis
- **Allergies**
  - Reaction to systemic drugs
  - Contact stomatitis
- **Infections**
  - Candidiasis
  - Scarlet fever
- **Immunologically-mediated diseases**
  - Lichen planus
  - Lupus erythematosus
- **Premalignant Lesions**
  - Erythroleukoplakia
  - Actinic cheilitis
- **Miscellaneous**
  - Erythema migrans
  - Verruciform xanthoma

Reactive lesions, including physical and chemical injuries, and allergic reactions, frequently manifest as white lesions, red lesions, or a combination thereof. White hyperkeratotic reactions to chronic trauma or friction, equivalent to callus formation on the skin, are very common in the mouth. Inflammation of the oral mucosa (mucositis) is commonly seen as a result of a non-specific irritation or due to specific insults (e.g. radiation or chemotherapy), presenting as focal or more often diffuse erythema. Burns of thermal or chemical etiology may affect the mucosa provoking white, red or white/red lesions. Similarly, heat generated by smoking (especially pipe or cigar) causes a characteristic non-premalignant, white/red lesion of the palate, called nicotine stomatitis. Finally, a number of systemic drugs or local factors (including toothpaste, mouthwash, cinnamon-containing products, etc.) may elicit an allergic response of the mucosa that assumes a white, red or white/red appearance. Essential to the diagnosis of all these lesions is the identification of a causative agent, e.g. an ill fitting denture, a check biting habit, a history of previous radiation treatment or chemotherapy, a systemic drug known to induce lichenoid eruptions, or a cinnamon-containing product. Therefore, a complete history that will reveal a temporal and spatial relationship between the potential cause and the lesion is of paramount importance. Confirmation of the diagnosis requires discontinuation of the suspected causative agent, which should result in disappearance of the lesion, thus establishing a cause-and-effect relationship. If the lesion (or part of it) fails to involute despite elimination of the traumatic or allergic agent, biopsy to rule out other pathology is mandated.

White patches or plaques of the oral mucosa that cannot be wiped off and cannot be characterized clinically as any other specific disease entity are labeled as idiopathic leukoplakia. The exact etiology of these lesions is debatable and the list of possible contributing factors is still evolving; however, there is no doubt that tobacco is the main factor associated with their development. It is also proven that leukoplakias are premalignant lesions; although the risk for malignant changes varies according to the anatomic location, clinical presentation and geographic distribution, an overall malignant transformation rate of 4-5% has been reported. Leukoplakic lesions have a variegated clinical appearance, including thin, homogeneous (or thick), granular (or nodular), verrucous (or verruciform), and speckled types. Even more impressive is the histopathologic spectrum of these lesions, which ranges from benign hyperkeratosis and acanthosis, to varying degrees of dysplasia (mild, moderate, or severe), to carcinoma-in-situ, and finally invasive squamous cell carcinoma. Given the premalignant nature and uncertainty of the histopathologic nature, biopsy of leukoplakias (which should include the most suspicious areas for dysplasia or malignancy) is mandatory.

Other premalignant lesions that cause a white appearance of the oral mucosa include tobacco pouch keratosis and submucous fibrosis related to chronic use of smokeless tobacco or betel quid, respectively. Actinic cheilitis refers to a sun-induced premalignant lesion of the lower lip, the clinical appearance of which varies from leukoplakic to erythematous to ulcerated. Idiopathic leukoplakias of the oral mucosa may also have a red component in which case they are called erythroleukoplakias. Presence of a red component is generally linked to a higher propensity of histopathologic dysplastic or carcinomatous changes. Accordingly, pure red oral premalignant lesions, called erythroplakias, are almost always histopathologically diagnosed as severe dysplasia, carcinoma in situ, or invasive cancer.

White, red, or white/red lesions may also represent manifestations of infectious diseases. The most common disease of this category is the fungal infection candidiasis, which appears as a predominantly white (pseudomembranous or hyperplastic) or red (erythematous) lesion. Development of candidiasis is usually related to an underlying predisposing factor that causes either immunosuppression (e.g. HIV infection, systemic debilitating diseases, use of topical corticosteroids) or an upset of the oral microflora (e.g. use of wide-spectrum antibiotics). Local factors, such as continuous denture wearing (denture stomatitis) or reduced vertical dimension (angular cheilitis) may also contribute to the pathogenesis of candidiasis. The white pseudomembrane of pseudomembranous candidiasis can be characteristically wiped off, allowing its discrimination

from leukoplakias and other not wipeable lesions. However, other white lesions can be also rubbed off (e.g. white coated tongue or sloughing traumatic lesions), while a non-wipeable, leukoplakic or hyperplastic variant of candidiasis, a possibly premalignant lesion, also exists. Erythematous candidiasis appears similar to other diffuse red lesions, such as mucositis, erythroplakia, or glossitis due to anemia or vitamin deficiency. Therefore, definitive diagnosis requires demonstration of candidal hyphae on PAS-stained cytologic smears or tissue sections, or growth of such organisms on culture. Moreover, the possible underlying cause should be identified and corrected.

White lesions may also result from other infections, including syphilis and childhood infections; the latter may additionally cause red or white/red lesions. A contributing history of sexually transmitted diseases or recent contact with infected individuals, along with evidence of the systemic manifestations of these illnesses should point to the correct diagnosis. Likewise, infectious diseases may be responsible for the appearance of red gingival or mucosal lesions, the most common being gingivitis and periodontitis. Identification of local factors (dental plaque and calculus) and response to conservative treatment will confirm the diagnosis, eliminating the need for biopsy, which should be reserved for atypical or recalcitrant cases. Finally, hairy leukoplakia, an Epstein-Barr virus-related white lesion affecting mainly the lateral border of the tongue of immunocompromised patients, is a marker of HIV infection and progression to AIDS. Definitive diagnosis of hairy leukoplakia requires biopsy and demonstration of EBV within the lesion.

Lichen planus represents an immunologically-mediated condition that affects the skin, the oral mucosa, or both. Various clinical presentations are possible, commonly including white lesions in a reticular pattern and a bilateral distribution, or atrophic red areas, which may affect the gingival (desquamative gingivitis) or other mucosal areas. A white plaque-like presentation is less common, while quite frequent are lesions featuring a combination of white and/or erythematous lesions; the latter pattern may be also accompanied by erosions in the erosive and bullous forms of the disease. A classic clinical presentation may be sufficient for diagnosis; however cases with equivocal clinical features should be subjected to biopsy. Given the purported relationship between lichen planus (especially its erosive form) and squamous cell carcinoma, biopsy will also serve to rule out the possibility of dysplasia or cancer in suspicious lesions. Lupus erythematosus, on the other hand, is an autoimmune disorder, which is classified into two major types: a discoid form that mainly affects the skin and a systemic form that also affects the kidneys and other organs. Both these types can have oral manifestations that are very similar to those of lichen planus. Identification of dermatologic and systemic manifestations of the disease, histopathologic and direct immunofluorescence analysis of biopsied lesional tissue, and detection of specific autoantibodies in serum (the latter being positive only in systemic lupus), will allow discrimination of lupus lesions from other similarly appearing oral white lesions.

Various vascular lesions of traumatic, neoplastic or other etiology frequently present as red lesions of the oral mucosa. Among these lesions, petechiae and ecchymoses will be covered separately, while pyogenic granulomas will be described along with other common oral swellings. Hemangiomas are common childhood neoplasms, which produce a red tumefaction, especially when they are superficially located. Sturge-Weber angiomatosis, a rare developmental condition exhibiting hamartomatous vascular proliferation of the tissues of the brain and face, may also affect intraoral sites; diffuse involvement of the facial skin by a vascular malformation that follows the distribution of the trigeminal nerve (port wine stain or nevus flammeus) and convulsion and other neurologic manifestations due to meningeal angiomatosis are highly characteristic of this syndrome. Digital pressure on hemangiomas or vascular malformations produces blanching, thus facilitating their distinction from similarly looking lesions. If biopsy is necessary, caution should be exercised to avoid excessive hemorrhage. Blanching on pressure is also noted with the telangiectatic lesions of hereditary hemorrhagic telangiectasia, which additionally involves the skin and other mucosal sites. Telangiectatic vessels may also be seen as a component of CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), which in addition to a characteristic constellation of manifestations also features a relatively specific laboratory test (anticentromere antibodies). Hematomas, on the other hand, represent extravasation of blood due to trauma; these lesions do not blanch on pressure and are expected to change color and disappear in a matter of weeks, as a result of blood degradation. Kaposi's sarcoma, the most common malignant tumor of HIV-positive patients, may also appear as a red lesion; multiplicity with frequent concurrent involvement of skin and mucosal sites, predilection for hard palate and gingiva, occurence of complications such as pain, necrosis and bleeding, and, most importantly, immunocompromised status, are all features that suggest a diagnosis of Kaposi's sarcoma; nonetheless, definitive diagnosis awaits the results of the biopsy, while, in the absence of a history of immunosuppresion, assessment of HIV status is in order.

A few systemic diseases may generate white or red oral

lesions. Uremic stomatitis as a complication of renal failure is a rare cause of white lesions. An odor of ammonia or urine on the patient's breath along with clinical signs of renal failure is characteristic. On the other hand, diffuse erythema of the oral mucosa, especially involving the tongue (glossitis) and the lips (cheilitis) can be caused by systemic conditions, such as anemias, including iron deficiency anemia and pernicious anemia, and deficiency of vitamins of the B complex. In these instances, laboratory blood tests are of paramount diagnostic importance and replacement therapy should be curative. Finally, oral red lesions rarely accompany the characteristic skin lesions of psoriasis.

Another group of diseases that can cause white oral mucosal lesions are hereditary in origin and are collectively known as genokeratoses. Common features include a diffuse distribution of the lesions often in a bilateral pattern, a positive family history, and a concurrent occurrence of compatible skin lesions, as many of these disorders affect cutaneous sites as well. Leukoedema, although not a hereditary condition, is also included in this group; it is mainly seen in blacks and, characteristically, its white color diminishes or disappears upon stretching of the mucosa. The remaining of the genokeratoses have sufficiently specific clinical and especially histopathologic features so that combination of clinical examination and biopsy should afford a definitive diagnosis.

Lastly, miscellaneous other conditions, which cannot be conveniently classified into any of the aforementioned categories, occasionally cause oral white or red lesions. Coated tongue and hairy tongue can both appear as diffuse white lesions on the dorsal surface of tongue; the former can be easily rubbed off and should be distinguished from pseudomembranous candidiasis, while the latter has an easily recognizable clinical appearance caused by elongation of the filiform papillae. Erythema migrans is a benign condition of unknown etiology which usually involves the tongue (geographic tongue). The characteristic clinical presentation, featuring irregular zones of erythema surrounded by a slightly elevated serpentine or scalloped border, and its tendency to migrate over time are relatively pathognomonic. Skin graft may also be responsible for a white appearance of the oral mucosa; questioning for previous surgery and grafting in the area will lead to the correct diagnosis. Finally, Fordyce's granules, gingival cysts, and verruciform xanthoma produce a whitish/yellowish appearance of the mucosa and are described in the following section dealing with yellow-appearing lesions.

B2. Yellow lesions

The relatively small list of conditions that may present as yellow oral lesions is presented in Table 4, classified according to the corresponding tissue of origin. Some of these lesions are not pathologic, but rather represent accessory or ectopic normal tissues, such as accessory lymphoid aggregates or ectopic sebaceous glands (Fordyce's granules), and are readily recognized as such. Lymphoepithelial cysts and lipomas present as small, yellowish submucosal nodules or masses; a common finding of both these lesions is the identification of superficial blood vessels. Superficial abscess of dental or periodontal etiology may also have a yellow hue; the presence of a non-vital tooth or a deep periodontal pocket will suggest the diagnosis. Pyostomatitis vegetans is an unusual oral manifestation of inflammatory bowel disease, characterized by multiple, linear pustules of the oral mucosa in a "snail track" configuration. Gingival cysts may affect newborns as well as adults. In newborns, gingival cysts present as numerous nodules on the alveolar ridge which rupture spontaneously, while in adults, they appear as solitary gingival lesions, excisional biopsy of which is curative. Verruciform xanthoma is a rare oral hyperplastic condition with a papillary surface, which is occasionally yellow; however, white or red presentations are also possible. Finally, jaundice, a clinical manifestation of hyperlibirubinemia, may be severe enough to generate a diffuse, yellow appearance of the oral mucosa, always in combination with the characteristic yellow discoloration of the sclera.

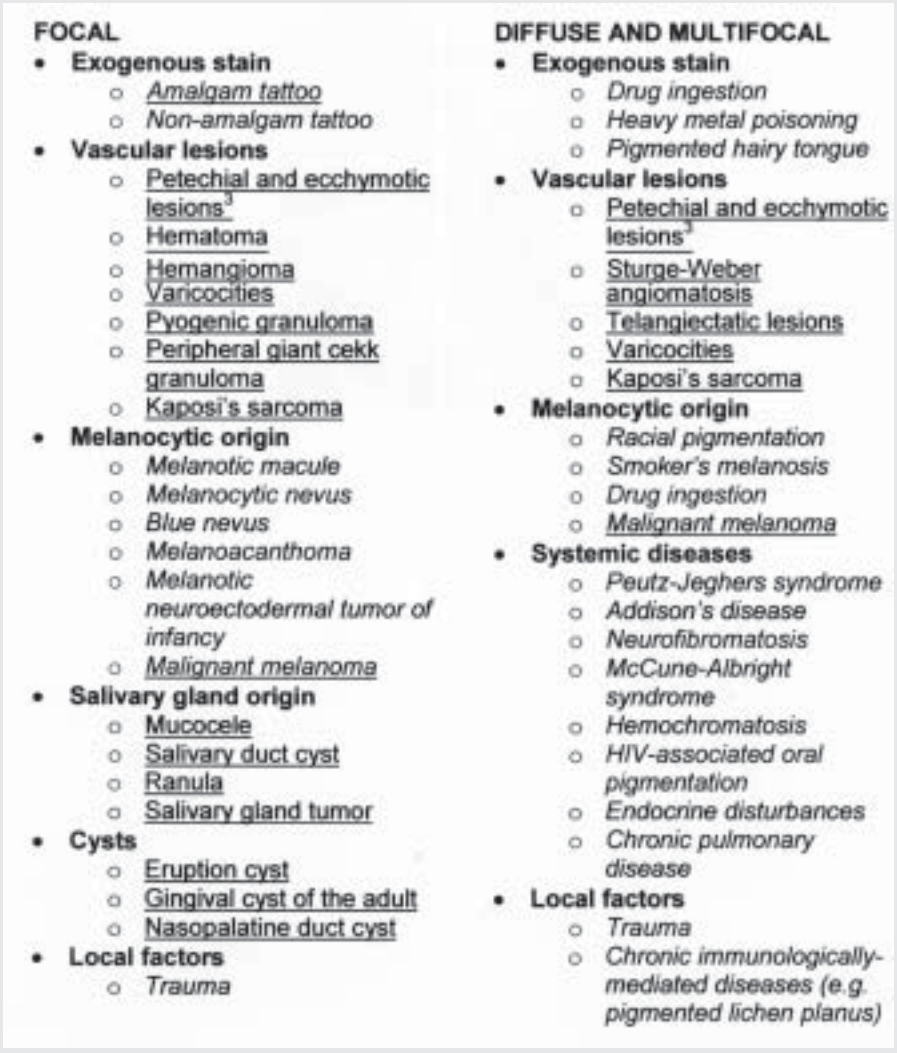
Table 4 – Yellow lesions

- **Sebaceous glands**
  - Fordyce granules
- **Lymphoid tissue**
  - Accessory lymphoid aggregate
  - Lymphoepithelial cyst
- **Fat**
  - Lipoma
- **Pus**
  - Superficial abscess
  - Pyostomatitis vegetans
- **Bilirubin**
  - Jaundice
- **Xanthoma cells**
  - Verruciform xanthoma
- **Cystic fluid**
  - Gingival cyst

B3. Pigmented lesions

The various conditions that cause focal or diffuse pigmentation of the oral mucosa are presented in Table 5, classified on the basis of their etiology or origin. Although these lesions may assume a multitude of various colors, they can be generally distinguished into those that are predominantly blue/purple and those that are mainly brown/gray/black. In most instances, blue/purple discoloration of oral mucosa is produced by blood-containing vascular

Table 5[1] – Pigmented lesions: blue/purple or *brown/gray/black lesions*



FOCAL

- **Exogenous stain**
  - *Amalgam tattoo*
  - *Non-amalgam tattoo*
- **Vascular lesions**
  - Petechial and ecchymotic lesions[3]
  - Hematoma
  - Hemangioma
  - Varicocities
  - Pyogenic granuloma
  - Peripheral giant cekk granuloma
  - Kaposi's sarcoma
- **Melanocytic origin**
  - *Melanotic macule*
  - *Melanocytic nevus*
  - *Blue nevus*
  - *Melanoacanthoma*
  - *Melanotic neuroectodermal tumor of infancy*
  - *Malignant melanoma*
- **Salivary gland origin**
  - Mucocele
  - Salivary duct cyst
  - Ranula
  - Salivary gland tumor
- **Cysts**
  - Eruption cyst
  - Gingival cyst of the adult
  - Nasopalatine duct cyst
- **Local factors**
  - *Trauma*

DIFFUSE AND MULTIFOCAL

- **Exogenous stain**
  - *Drug ingestion*
  - *Heavy metal poisoning*
  - *Pigmented hairy tongue*
- **Vascular lesions**
  - Petechial and ecchymotic lesions[3]
  - Sturge-Weber angiomatosis
  - Telangiectatic lesions
  - Varicocities
  - Kaposi's sarcoma
- **Melanocytic origin**
  - *Racial pigmentation*
  - *Smoker's melanosis*
  - *Drug ingestion*
  - *Malignant melanoma*
- **Systemic diseases**
  - *Peutz-Jeghers syndrome*
  - *Addison's disease*
  - *Neurofibromatosis*
  - *McCune-Albright syndrome*
  - *Hemochromatosis*
  - *HIV-associated oral pigmentation*
  - *Endocrine disturbances*
  - *Chronic pulmonary disease*
- **Local factors**
  - *Trauma*
  - *Chronic immunologically-mediated diseases (e.g. pigmented lichen planus)*

lesions, mucus-containing salivary gland lesions, or fluid-containing cysts. In contrast, a brown/gray/black discoloration usually ensues from accumulation of either exogenous stain or melanin.

Amalgam tattoo represents on of the most common focal pigmentations of the oral cavity. Unless visible on x-rays, these lesions should be biopsied to rule out other focal pigmented lesions of pathologic significance. Rare non-amalgam, e.g. graphite, tattoos of the oral mucosa have been also described. Additionally, exogenous stains may account for diffuse pigmentations of oral mucosa, as is the case with heavy metal ingestion, which often produces a linear pigmented pattern along the free gingival margin. A history of exposure to heavy metals due to occupation or for medical reasons will confirm the clinical impression. Drug ingestion may also induce diffuse pigmentation of the oral mucosa due to stimulation of melanin production or because of deposition of drug metabolites. Knowledge of the list of medications that are associated with oral discoloration and the specific pattern caused by each one is essential for diagnosis, which, in most cases, should be verified with biopsy. Exogenous stain from tobacco and food is also responsible for the usual pigmented appearance of hairy tongue.

The vascular lesions that were described previously as being associated with a red appearance of the oral mucosa may also be responsible for bluish/purple discoloration. Interestingly, varicocities, common lesions of the ventral tongue and lower lip of older adults, almost always have a

bluish or purple color; similar to hemangiomas, varicocities blanch with compression, unless thrombosis has occurred. Peripheral giant cell granuloma is most likely to be bluish and cause a superficial bone erosion compared to pyogenic granuloma; moreover, the latter may occur anywhere in the oral mucosa as opposed to the exclusively gingival location of a peripheral giant cell granuloma.

Certain lesions of salivary gland origin also generate a focal bluish discoloration of the oral mucosa. Mucocele is a very common lesion which results from extravasation of mucin in the connective tissue; when the spillage occurs close to the epithelium, it imparts a bluish translucent hue to the swelling. A history of trauma can be often elicited, however definitive diagnosis and treatment lies on conservative surgical excision and histopathologic examination. When a mucocele occurs in the floor of the mouth, it is called ranula; ranulas may enlarge significantly and should be differentiated from other swellings of the floor of the mouth (discussed later). Salivary duct cysts are similar to mucoceles, differing only in that the mucin is not spilled but is retained within a dilated duct. Finally, salivary gland tumors (e.g. mucoepidermoid carcinomas) can occasionally produce a bluish swelling, especially when they have a mucin-rich content and are located in a superficial location. In these cases, prompt biopsy is warranted.

Gingival cyst of the adult, also described as a potential cause of a yellow lesion, may occasionally appear as a focal, bluish gingival swelling. Eruption cysts also frequently present as blue or purplish swelling on the alveolar ridge, overlying the crown of an erupting tooth; in these cases, the color is usually due to trauma-induced hemorrhage in the cystic cavity. Nasopalatine duct cyst, a common developmental cyst in the area of the incisive canal, may feature a blue/purple color; biopsy and surgical enucleation are recommended.

Focal or diffuse pigmented lesions of the oral mucosa, especially those with a predominantly black, gray or brown color, should always evoke a differential diagnosis of melanin-producing diseases or conditions, which range from completely innocuous (physiological pigmentation) to fatal (melanoma). Physiologic or racial pigmentation occurs in individuals with dark-complexion, more often affecting the gingiva. Although other conditions may cause a similar appearance, the persistent nature of the condition in blacks or dark-skinned whites is usually diagnostic. Cigarette or pipe smoking, or drug-ingestion may stimulate melanin deposition in a diffuse distribution. Correlation of the smoking or medical history with the clinical presentation will point to the etiologic factor; further confirmation is derived from the gradual fading of the areas of hyperpigmentation upon discontinuation of smoking or the responsible medication. Nonetheless, atypical presentations and clinical changes should herald the need for biopsy. Focal benign melanin pigmentations also occur, including melanotic macules, nevi, and melanoacanthomas; biopsy and histopathologic examination will differentiate these lesions from one another and from other pigmented conditions, including melanoma. The latter is a highly aggressive malignant neoplasm, which arises as a focal hyperpigmented area with asymmetry, irregular borders and different mixtures of color to rapidly evolve into a diffuse lesion with frequent ulceration or tumefaction. Palate and maxillary gingiva represent the most frequent oral sites affected by melanoma, definitive diagnosis of which necessitates histopathologic confirmation.

Chronic trauma or irritation is an uncommon cause of melanin pigmentation of the oral mucosa. It is well established that certain autoimmune conditions produce chronic inflammatory lesions of the oral mucosa that may eventually develop a pigmented component, as is the case for pigmented lichen planus. Similarly, chronic irritation of oral mucosa, such as chronic cheek biting, can result in hyperpigmentation. Identification of the nature of these lesions will depend on the recognition of their usual clinical features, which have been already described.

Finally, numerous systemic diseases and syndromes are accompanied by diffuse or multifocal oral pigmentations. For example, both neurofibromatosis and McCune-Albright syndrome feature characteristic café-au-lait macules which may involve not only the skin but also the oral mucosa. Peutz-Jeghers syndrome shows multifocal macular pigmentations that predominantly affect perioral locations, sometimes extending into the mucosa. Addison's disease may produce progressive diffuse or multifocal pigmentation of the oral mucosa, along with bronzing of the skin and hyperpigmentation over pressure points; a history of recent onset and progressive worsening is typical. Hemochromatosis may also induce oral and skin pigmentations mainly due to iron deposition; the oral lesions diffusely affect the palate or the gingiva and may look identical to other diffuse pigmented lesions described here. In all these instances, it is the knowledge of the various systemic signs and symptoms of these diseases which will allow their discrimination, based on information obtained from history, physical examination, and specific laboratory tests. Biopsy may also be useful, especially to rule out melanoma, while referral to the appropriate specialist for management of these conditions is indicated.

B4. Petechial and ecchymotic lesions

As mentioned previously, petechiae and ecchymoses vary in their clinical appearance from red to blue to purple, depending on the degree of degradation of the extravasated blood and the depth of the lesion. Distinction between petechiae and ecchymoses is based on size, the former being minute in size and the latter measuring over 2cm. Both focal and diffuse presentations are possible, as related to the various causes of these lesions (Table 6). In general,

Table 6 – Petechial and ecchymotic lesions

- **Physical injuries**
  - Non-specific trauma (e.g. tooth bite, denture trauma)
  - Trauma from fellatio
  - Increased intrathoracic pressure (e.g. coughing, vomiting)
- **Infections**
  - Infectious mononucleosis
  - Upper respiratory infections
- **Bleeding disorders**
  - Increased fragility of the vessels
    - Scurvy
    - Infectious and hypersensitivity vasculatides
    - Ehlers-Danlos syndrome
  - Disorders of platelets
    - Decreased or ineffective production
      - Aplastic anemia
      - Bone marrow suppression by drugs, radiation, or infections
      - Bone marrow infiltration (leukemia, disseminated cancer)
      - Osteopetrosis
      - Megaloblastic anemia
    - Increased destruction
      - Idiopathic thrombocytopenic purpura
      - Drug-induced thrombocytopenia
      - Infections (e.g. infectious mononucleosis, HIV infection, CMV infection)
      - Thrombotic microangiopathies
      - Disseminated intravascular coagulation
      - Kasabach-Merritt syndrome
    - Increased sequestration
      - Splenomegaly
    - Dilution due to transfusions
    - Dysfunction
      - Aspirin ingestion
      - Uremia
      - Von Willebrand disease
  - Coagulation disorders
    - Hemophilia A
    - Hemophilia B
    - Von Willebrand disease
    - Vitamin K deficiency
    - Disseminated intravascular coagulation

petechiae and ecchymoses do not blanch on pressure, due to the extravascular localization of the accumulated blood.

Various traumatic insults sever blood vessels causing blood extravasation. Among those, orogenital contact (fellatio) is a common cause of palatal petechiae. Increased intrathoracic pressure as that provoked by coughing or vomiting, may also produce palatal hemorrhage. In all these instances, history of a recent injury of the affected area will point to the correct diagnosis. However, if the observed lesions are associated with minimal trauma or no trauma at all, a bleeding disorder should be suspected.

Palatal petechiae are common manifestations of infectious mononucleosis, which mainly affects teenagers and young adults. Accompanying signs of fever, lymphadenopathy, pharyngitis, and tonsillitis, and symptoms of fatigue and malaise are suggestive of the diagnosis, which is confirmed through laboratory procedures. Other upper respiratory tract infections may also produce palatal petechiae, possibly as a consequence of sucking an itching palate.

Bleeding diathesis is the result of a long list of conditions that cause increased fragility of blood vessels, platelet or clotting deficiencies. Hemorrhagic lesions may involve any mucosal or skin surface. Other systemic symptoms and signs are also quite common, varying in character and severity depending on the exact cause of the hemorrhagic diathesis. Oral petechiae or ecchymoses may be accompanied by other oral manifestations of the underlying disease, such as gingivitis and spontaneous gingival bleeding, ulcers, and prolonged bleeding after surgical procedures. Clinical and laboratory tests for evaluation of the various factors involved in hemostasis are of paramount importance for the diagnosis. Because of the multitude and complexity of the possible etiologies, referral to an internist or hematologist is necessary.

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