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Pigmented lesions of the oral cavity

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Healthy oral mucous membranes are normally various shades of red. When either the patient or the clinician notices areas of pigmentation, there is often an element of increased concern. The population today is better educated regarding the malignant potential of pigmented skin lesions, and this awareness may lead many to see a dermatologist for evaluation of skin pigmentations. Likewise, patients may notice an area of increased pigment in the oral cavity and seek evaluation from a dentist. The range of diagnoses extends from variations of physiologic pigmentation to benign and malignant neoplasms. A patient's anxiety may be heightened because almost everyone knows someone who has been diagnosed with cancer.

Clinicians should evaluate and diagnose all alterations in pigment. For example, dentists see amalgam tattoos in a relatively high percentage of patients who have had amalgam restorations. They rarely inform their patients of this occurrence or document the clinical examination findings. Recently, with the ease of digital photography, documenting even subtle changes of the oral mucosa into an electronic dental record is advisable.

The management of pigmented tissue varies based on diagnosis, from the extremes of patient reassurance to radical surgical excision.

This article delineates the factors that help the clinician differentially diagnose pigmented lesions of the oral cavity. The parameters of care regarding the spectrum of pigmentations are also reviewed.

Diagnostic approach in the evaluation of oral pigmentation

It is important that clinicians approach the diagnosis and management of oral pigmentations in a logical and systematic manner. This approach will ensure consistency and the highest quality of care.

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The diagnosis of any lesion should start with a complete and accurate history. The history should report when and how the patient first became aware of the lesion and how it has changed since first noticed. Any symptoms such as pain or an altered sensation that are associated with the lesion should be noted. The dentist must also determine if there are any other lesions elsewhere on the skin, including both the exposed and the nonexposed skin. The patient should also be queried regarding past treatment for these lesions.

A review of systems to discover symptoms of an underlying endocrine, neurologic, cardiovascular, hematologic, or gastrointestinal disorder should be thoughtfully performed. Previous medical and surgical history of other lesions that may have been atypical or malignant may provide additional critical information. Finally, a family history also is important to consider possible hereditary systemic disease that might manifest as pigmented oral lesions.

The clinical evaluation of a lesion should include observation of the lesion by first drying the area with gauze, applying digital palpation to the area to assess texture changes and to determine whether the lesion is fixed to the tissue or movable, and then applying pressure to blanch the area and observe for changes in vascularity. Other observations regarding the lesion should include a pain assessment and or noting a color alteration when the tissue is stretched. One must also make note if the pigmented area is in a site of repeated irritation or trauma or is associated with an amalgam restoration. These factors are necessary to develop a working clinical diagnosis, which will be the basis for treatment. Because the clinician is often uncertain of the definitive diagnosis based solely on clinical appearance, a biopsy is usually indicated. For example, an oral melanoma can clinically appear completely innocuous. A biopsy would provide a definitive diagnosis. Additionally, if any lesion changes without resolution, a biopsy is absolutely indicated. The use of digital records and the ease of digital photography help with documentation. If a pigmented lesion, such as a presumed amalgam tattoo, is clinically diagnosed and monitored, follow-up appointments for the patient are mandatory. One cannot assume that a patient's failure to return indicates that there has been no change in the lesion. Many oral cancer patients are aware of changes for months before they seek help, postponing necessary treatment and worsening the prognosis.

Pigmented oral lesions of benign melanocytic origin

Physiologic pigmentation, melanoplakia, melanosis

All people except albinos have some degree of physiologic melanin pigmentation distributed throughout the epidermis. Melanin is thought to be produced and secreted by the dendritic melanocytes in the basal layer of the epidermis. The melanin is picked up by the adjacent basal cells of the

epithelium. Melanoplakia is a benign variation of this melanin pigment and is not associated with aggressive change.

With melanoplakia, the pigmentation varies in its clinical presentation from light brown to blue-black depending on the amount of melanin present and its depth in the tissue. The deeper and heavier the deposits, the darker the lesions appear.

Light-skinned individuals typically have a relatively even coloration throughout the oral cavity. Darker-skinned individuals often have areas of pigmentation in various configurations and sizes that can be located on any surface of the oral mucosa (Fig. 1) [1]. It is common for inflammatory lesions to heal with hyperpigmentation, especially in the perioral region.

Hyperpigmentation of oral mucosa also may be seen during pregnancy or in women taking oral contraceptives. This light-brown pigmentation of the gingival and buccal mucosa is temporary. It is related to the increased levels of estrogen and progesterone, which stimulate melanocytes [2].

Smokers also have melanosis. One theory is that this presentation is related to nicotine's effect on melanocytes. Smoking cessation usually results in gradual disappearance of the melanosis.

Often the history and the clinical presentation indicate that these areas of melanin pigmentation require no treatment. Appropriate follow-up is recommended, as is patient education in self-examination and self-monitoring for noted changes in the pigmentation.

Ephelis

Ephelides are sun-induced freckles, which are most common in fair-skinned individuals, especially those with red or auburn hair. They are more common in children and are less frequent with increasing age.

They are usually uniform, multiple, light tan in color, and less than 3 mm with regularly defined borders. They are transient and related to sun exposure. They often appear on the vermilion border of the lips, with greater

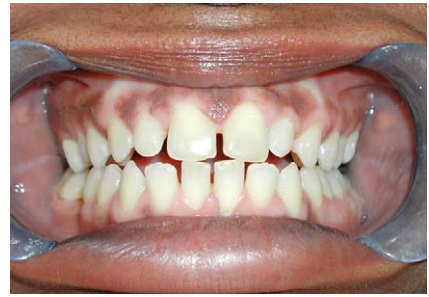

Fig. 1. Melanosis.

frequency on the lower lip. Because ephelides require sun exposure, they do not occur intraorally [3].

Histologically there is increased pigmentation of the basal cell layer without an increase in the number of melanocytes or elongation of the rete pegs. The epidermis is normal.

These lesions are of no concern in children. In adults, however, there is an associated two- to threefold increased incidence of melanoma of the skin [2].

Lentigo

Lentigos are more common in adults and persist indefinitely. They are common on the face and in the perioral region. They are related to chronic sun damage, although they do not change in color in response to sun exposure. They are tan to dark brown in color and range in size from 2 mm to 2 cm. Histologically, there is elongation of the rete pegs and hyperplasia of basal melanocytes. The increased melanin deposition is associated with an increased number of melanocytes [3]. Lentigos are more irregular in color and outline than ephelides. Changes in lentigos should raise suspicion of malignant change (lentigo maligna) and is an absolute indication for biopsy and histologic examination (Fig. 2). Typically lentigos that gradually enlarge and expand slowly and laterally for many years should raise suspicion for lentigo maligna and be considered melanoma in situ until proven otherwise by biopsy.

Melanotic macule

Melanotic macules are discrete, macular areas of hyperpigmentation often occurring on the lips. They are present in up to 3% of the population. They are dark brown to tan in color and can be up to 1 cm in diameter. They appear similar to ephelides but are not associated with sun exposure. In a study of 105 patients with melanotic macules, they were located most commonly on the vermillion border of the lips (30.5%): 94% on the lower

Fig. 2. Lentigo.

lip, 28% on the gingival mucosa, and 16.2% on the buccal mucosa (Fig. 3) [3]. They are usually seen in patients 35 to 42 years of age and are more common in females. There is a positive family history in 14% of cases.

Histologically, there is increased basal pigmentation at the tips of the rete pegs. There is also extravasated pigment and pigment-laden macrophages in the upper portions of the connective tissue without atypia [4]. They usually have a negative immunohistochemical staining with HMB-45 antibody (a melanocyte-specific antibody) and electron microscopy showing normal number and morphology of melanocytes [5].

Melanotic pigmentation is also seen in some HIV-infected patients. This pigmentation can appear before the diagnosis of HIV is determined. Ficarra et al [6] studied 217 patients seropositive for HIV for over a 2-year period; 6.4% developed oral pigmentation. The majority of these lesions appeared on the buccal mucosa. The slight increase in melanotic macules/melanosis in the HIV group could be related to zidovudine or other medications used to treat the disease. Immunohistochemical studies with HMB-45 and proliferating cell nuclear antigen, an auxiliary protein of DNA polymerase-delta that plays a critical role in the initiation of cell proliferation, suggest that there is a stimulation of melanocytes [7]. The pigmentation may also be caused by adrenal dysfunction causing an increase in corticotrophin hormone (ACTH), which increases melanocyte-stimulating hormone (MSH).

Once the diagnosis is established by biopsy, no additional treatment is necessary, but often the patient may, for cosmetic reasons, request that they be removed.

Pigmented lesions of benign, non-neoplastic hematologic or vascular origin

Varicosity

A varicosity is a distended vein, which is common in the oral cavity. They are commonly seen in the floor of the mouth and the ventral tongue. They can

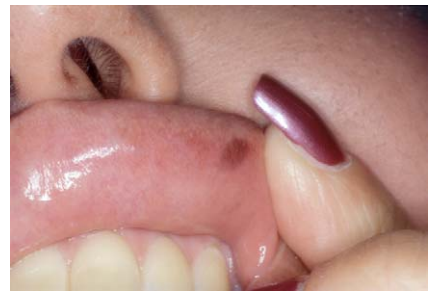

Fig. 3. Melanotic macule.

appear blue and bulbous, especially when several veins are involved. They can be large and resemble a mucocele, ranula, hemangioma, or aneurysm.

The clinical examination should include pressure to attempt to empty or blanch the lesion. Often the location of the proximal vessel can be determined by observing the fill pattern after blanching pressure. No treatment is required once the diagnosis is clinically determined. A clinician should be able to differentiate this entity from a caliber-persistent artery, which, as its name indicates, is a retained artery in the submucosal area of the lower lip. A caliber-persistent artery represents an extension of the inferior alveolar artery into the mucosal area.

Petechia, purpura, ecchymosis, hematoma, and telangiectasia

Petechiae, purpuras, and ecchymoses are submucosal hemorrhages. They all have the same mechanism of presentation and differ only in size. Petechiae are small, pinpoint hemorrhages, purpuras are 2 mm to 2 cm in diameter, and ecchymoses are areas larger than 2 cm in diameter. These lesions result from a slow hemorrhage where there is insufficient blood flow to create swelling. They are initially red and change to a blue-brown color within hours. They do not blanch with pressure. A hemorrhage that has sufficient blood flow to produce swelling is clinically observable as a hematoma.

A telangiectasia is a small, red, macular lesion that is composed of dilated capillaries under the epithelium. A telangiectasia will blanch with pressure and is seen in patients with Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia) and the syndrome of calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias (CREST syndrome) associated with progressive systemic sclerosis.

Petechial and ecchymotic patches often result from trauma and can be seen commonly at the junction of the hard and soft palate. They may be a sign of vomiting, coughing, or fellatio. Obtaining a patient history will help establish the diagnosis. Petechiae, purpura, and ecchymosis may also be a sign of infection such as mononucleosis or a sign of a bleeding disorder, such as idiopathic thrombocytopenia purpura or hemophilia.

If problems with hemostasis are suspected, evaluation for platelet deficiencies or platelet dysfunction, coagulation disorders, hematologic disorders, and liver disease such as advanced cirrhosis or liver failure should be considered. Laboratory tests, including a complete blood cell count including a platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio, should be ordered. Occasionally a bleeding time may also be helpful (Fig. 4).

Many patients take medications that can affect hemostasis. These medications include aspirin, clopidogrel (Plavix), warfarin (Coumadin), enoxaparin (Lovenox), and heparin, which are taken to prevent cerebral vascular accidents (stroke) and deep vein thrombosis. Warfarin is routinely

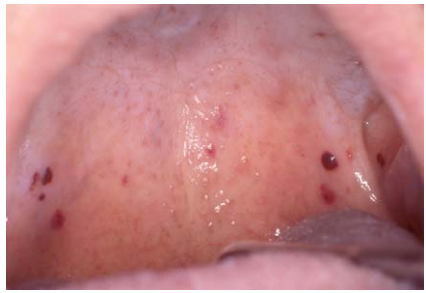

Fig. 4. Petechia from aplastic anemia, thrombocytopenia.

taken by patients with a prosthetic heart valve and by patients with atrial fibrillation. Other patients may be taking a daily tablet of aspirin, 81 mg, to prevent atherosclerotic cardiovascular disease. The result of patients' taking these medications ranges in the signs and symptoms of bleeding from petechiae to hemorrhage. Some patients may be poorly controlled or take a combination of medications that contribute to bleeding or hematologic problems. The dentist may be the first health care practitioner to observe changes suggesting an underlying bleeding disorder. Observable signs of a bleeding disorder warrant immediate medical consultation before invasive dental treatment. Medical risk/benefit determination and physician consultation should guide the dentist in the treatment of patient with bleeding disorders.

Pigmented lesions of salivary gland origin

Mucocele

Mucoceles are common oral lesions that result from the extravasation of saliva from the duct of a minor salivary gland. They are usually located on the mucosal surface of the lower lip but can occur throughout the oral cavity wherever minor salivary glands are located. They may be subjected to repeated trauma as they become large and indurated. The mucocele (mucous extravasation phenomena) is to be differentiated from the mucous retention cyst.

Clinically mucoceles are movable over the submucosa but are attached to the overlying mucosa. They appear as blue nodules that do not blanch with pressure.

Ranula

A ranula is a blue mucocele that develops in the floor of the mouth. It can become very large from the mucous extravasation phenomena. Ranulae protrude from the floor of the mouth when the tongue is raised. The name is based on the Latin for frog, *rana*.

Ranulae are treated surgically by marsupialization and close follow-up. If recurrence is noted, a more radical surgical approach is indicated.

Pigmented lesions of benign and malignant neoplastic melanocytic origin

Nevi

Nevi are congenital or acquired benign tumors of nevus cells and are commonly referred to as "moles." They are composed of a collection of cells that are cytologically identical to melanocytes but lack dendrites. The origin of these cells is not clear. It is thought that they arise from the neural crest or that they develop from altered resident melanocytes. They are usually pigmented, ranging in color from gray to light brown to black, and, in contrast to melanotic macules, are slightly raised when of the intramucosal or compound variety.

Although nevi are common lesions that are seen on the skin in the large majority of the population, they are rare intraorally. They can be seen in persons of all ages and are usually less than 5 mm in diameter. When seen intraorally, they are most commonly observed on the hard palate.

Histologically, nevi are classified into subtypes that reflect the location of the nevus cells in the epithelium and connective tissue. Junctional nevi are confined in the epithelium at the connective tissue junction; intradermal nevi or intramucosal nevi are located in the lamina propria and do not contact the basement membrane; and compound nevi are in a combination of zones (ie, both the epithelium and the connective tissue) [8]. Another type of nevus, composed of spindle cells located in the connective tissue, is called a common blue nevus. Clinically the blue nevus appears more darkly pigmented than other nevi. It can be moved over the submucosal structures but cannot be moved independently from the mucosa. Occasionally, a nevus is also found to have a combination of types histologically. For example, when an intramucosal nevus and a common blue nevus are associated on histopathology, the pigmented lesion is referred to as a combined nevus. Combined nevi are rare, with few cases reported occurring on the oral mucosa [9]. Finally, a rare histologic variant of the blue nevus, the epithelioid blue nevus, has been recently reported on the oral mucosa [10]. Clinically, the epithelioid blue nevus is indistinguishable from the blue nevus.

Buchner and Hansen [11] reviewed 191 cases of oral nevi and found that 55% were intramucosal type, 32% were common blue nevi, 6% were compound nevi, 5% were junctional nevi, and 2% were combined. In this study, 41% of all nevi were found on the hard palate, 20% on the buccal mucosa, 12% on the vermilion border, and 11.5% on the gingiva. They were rarely found on the soft palate, tongue, and retromolar pad (Fig. 5).

The potential for malignant transformation of a benign nevus is thought to be low. Because it is difficult to make an accurate, clinically based

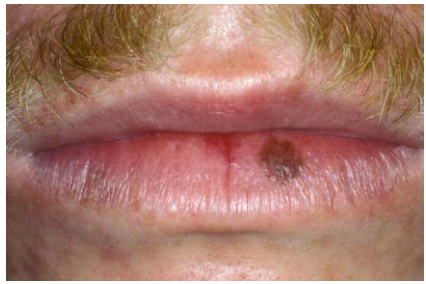

Fig. 5. Nevus.

diagnosis, it is recommended that any oral pigment-producing lesion be biopsied.

Melanoma

Mucosal melanomas are considered rare. The incidence is 0.15 cases per 100,000 persons in the United States [12], less than 4% of all melanomas. When found intraorally, mucosal melanoma often presents a difficult diagnostic challenge, because there is a lack of melanin in up to 35% of cases. Unlike cutaneous melanoma, mucosal melanomas do not have precursor lesions and risk factors, making them difficult to diagnose (Fig. 6).

The initial presentation of melanoma varies. The patient or the dentist may notice a rapid change in a pigmented area. Unfortunately, intraoral mucosal melanomas may also be amelanotic and are often asymptomatic.

The most common site for mucosal melanomas is in the head and neck (55.4%), with 55% of those in the oral cavity [12,13]. The most common

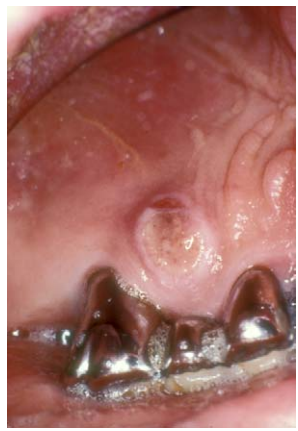

Fig. 6. Amelanotic melanoma.

sites are the hard and soft palate (40% of lesions). Mucosal melanoma is seen most commonly in patients between the ages of 50 and 80 years; the average age at presentation is 56 years. There is no gender difference, but women had a better 5-year survival rate than men (37% versus 9%). The overall 5-year survival rate is 15% [14]. Racial differences are a factor with oral melanoma; blacks have a three to four times greater risk than whites. This increased risk may result from the common finding of oral pigmentation in darker skinned individuals: clinicians may often attribute these pigmentations of the oral mucosa to normal melanosis and not diagnose the lesion appropriately.

Melanocytes originate from the neural crest cells and migrate to the skin where their function is not known. Pre-existing melanocytic lesions are noted in about one third of cases of mucosal melanoma in the head and neck region [15]. Melanomas are characterized by three growth phases, a macular phase, a pigmented plaque phase, and a nodular phase. The histopathologic classification of oral melanoma is different from that of cutaneous melanoma. Classification of oral mucosal melanomas is difficult because most are detected late, when they are large and aggressive masses. At the 1995 Western Society of Teachers of Oral Pathology Banff Workshop, a classification was proposed based on histologic pattern: in situ, invasive, and combined in situ and invasive [13].

The Breslow classification system is the preferred staging system for skin melanomas. The clinical staging system has been devised with three stages: stage I (clinically localized disease), stage II (regional lymph node disease), and stage III (distant disease). At present there is no accepted staging classification for mucosal lesions. Mucosal melanoma lesions are more aggressive than cutaneous melanoma; 85% are invasive at the time of diagnosis [13].

The diagnosis of a mucosa melanoma is complicated by the finding that two thirds of oral melanomas are lacking pigment (amelanotic), making prognosis poorer [15] (Fig. 6). The presenting clinical characteristic for an amelanotic melanoma can be a mass or swelling, but there is no defining clinical characteristic.

Treatment of oral mucosal melanomas varies from conservative radiation to radical resection. Surgery alone (56%) or surgery and radiation (19%) are the most common treatment modalities [12,16]. Mucosal melanomas have been considered resistant of radiotherapy, and therefore the role of radiotherapy in management has been controversial. It is generally accepted that surgical excision of the tumor, followed by radiation therapy for residual disease or nodal involvement, is the best course. Neck dissection is reserved for patients who have clinically evident nodal involvement and, when combined with radiation therapy, has a beneficial impact on local control and overall survival. The survival rates are poor, however, regardless of the treatment, perhaps because the rich vascular and lymphatic mucosal and submucosal network in the area where primary mucosal

melanomas occur allows spread early in the course of the disease. Oral melanomas, as noted, tend to present at a later stage of the disease and may be associated with nodal involvement [16]. This late presentation results in a median survival rate for all mucosal melanomas of just 2 years.

Melanoacanthoma

Melanoacanthoma is a benign lesion that can be clinically confused with melanoma. It can rapidly increase in size to several centimeters in a few weeks. The pigmented lesion is flat or slightly raised and is most common on the buccal mucosa or attached gingiva in black women in their third and fourth decades [17,18].

The pathogenesis of oral melanoacanthoma is unknown. They arise spontaneously or following trauma, which may be they are seen on the buccal mucosa and the masticatory mucosa that is subjected to repeated minor trauma. The histologic findings include melanocytes that extend up into the epithelium. Spongiosis also is noted. The findings of chronic inflammation and slightly increased vascularity suggest a reactive process [18].

Melanoacanthomas have no malignant potential, although a biopsy is indicated to distinguish melanoacanthoma from a melanoma. Many spontaneously resolve after biopsy. After histopathologic confirmation, additional treatment is not needed.

Pigmented lesions of benign and malignant neoplastic vascular origin or abnormal vascular morphogenesis

Lymphangioma

Lymphangioma is a congenital proliferation of dilated lymphatic channels that reach high into the lamina propria. They are similar to the hemangioma but are less common. Clinically they are less blue than the hemangioma, ranging from nearly transparent to pink and light blue. They are usually pebbly, translucent, and are often located on the dorsum of the tongue. If the tongue is involved, lymphangioma is associated with macroglossia. These lesions, however, can be found anywhere in the oral mucosal tissue. In fact, in neonates the lesion tends to be bilateral and located on the mandibular ridges. Aspiration of the lesion yields lymph fluid.

If the location of the lesion results in irritation from mastication and routine oral function, surgical excision is indicated [1].

Hemangioma/vascular malformations

A hemangioma is a benign tumor of blood vessels that can be either congenital or traumatic in origin. Hemangiomas appear similar to other

vascular lesions that result from dilated blood vessels. Hemangiomas, however, result from the formation of new blood vessels. They frequently occur early in life but can develop at any time, and various types are distinguished. A cavernous hemangioma may appear as a dome-shaped bluish lesion, which commonly is located on the lips but can occur at any location in the oral cavity. Hemangiomas can be of any size; if large, they can be easily traumatized, resulting in bleeding. They blanch when pressure is applied to the afferent vessel; this blanching helps differentiate a hemangioma from a cyst or mucocele.

Cavernous hemangiomas are not dangerous but may need to be surgically removed or sclerosed. The lesion may be larger than visualized, so an angiogram should be ordered to determine the exact size before removal.

A capillary hemangioma is a hamartomatous proliferation of vascular endothelial cells. These lesions are small and may or may not involute in childhood. Often no treatment is needed or indicated. A juvenile hemangioma (strawberry hemangioma) is a specific subtype of hemangioma. These hemangiomas are not present at birth but form soon after birth and frequently involute during adolescence.

Another vascular lesion is a vascular malformation. Vascular malformations usually persist throughout life and do not spontaneously involute. Various types of vascular malformations have been defined and can be broadly classified as arteriovenous malformation, venous malformation, or capillary malformation, based on the tissue involved. Arteriovenous malformations are high-flow lesions, simply characterized by abnormal connections between arteries and veins where arterial blood is shunted to the veins. Venous malformations are caused by errors in the venous system. Venous malformations become more evident as a child ages.

Capillary vascular malformations are often comprised of dilated capillary venules. There is no evidence of proliferation of endothelial cells in this type of malformation. These lesions (including port-wine stains) typically grow in proportion to the growth of the child and tend to darken with age. Port-wine stains on the face may raise concerns for Sturge-Weber syndrome. Sturge-Weber syndrome is a neurocutaneous disorder with venous malformations or capillary malformations involving the leptomeninges and the skin of the face. Sturge-Weber syndrome can be associated with significant neurologic defects such as seizures, mental retardation, and focal deficits. In general, when indicated, vascular malformations are surgically treated.

Kaposi's sarcoma

Kaposi's sarcoma was a common oral finding in HIV-positive patients before the introduction of the highly active antiretroviral therapies. When present, Kaposi's sarcomas are most commonly found on the hard palate,

although they can occur in any location. Initially Kaposi's sarcoma appears as a small, flat, red to purple macule or patches. It then can become nodular and bleed if traumatized. Kaposi's sarcomas can become large and interfere with eating or become unsightly. They are reportedly associated with human herpes virus 8. These lesions are less commonly observed because of improved HIV medication regimens.

Small lesions can be surgically debulked. The larger lesions can be injected with vinblastine or sclerosing solutions or treated with radiation [19].

Pigmented lesions related to exogenous deposits

Amalgam tattoo (focal argyrosis)

Deposition of amalgam restorative material into the oral mucosa is the most common reason for pigmentation in the oral cavity. These deposits are twice as common as melanotic macules and 10 times as common as oral nevi [20].

Amalgam tattoos result from the accidental implantation of dental amalgam during routine dental treatment and are a common occurrence. They present as pigmented macules that vary in size and shape. The lesion's location could provide clues to its origin. For example, the lesion often is in close proximity to a tooth with an amalgam restoration, to an endodontically treated tooth with a retrograde amalgam or silver point filling, or to an extraction site where amalgam could have fallen into the socket. The gingiva, buccal mucosa, and alveolar mucosa are the most frequent locations (71%) (Fig. 7) [20]. Occasionally radiographs that show opaque particles in the lesion's location can confirm the clinical diagnosis. The absence of this radiographic finding does not eliminate amalgam tattoo from the differential diagnosis.

Initial inflammation subsides within 4 weeks. Amalgam particles too large to be phagocytosed undergo corrosion. The amalgam particle acts as

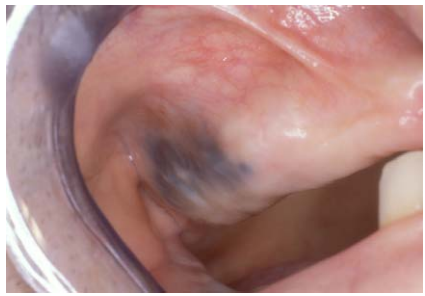

Fig. 7. Amalgam tattoo.

a small galvanic unit that causes mercury release. The silver is the last metal to be released. The silver sulfide corrosion product causes the tissue pigmentation [21].

Heavy-metal pigmentation

Heavy metals, such as arsenic, bismuth, platinum, lead, and mercury, when deposited in the mucosa, can cause hyperpigmentation without stimulating melanin. Most heavy metals also cause neurologic disorders and can cause sialorrhea. Arsenic may produce leukoplakic lesions. Lead produces a characteristic generalized gray hue or lines on the gingiva. Mercury causes a slate-gray gingival hyperpigmentation. Gold and bismuth produce a blue-black to brown discoloration on the gingiva [1].

Drug-induced pigmentations

Multifocal mucosal pigmentations may be a side effect of drug therapy. Drugs commonly associated with oral mucosal pigmentation include zidovudine, clofazimine, estrogen, cyclophosphamide, ketoconazole, minocycline, estrogen, busulfan, doxorubicin, 5-fluorouracil, and antimalarial agents such as quinacrine hydrochloride, chloroquine, and hydroxychloroquine (Fig. 8) [22–24].

In predisposed individuals drugs may also cause an inflammatory reaction with subsequent postinflammatory hyperpigmentation in fixed drug reactions [25]. Fixed drug eruptions present as well-demarcated areas of hyperpigmentation commonly affecting the oral mucosa and lips. Drugs such as arsenic directly induce pigmentation by combining with sulphydryl groups in the epidermal cells, promoting the action of tyrosinase [2]. Other drugs, such as phenothiazines and minocycline, may react directly with melanin to form a drug–pigment complex. Most often minocycline pigmentation involves the bone and causes boney pigmentation that penetrates through the mucosa and makes the mucosa appear gray.

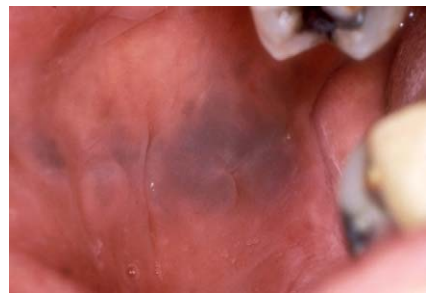

Fig. 8. Melanosis secondary to hydroxychloroquine sulfate (Plaquenil).

Pigmented lesions related to underlying endocrine disorders

Several endocrine disorders are associated with changes in oral pigmentation. They include Albright's syndrome, Addison's disease, Cushing's disease, acromegaly, and hyperthyroidism.

Albright's syndrome consists of polyostotic fibrous dysplasia, abnormal pigmentation, and, in females, precocious puberty. The abnormal excessive pigmentation is usually limited to the trunk and thighs, but pigmented macules have been reported on the lips. The lesions are classically described as café au-lait spots.

Addison's disease is caused by adrenocortical insufficiency that is either primary or secondary. The resultant lack of glucocorticoid production from the adrenal cortex stimulates the anterior pituitary to produce ACTH. ACTH has a melanocyte stimulatory action, hence the pigmentation. Hyperpigmentation is seen in areas where there is minor irritation or friction. Areas likely to be affected include the buccal mucosa, lips, tongue, and gingiva, but hyperpigmentation may affect any part of the oral mucosa. The pigmentation is not pathognomonic. Clinically there is a diffuse brownish or black pigmentation caused by melanin deposition in the basal layer of the epithelium.

Acromegaly is seen when there is excessive growth hormone, usually as a result of a pituitary tumor. Hyperpigmentation is clinically and etiologically similar to Addison's disease and occurs in about 40% of patients with acromegaly.

Cushing's disease results from excessive ACTH production from a pituitary tumor. The excessive ACTH production causes hyperpigmentation from excessive MSH in conjunction with excessive ACTH. The pattern of hyperpigmentation is similar to that in Addison's disease.

More commonly noted is Cushing's syndrome. Cushing's syndrome results in findings clinically similar to those seen with Cushing's disease. Cushing's syndrome, however, is caused by excessive ingestion of glucocorticoid medication, whereas in Cushing's disease excessive cortisol is produced by excessive ACTH production.

Approximately 10% of hyperthyroid patients may also develop hyperpigmentation similar to that seen in Addison's disease. This hyperpigmentation may result from an increase in MSH in untreated chronic active hyperthyroidism.

Pigmented lesions related to other systemic diseases

Hemochromatosis

Hemochromatosis or bronze diabetes in an inherited autosomal recessive disease with increased iron absorption that results in cirrhosis, diabetes, and cardiac failure. The bluish-gray pigmentation on the hard palate and gingiva

was once thought to be caused by iron deposits but seems to result from increased melanin production.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder with a high degree of penetrance [26]. There is a high degree of clinical variability. The typical presentation is irregular pigmented patches of dark brown or black up to 5 mm in diameter on the buccal mucosa and perioral region. The lesions may also be found on the gingiva and hard palate. The perioral distribution concentrates on the lower lip, and the patches are usually 1 mm in size. This perioral pigmentation often fades in early adulthood [27]. Histologically there is an increase in melanin in the basal layer of the epidermis.

Peutz-Jeghers syndrome is associated with benign intestinal polyposis, most commonly in the jejunum and ileum. Although these polyps are benign, gastrointestinal malignancies may require monitoring by regular endoscopy [26].

Summary

Pigmented lesions of the oral mucosa range from the extremely common and harmless, (eg, amalgam tattoo) to the rare and deadly (eg, malignant melanoma). Various pigmented lesions can have similar clinical presentations, posing a diagnostic dilemma for the dentist. It is sound clinical practice to perform a biopsy to obtain a definitive diagnosis.

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