Oral Medicine

Pigmented Lesions of the Oral Mucosa

Healthy oral soft tissues present a typical pink to red with slight variations of color due to many reasons presence or absence of keratin on the surface epithelium, the quantity, superficial or deep location of blood vessels in the subjacent stroma, the existence of lobules of adipocytes, the absence of melanin pigmentation in the basal cell layer of the epithelium oral and perioral pigmentation may be physiologic in nature, particularly in individuals with dark skin complexion, in the course of disease, the oral mucosa and perioral tissues can assume a variety of discolorations, including brown, blue, gray, and black.

Such color changes are often attributed to the deposition, production, or increased accumulation of various endogenous or exogenous pigmented substances. However, **although** an area may appear pigmented, the discoloration may not be related to actual pigment but rather to the deposition or accumulation of organic or inorganic substances, including various metals and drug metabolites.

The most common endogenous sources of mucosal color change is hemoglobin, hemosiderin, and melanin.

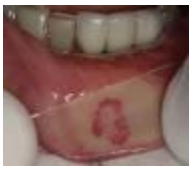
ENDOGENOUS PIGMENTATION

Melanin is found universally in nature. Melanin is the pigment derivative of tyrosine and is synthesized by melanocytes, which typically reside in the basal cell layer of the epithelium. Investigations into normal melanocyte homeostasis have yielded the discovery that keratinocytes actually control melanocytic growth. Yet the mechanisms by which melanocytes are stimulated to undergo cell division remain poorly understood. Their presence in the skin is thought to protect against the damaging effects of actinic irradiation. They also act as scavengers in protecting against various cytotoxic intermediates. The role of melanocytes in oral epithelium is not clear. Melanin is synthesized within specialized structures known as melanosomes. Melanin is actually composed of eumelanin, which is a brown-black pigment, and pheomelanin, which has a red-yellow color. The term melanosis is frequently used to describe diffuse hyperpigmentation.

Overproduction of melanin may be caused by a variety of mechanisms, the most common of which is related to increased sun exposure. However, intraorally, hyperpigmentation is more commonly a consequence of physiologic or idiopathic sources, neoplasia, medication or oral contraceptive use, high serum concentrations of pituitary adrenocorticotropic hormone (ACTH), postinflammatory changes, and genetic or autoimmune disease. Therefore, the presence or absence of systemic signs and symptoms, including cutaneous hyperpigmentation, is of great importance to elucidate the cause of oral pigmentation. However, if the etiology of the pigmentation cannot be clinically ascertained, a tissue biopsy is warranted for definitive diagnosis. This is critical because malignant melanoma may present with a deceptively benign clinical appearance.

In addition to biopsy and histologic study, various laboratory and clinical tests, including diascopy (Diascopy is a test for blanchability performed by applying

pressure with a finger or glass slide and observing color changes. It is used to determine whether a lesion is vascular (inflammatory or congenital), nonvascular (nevus), or hemorrhagic (petechia or purpura). Hemorrhagic lesions and nonvascular lesions do not blanch; inflammatory lesions do)



radiography, and blood tests, may be necessary for definitive diagnosis of oral pigmentation. Dermascopy, also known as epiluminescence microscopy, is another increasingly employed clinical test that can be useful in the diagnosis of melanocytic lesions. Several studies have described the use of dermascopy in the evaluation of labial and anterior lingual pigmentation. Briefly, this noninvasive technique is performed through the use of a handheld surface microscope using incident light and oil immersion.

Freckle/Ephelis

The cutaneous freckle, or ephelis, is a commonly occurring, asymptomatic, small (1–3 mm), well-circumscribed, tan- or brown-colored macule that is often seen on the sun-exposed regions of the facial and perioral skin. Ephelides are most commonly observed in light-skinned individuals and are quite prevalent in red- or light blond–haired individuals. Freckles are thought to be developmental in origin. Ephelides are usually more abundant in number and darker in intensity during childhood and adolescence. Freckles tend to become darker during periods of prolonged sun exposure (spring, summer) and less intense during the autumn and winter months. Yet the increase in pigmentation is solely related to an increase in melanin production without a concomitant increase in the number of melanocytes. With increasing age, the number of ephelides and color intensity tends to diminish. In general, no therapeutic intervention is required.

Oral/Labial Melanotic Macule

The melanotic macule is a unique, benign, pigmented lesion that has no known dermal counterpart. Melanotic macules are the most common oral lesions of melanocytic origin. Trauma has been postulated to play a role. Sun exposure is not a precipitating factor. Melanotic macules develop more frequently in females, usually in the lower lip (labial melanotic macule) and gingiva. However, any mucosal site may be affected. Although the lesion may develop at any age, it generally tends to present in adulthood. Congenital melanotic macules have also been described occurring primarily in the tongue. Overall, melanotic macules tend to be small (<1 cm), well circumscribed, oval or irregular in outline, and often uniformly pigmented. Once the lesion reaches a certain size, it does not tend to enlarge further. Unlike an ephelis, a melanotic macule does not become darker with continued sun exposure. Overall, the oral melanotic macule is a relatively innocuous lesion, does not represent a melanocytic proliferation, and does not generally recur following surgical removal.

Oral Melanoacanthoma

Benign, melanocytic lesion that is unique to the mucosal tissues. Oral melanoacanthoma is an innocuous melanocytic lesion that may spontaneously resolve, with or without surgical intervention. Although the term melanoacanthoma may imply

a neoplastic process, the oral lesion is actually reactive in nature. Most patients report a rapid onset; and acute trauma or a history of chronic irritation usually precedes the development of the lesion. A biopsy is always warranted to confirm the diagnosis, but once established, no further treatment is required. The biopsy procedure itself may lead to spontaneous regression of the lesion. The underlying source of the irritation should be eliminated to minimize recurrence.

Oral melanoacanthoma usually presents as a rapidly enlarging, ill-defined, darkly pigmented macular or plaque-like lesion, and mostly develop in black females. Although lesions may present over a wide age range, the majority occur between the third and fourth decades of life. Typically, melanoacanthoma presents as a solitary lesion; however, bilateral and multifocal lesions have been reported. Oral melanoacanthomas are generally asymptomatic; however, pain has been reported. Although any mucosal surface may be involved, close to 50% of melanoacanthomas arise on the buccal mucosa. The size of the lesion is variable, ranging from small and localized to large, diffuse areas of involvement, measuring several centimeters in diameter. The borders are typically irregular in appearance, and the pigmentation may or may not be uniform. Although there is a recognized cutaneous melanoacanthoma, it is clear that the similarities with oral melanoacanthoma lie solely in the nomenclature. Cutaneous melanoacanthoma represents a pigmented variant of seborrheic keratosis and typically occurs in older Caucasian patients. Dermatosis papulosa nigra is a relatively common facial condition that typically manifests in older black patients, often female, and represents multiple pigmented seborrheic keratoses. These small papules are often identified in the malar and preauricular regions of the face.

Microscopically, oral melanoacanthomas are characterized by a proliferation of benign, dendritic melanocytes throughout the full thickness of an acanthotic and spongiotic epithelium. A mild lymphocytic infiltrate with exocytosis is also characteristic. Occasional eosinophils may be observed.

Diagnosis of oral melanoacanthoma may resemble other melanocytic lesions, such as pigmented nevus, melanotic macule, and melanoma, a biopsy is considered to obtain a definitive diagnosis.

Melanocytic Nevus

Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise as a consequence of melanocytic growth and proliferation. In the oral cavity, the intramucosal nevus is most frequently observed, followed by the common blue nevus both genetic and environmental factors are thought to play a role in nevogenesis. The effect of sun exposure on the development of cutaneous nevi is well recognized. However, there are also age- and location-dependent differences in the presentation, number, and distribution of nevi. Although most melanocytic nevi are acquired, some may present as congenital lesions (including in the oral cavity). Moreover, there are several examples of increased nevus susceptibility in various inherited diseases, thus confirming the role of genetics. Familial atypical multiple mole melanoma syndrome is characterized by the formation of histologically atypical nevi; epithelioid blue nevus may be associated with the Carney complex; markedly increased numbers of common nevi are characteristic in patients with Turner's syndrome.

Cutaneous nevi are a common occurrence. The adult patient may have several nevi; some individuals may have dozens. The total number of nevi tends to be higher in males than females. In contrast, oral melanocytic nevi are rare, typically present as solitary lesions, and may be more common in females. Lesions are usually

asymptomatic and often present as a small (<1 cm), solitary, brown or blue, well-circumscribed nodule or macule. Oral nevi may develop at any age; however, most are identified in patients over the age of 30. The hard palate represents the most common site, followed by the buccal and labial mucosae and gingiva. the nevus cells initially maintain their localization to the basal layer, residing at the junction of the epithelium and the basement membrane and underlying connective tissue. These junctional nevi are usually small (<5 mm), macular or nonpalpable, and tan to brown in appearance. Over time, the clustered melanocytes are thought to proliferate down into the connective tissue, often in the form of variably sized nests of relatively small, rounded cells. Nonetheless, some nevus cells are still seen at the epithelial–connective tissue interface. Such nevi often assume a dome-shaped appearance and are referred to as compound nevi. As the lesion further matures, the nevus cells completely lose their association with the epithelial layer and become confined to the submucosal tissue, often with an associated decrease in the amount of pigmentation. At this point, the lesion is given the designation of intramucosal nevus and, clinically, may appear brown or tan or even resemble the color of the surrounding mucosa. The "common" blue nevus, which is the most frequent histologic variant seen in the oral cavity, is characterized by an intramucosal proliferation of pigment-laden, spindle-shaped melanocytes. The blue nevus is described as such because the melanocytes may reside deep in the connective tissue and the overlying blood vessels often dampen the brown coloration of melanin, which may yield a blue tint.
Biopsy is necessary for diagnostic confirmation of an oral melanocytic nevus since the clinical diagnosis includes a variety of other focally pigmented lesions, including malignant melanoma. Various vascular phenomena may also be considered in the differential diagnosis. Complete but conservative surgical excision is the treatment of choice for oral lesions.

Malignant Melanoma

Malignant melanoma is the least common but most deadly of all primary skin cancers. Similar to other malignancies, extrinsic and intrinsic factors play a role in the pathogenesis of melanoma. A history of multiple episodes of acute sun exposure, especially at a young age; immunosuppression; the presence of multiple cutaneous nevi; and a family history of melanoma are all known risk factors for the development of cutaneous melanoma.
Cutaneous melanoma is most common among white populations that live in the sunbelt regions of the world. However, mortality rates are higher in blacks and Hispanics.
Epidemiologic studies suggest that the incidence is increasing in patients, especially males older than 45 years. In contrast, the incidence is decreasing in patients younger than 40 years. Overall, there is a male predilection, but melanoma is one of the most commonly occurring cancers in women of child-bearing age. Oral melanoma may develop at any age, but most present over the age of 50. Any mucosal site may be affected; however, the palate represents the single most common site of involvement. The maxillary gingiva/alveolar crest is the second most frequent site Oral melanomas have no distinctive clinical appearance. They may be macular, plaquelike or mass forming, well circumscribed or irregular, and exhibit focal or diffuse areas of brown, blue, or black pigmentation Up to one-third of oral melanomas may exhibit little or no clinical evidence of pigmentation (amelanosis)., In some cases, oral melanomas may present with what appear to be multifocal areas of pigmentation. This phenomenon is often explained by the fact that some tumors may exhibit both melanotic and

amelanotic areas. Additional signs and symptoms that may be associated with oral melanoma are nonspecific and similar to those observed with other malignancies. Ulceration, pain, tooth mobility or spontaneous exfoliation, root resorption, bone loss, and paresthesia/anesthesia may be evident. However, in some patients, the tumors may be completely asymptomatic. Oral mucosal malignant melanoma is associated with a very poor prognosis. Studies have demonstrated five-year survival rates of 15%–40%. The palate shows the worst prognosis compared to other intraoral sites. Regional lymphatic metastases are frequently identified and contribute to the poor survival rates. Less than 10% of patients with distant metastases survive after five years. The 10-year-survival rate is 0%. Ablative surgery with wide margins remains the treatment of choice.

MULTIFOCAL/DIFFUSE PIGMENTATION

Physiologic Pigmentation

The most common multifocal or diffuse oral mucosal pigmentation is physiologic pigmentation.Dark-skinned individuals, including blacks, Asians, and Latinos, frequently show patchy to generalized hyperpigmentation of the oral mucosal tissues. Although in many patients, the pigment is restricted to the gingiva, melanosis of other mucosal surfaces is not uncommon. The pigment is typically first observed during childhood and does not develop de novo in the adult. The sudden or gradual onset of diffuse mucosal pigmentation in adulthood, even in darker-skinned patients, should alert the clinician to consider a pathological condition.

Drug-Induced Melanosis

Medications may induce a variety of different forms of mucocutaneous pigmentation, including melanosis. The chief drugs implicated in drug-induced melanosis are the antimalarials, including chloroquine, hydroxychloroquine, and quinacrine. These medications are typically used for the treatment of autoimmune disease. Other common classes of medications that induce melanosis include the phenothiazines, such as chlorpromazine, oral contraceptives, and cytotoxic medications such as cyclophosphamide and busulfan. It has been estimated that 10%- 20% of all cases of acquired melanocytic pigmentation may be drug induced. Intraorally, the pigment can be diffuse yet localized to one mucosal surface, often the hard palate or it can be multifocal and involve multiple surfaces. Some drugs may even be associated with a specific pattern of pigmentation. Much like other forms of diffuse pigmentation, the lesions are flat and without any evidence of nodularity or swelling. Sun exposure may exacerbate cutaneous drug-induced pigmentation.

Smoker's Melanosis

Diffuse melanosis of the anterior vestibular maxillary and mandibular gingivae, buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers. Most smokers (including heavy smokers) usually fail to show such changes. However, in certain individuals, melanin synthesis may be stimulated by tobacco smoke products. Indeed, among dark-skinned individuals who normally exhibit physiologic pigmentation, smoking stimulates a further increase in oral pigmentation. The pigmented areas are brown, flat, and irregular; some are even geographic or map like in configuration. The mechanism by which smoking induces the pigmentation remains unknown. Smokeless tobacco (snuff) does not appear to be associated with an increase in oral melanosis. Thus, it is possible that one or more of

the chemical compounds incorporated within cigarettes, rather than the actual tobacco, may be causative. Another possibility is that the heat of the smoke may stimulate the pigmentation. However, passive smoking in children may result in increased gingival pigmentation. Epidemiologic studies suggest that oral melanosis increases prominently during the first year of smoking. A reduction in smoking may lead to fading of the pigmentation. Unlike other smoking-related oral conditions, smoker's melanosis is not a preneoplastic condition. Alcohol has also been associated with increased oral pigmentation. In alcoholics, the posterior regions of the mouth, including the soft palate, tend to be more frequently pigmented than other areas. It has been suggested that alcoholic melanosis may be associated with a higher risk of cancers of the upper aerodigestive tract. Diffuse or patchy melanotic pigmentation is also associated with oral submucous fibrosis.

Postinflammatory (Inflammatory) Hyperpigmentation

Postinflammatory hyperpigmentation is a well-recognized phenomenon that tends to develop more commonly in dark-skinned individuals. Most cases present as either focal or diffuse pigmentation in areas that were subjected to previous injury or inflammation. The acne prone face is a relatively common site for this phenomenon. Although unusual, postinflammatory pigmentation may also develop in the oral cavity. In rare cases, the mucosa overlying a nonmelanocytic malignancy may become pigmented. Oral pigmentation has also been described in patients with lichen planus (lichen planus pigmentosus). This phenomenon has been described in various races, including Caucasians. In addition to the typical microscopic features associated with lichen planus, there is also evidence of basilar hyperpigmentation and melanin incontinence. Upon resolution of the lichenoid lesion, in most cases, the pigmentation eventually does subside. Although it may be mere semantics, it is unclear whether lichen planus–associated pigmentation should be appropriately characterized as postinflammatory or inflammatory pigmentation. In addition, spontaneous postsurgical healing pigmentation of palatal donor sites for free gingival grafts has been reported.

Melasma (Chloasma)

Melasma is a relatively common, acquired symmetric melanosis that typically develops on sun-exposed areas of the skin and frequently on the face. The forehead, cheeks, upper lips, and chin are the most commonly affected areas. There is a distinct female predilection, and most cases arise in darker-skinned individuals. Unlike other forms of diffuse melanosis, melasma tends to evolve rather rapidly over a period of a few weeks. The term melasma has been used to describe any form of generalized facial hyperpigmentation, including those related to postinflammatory changes and medication use. However, the term is most appropriately used to describe the pigmentary changes associated with sun exposure and hormonal factors, including pregnancy and contraceptive hormones. Both pregnancy and use of oral contraceptives have also been associated with oral mucosal melanosis. Rare cases of idiopathic melasma have also been described in females and, much less commonly in males.

Melasma may spontaneously resolve after parturition, cessation of the exogenous hormones, or regulation of endogenous sex hormone levels.

MELANOSIS ASSOCIATED WITH SYSTEMIC OR GENETIC DISEASE

Hypoadrenocorticism (Adrenal Insufficiency or Addison's Disease)

Hypoadrenocorticism is a potentially life-threatening disease, as much for its systemic complications as its underdiagnosis. A variety of etiologies may precipitate adrenal insufficiency. In adults, autoimmune disease represents one of the most common causes where the majority of patients show the presence of circulating autoantibodies to steroidogenic enzyme 21-hydroxylase. However, infectious agents, neoplasia, trauma, certain medications, and iatrogenic causes may lead to adrenal destruction or an impairment of endogenous steroid production. In rare cases, adrenal insufficiency may also be a consequence of genetic disease. Regardless of etiology, the end result is essentially the same; that is, a decrease in endogenous corticosteroid levels. As steroid levels decrease, there is a compensatory activation of ACTH secretion from the anterior pituitary gland. ACTH then acts on the adrenal cortex to stimulate steroid production and ACTH secretion stops. If low steroid levels persist, there is a loss of feedback inhibition, resulting in persistent secretion of ACTH into the serum. Concurrently, the serum levels of α-melanocyte-stimulating hormone (α-MSH) also increase. At the molecular level, this is explained by the fact that the precursor proopiomelanocortin gene contains the sequences of both the ACTH and α-MSH genes. Both α-MSH and ACTH are also thought to have stimulatory effects on melanocytes. However, the exact mechanism by which melanin synthesis increases remains unclear.

Weakness, poorly defined fatigue, and depression are some of the typical presenting signs of the illness. However, in some patients, the first sign of disease may be mucocutaneous hyperpigmentation. Generalized bronzing of the skin and diffuse but patchy melanosis of the oral mucosa are hallmarks of hypoadrenocorticism. Any oral surface may be affected. In some patients, oral melanosis may be the first manifestation of their adrenal disease. Diffuse hyperpigmentation is more commonly associated with chronic rather than acute-onset disease.

Thus, the differential diagnosis includes other causes of diffuse pigmentation, including physiologic and drug-induced pigmentation. Laboratory tests, including the evaluation of serum cortisol and electrolyte levels, are necessary to make a diagnosis of addisonian hyperpigmentation.

Treatment consists of exogenous steroid replacement therapy with glucocorticoids and mineralocorticoids. There is evidence supporting the use of adrenal androgens such as dehydroepiandrosterone to improve the quality of life of patients with Addison's disease. With appropriate therapy, the pigmentation will eventually resolve.

Cushing's Syndrome/Cushing's Disease

Cushing's syndrome develops as a consequence of prolonged exposure to relatively high concentrations of endogenous or exogenous corticosteroids. Most cases are iatrogenic in origin and associated with poorly controlled or unmonitored use of topical or systemic steroids. Cushing's syndrome may also arise as a result of various endogenous etiologies, including an activating pituitary tumor (Cushing's disease) and a primary, activating, adrenal pathology (hyperadrenocorticism), as well as ectopic secretion of corticosteroids, ACTH, or corticotropin-releasing hormone by various neoplasms. Cushing's syndrome is more prevalent in female patients. However, prepubertal onset is more commonly seen in boys. Apart from the wide array of systemic complications, including weight gain and the characteristic "moon

facies," diffuse mucocutaneous pigmentation may be seen. The pattern of oral pigmentation is essentially identical to that seen in patients with adrenal insufficiency. Three main tests are used for the diagnosis of Cushing's syndrome: low-dose dexamethasone suppression test, midnight plasma cortisol, and 24-hour urinary free cortisol. The pigmentation often resolves following appropriate surgical, radiation, or drug therapy for the specific source of the endocrinopathy.

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominant disease. Clinical manifestations include intestinal polyposis, cancer susceptibility, and multiple, small, pigmented macules of the lips, perioral skin, hands, and feet. The macules may resemble ephelides, usually measuring <0.5 cm in diameter. However, the intensity of the macular pigment is not influenced by sun exposure. Although uncommon, similar-appearing lesions may also develop on the anterior tongue and buccal and labial mucosae. The lip and perioral pigmentation is highly distinctive, although not pathognomonic for this disease.

Café au Lait Pigmentation

Solitary, idiopathic café au lait ("coffee with milk") spots are occasionally observed in the general population, but multiple café au lait spots are often indicative of an underlying genetic disorder. Café au lait pigmentation may be identified in a number of different genetic diseases, including neurofibromatosis type I, McCune–Albright syndrome, and Noonan's syndrome Café au lait spots typically present as tan- or brown-colored, irregularly shaped macules of variable size. They may occur anywhere on the skin, although unusual, examples of similar-appearing oral macular pigmentation have been described in some patients.

HEMOGLOBIN AND IRON ASSOCIATED PIGMENTATION

Ecchymosis

Traumatic ecchymosis is common on the lips and face yet uncommon in the oral mucosa. Erythrocyte extravasation into the connective tissue will appear as a bright red macule or as a swelling if a hematoma forms. The lesion will assume a brown discoloration within a few days, after the hemoglobin is degraded to hemosiderin. The differential diagnosis must include other focally pigmented lesions. Patients taking anticoagulants may present with oral ecchymosis, particularly on the buccal mucosa or tongue, either of which can be traumatized while chewing. Ecchymoses of the oral mucosa may also be encountered in patients with liver cirrhosis, in patients with leukemia, and additionally, in patients with end-stage renal disease who are undergoing dialysis treatment.

Purpura/Petechiae

Capillary hemorrhages will appear red initially and turn brown in a few days once the extravasated red cells have lysed and have been degraded to hemosiderin. Petechiae are typically characterized as being pinpoint or slightly larger than pinpoint and purpura as multiple, small 2–4 mm collections of extravasated blood.

Oral purpura/petechiae may develop as a consequence of trauma, viral, or systemic disease. In most cases, the petechiae are identified on the soft palate, although any mucosal site may be affected. When trauma is suspected, the patient should be instructed to cease whatever activity may be contributing to the presence of the lesions. Within two weeks, the lesions should resolve. Failure to do so should arouse

suspicion of a hemorrhagic diathesis, a persistent infectious disease, or other systemic disease, and appropriate laboratory investigations must be undertaken.

Hemochromatosis

Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition (usually in the form of hemosiderin) in the liver and other organs and tissues. The cutaneous pigmentation is seen in over 90% of affected patients, regardless of the etiology of the disease. The primary oral manifestation of hemochromatosis is a blue-gray to brown pigmentation affecting mainly the palate and gingiva. Complications of hemochromatosis may include liver cirrhosis, diabetes, anemia, heart failure, hypertension, and bronzing of the skin.

EXOGENOUS PIGMENTATION

Amalgam Tattoo

The most common pigmented lesion in the oral mucosa is amalgam tattoo. By definition, these are iatrogenic in origin and typically a consequence of the inadvertent deposition of amalgam restorative material into the submucosal tissue. Amalgam tattoos may be found in up to 1%–3% of the general population. The lesions are typically small, asymptomatic, macular, and bluish gray or even black in appearance. They may be found on any mucosal surface. However, the gingiva, alveolar mucosa, buccal mucosa, and floor of the mouth represent the most common sites. The lesions are often found in the vicinity of teeth with large amalgam restorations or crowned teeth that probably had amalgams, around the apical region of endodontically treated teeth with retrograde restorations or obturated with silver points,and in areas in and around healed extraction sites. A typical differential diagnosis includes melanotic macule, nevus, and melanoma.. Amalgam tattoo of the head and neck skin may occur in dentists and represents an occupational hazard resulting from failure to use facial protective barriers.

Graphite Tattoos

Graphite tattoos are an unusual source of focal exogenous pigmentation. They are most commonly seen on the palate and gingiva and represent traumatic implantation of graphite particles from a pencil. The lesions may be indistinguishable from amalgam tattoos, often presenting as a solitary gray or black macule. Since the traumatic event often occurs in childhood, many patients may not report a history of injury.

Medicinal Metal-Induced Pigmentation

Historically, a variety of metallic compounds have been used medicinally for the treatment of various systemic diseases. Fortunately, with the advent of methotrexate for the treatment of rheumatoid arthritis, gold therapy is in less demand. Colloidal silver is another metal-based substance that has medicinal usage. Gold and colloidal silver have both been associated with diffuse cutaneous pigmentation. Silver may cause a generalized blue-gray discoloration (argyria), whereas gold-induced pigment may appear blue-gray or purple (chrysiasis). Rare examples of diffuse oral argyria have been reported. Chrysiasis does not involve the oral mucosal tissues since it is thought that exposure to ultraviolet light or other high-intensity light sources precipitate the pigmentation. However, oral lichenoid eruptions have been associated with systemic gold therapy.

In contrast to the systemic therapies, metal salts remain a component of some topical medications and other substances that are used in clinical practice. Examples include

silver nitrate and zinc oxide. Silver nitrate cautery has been used to treat recurrent aphthous stomatitis, and zinc oxide is a common component of sunblock creams. Both substances have been associated with focal mucocutaneous pigmentation. Using of zinc oxide containing sunblock in severely chaffed lips may result in the development of hyperpigmentation.

Heavy Metal Pigmentation

Diffuse oral pigmentation may be associated with ingestion of heavy metals. Nowadays, this phenomenon is unusually encountered. Yet it remains an occupational and health hazard for some individuals who work in certain industrial plants. Lead, mercury, bismuth, and arsenic have all been shown to be deposited in oral tissue if ingested in sufficient quantities or over an extended period of time.These ingested metal salts tend to extravasate from vessels in areas of chronic inflammation. Thus, in the oral cavity, the pigmentation is usually found along the free marginal gingiva, where it often dramatically outlines the gingival cuff. This metallic line usually has a gray to black appearance. In some patients, the oral pigmentation may be the first sign of heavy metal toxicity. Additional systemic signs and symptoms of heavy metal poisoning may include behavioral changes, neurologic disorders, intestinal pain, and sialorrhea. Diffuse mucocutaneous melanosis may also be observed in some affected individuals.

Drug-Induced Pigmentation

Minocycline, which is a tetracycline derivative and frequently used in the treatment of acne, is a relatively common cause of drug-induced nonmelanin-associated oral pigmentation. Similar to tetracycline, minocycline can cause pigmentation of developing teeth. Minocycline can also induce actual pigmentation of the oral soft tissues, as well as the skin and nails. Minocycline-induced soft tissue pigmentation may appear gray, brown, or black. Often the pigmentation is patchy or diffuse in its presentation.

Most patients are prescribed minocycline in early adulthood. When taken chronically, minocycline metabolites may become incorporated into the normal bone. Thus, although the teeth may be normal in appearance, the surrounding bone may appear green, blue, or even black. As a result, the palatal and alveolar mucosae may appear similarly and diffusely discolored. In addition, roots show a green color, whereas developing roots tend to be black.