Pigmented Lesions of the Oral Mucosa

Oral and perioral pigmentation may be physiologic or pathologic in origin. Physiologic pigmentation is typically brown in appearance. However, 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 a tributed 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.

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, as well as to act as scavengers in protecting against various cytotoxic intermediates. The role of melanocytes in oral epithelium is not clear.

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. Thus, the presence or absence of other systemic signs and symptoms, including cutaneous hyperpigmentation, is of great importance from the standpoint of diagnosing the cause of oral pigmentation. However, if the etiology of the pigment cannot be ascertained, a tissue biopsy is warranted for definitive diagnosis and is especially critical for the diagnosis of focal pigmentation since malignant melanoma can present in a variety of different configurations.

In addition to biopsy and histologic study, various laboratory and clinical tests, including diascopy, 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.

Focal Melanocytic Pigmentation:

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. Although the pigmentation itself is focal in nature, most patients have multiple freckles. 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. Although the etiology remains elusive, 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

Oral melanoacanthoma is another unusual, 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. 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.

Oral melanoacanthoma usually presents as a rapidly enlarging, ill-defined, darkly pigmented macular or plaque-like lesion, and most develop in black females.20,21 Although lesions may present over a wide age range, the majority occur between the third and fourth decades of life. In rare instances, multiple lesions may present simultaneously.

Oral melanoacanthomas are typically asymptomatic, although pain has been reported. Although any mucosal surface may be involved, the buccal mucosa is the most common site of occurrence. 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.

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 keratosis. These small papules are often identified in the malar and preauricular regions of the face.

Diagnosis

The clinical presentation, in association with the history, may be disconcerting and should lead the clinician to consider malignant melanoma in the differential diagnosis.

Melanocytic Nevus

Melanocytic nevi include a diverse group of clinically and/or microscopically distinct lesions. 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. In general, 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).

Familial atypical multiple mole and 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 average Caucasian 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.

Oral melanocytic nevi have no distinguishing clinical characteristics. Lesions are usually asymptomatic and often present as a small (<1 cm), solitary, brown or blue, well circumscribed nodule or macule. Up to 15% of oral nevi may not exhibit any evidence of clinical pigmentation. Once the lesion reaches a given size, its growth tends to cease and may remain static indefinitely.

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 nonpalp ble, 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 mucosalsubmucosal junction. 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.

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 sun belt regions of the world. However, mortality rates are higher in blacks and Hispanics. The incidence is increasing in patients, especially males, over the age of 45. The incidence is decreasing in patients under the age of 40. Overall, there is a male predilection, but melanoma is one of the most commonly occurring cancers in women of childbearing age.

The clinical characteristics of cutaneous melanoma are best described by the ABCDE criteria: asymmetry, irregular borders, and color variegation, diameter greater than 6 mm, and evolution or surface elevation. These criteria are very useful (although not absolute) in differentiating cutaneous melanoma from other focally, pigmented melanocytic lesions.

Primary mucosal melanomas comprise less than 1% of all melanomas. The majority develop in the head and neck, most in the sinonasal tract and oral cavity. The prevalence of oral melanoma appears to be higher among black-skinned and Japanese people than among other populations. The tumor presents more frequently in males than females.

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 is the second most frequent site. Oral melanomas have no distinctive clinical appearance. They may be macular, plaque-like 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. Thus, the clinical differential diagnosis may be quite extensive. It is for this reason that a biopsy of any persistent solitary pigmented lesion is always warranted. Oral mucosal malignant melanoma is associated with a very poor prognosis. Studies have demonstrated 5-year survival rates of 15 40%.Regional lymphatic metastases are frequently identified and contribute to the

poor survival rates. Less than 10% of patients with distant metastases survive after 5 years.

Multifocal/Diffuse Pigmentation

Physiologic Pigmentation

Physiologic pigmentation is the most common source of multifocal or diffuse oral mucosal pigmentation. Dark-complexioned individuals, including blacks, Asians, and South-Americans, 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 often observed in childhood and usually does not develop de novo in the adult. If there is a sudden or gradual onset of diffuse mucosal pigmentation in adulthood, even in darker-skinned patients, other sources for the melanosis should be given consideration.

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, quinacrine, and others. Other common classes of medications that induce melanosis include the phenothiazines, such as chlorpromazine , oral contraceptives, and cytotoxic medications such as cyclophosphamide and busulfan .

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 facial 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, it is probable that in certain individuals, melanin synthesis is 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. 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 characteristically associated with oral submucous fibrosis. Unlike smoker's melanosis, oral submucous fibrosis is a preneoplastic condition caused by habitual chewing of areca (betel) nut.

Post inflammatory (Inflammatory) Hyperpigmentation

Postinflammatory hyperpigmentation is a well-recognized phenomenon that tends to develop more commonly in darkcomplexioned 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).

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. Sun exposure tends to be an exacerbating, if not precipitating, event. The term melasma is most appropriately used to describe the pigmentary changes associated with pregnancy or ingestion of 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, 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,Addison's Disease)

Hypoadrenocorticism is a potentially life-threatening disease, as much for its systemic complications as it's under diagnosis. A variety of etiologies may precipitate adrenal insufficiency. In adults, autoimmune disease represents one of the most

common causes. 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 a-melanocyte-stimulating hormone (a-MSH) also increase.

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.

The diagnosis of oral addisonian pigmentation requires a clinicopathologic correlation. Endocrinopathic disease should be suspected whenever oral melanosis is accompanied by cutaneous bronzing. Treatment consists of exogenous steroid replacement therapy. 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.

Overall, 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 in a subset of patients, specifically those whose pathology is associated with increased ACTH secretion. Thus, in most cases, the affected patients have a primary pituitary neoplasm. The

pattern of oral pigmentation is essentially identical to that seen in patients with adrenal insufficiency.
Serum steroid and ACTH determinations will aid in the diagnosis, and the pigment often resolves following appropriate surgical, radiation, or medicinal therapy for the specific source of the endocrinopathy.

Hyperthyroidism (Graves'Disease)

Melanosis is a common consequence of hyperthyroidism (Graves' disease), especially in dark-skinned individuals. The pigmentation tends to resolve following treatment of the thyroid abnormality. The mechanism by which excessive thyroid activity stimulates melanin synthesis remains unclear.

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.

DEPIGMENTATION

Vitiligo

Common, acquired, autoimmune disease that is associated with hypomelanosis. Although the etiology and mechanisms remain unknown, the end result is a destruction of the melanocytes. In most cases, vitiligo is characterized by bilateral, symmetric areas of relatively generalized hypomelanosis. The vitiligenous lesions often present as well-circumscribed, round, oval or elongated, pale or white-colored macules that may coalesce into larger areas of diffuse depigmentation. As

the disease progresses, additional areas of involvement may become apparent. Topical corticosteroids and topical or, more commonly, systemic photochemotherapies (psoralen and ultraviolet A exposure) have proven to be effective nonsurgical therapies.

Hemoglobin and Iron- Associated Pigmentation

Ecchymosis

Traumatic ecchymosis is common on the lips and face yet is uncommon in the oral mucosa, except in cases related to blunt-force trauma and oral intubation. Immediately following the traumatic event, erythrocyte extravasation into the submucosa will appear as a bright red macule or as a swelling if a hematoma forms. The lesion will assume a brown coloration within a few days, after the hemoglobin is degraded to hemosiderin. patients taking anticoagulant drugs 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, leukemia, and end-stage renal disease 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. The distinction between purpura and petechiae is essentially semantic and based solely on the size of the focal hemorrhages. Petechiae are typically characterized as being pinpoint or slightly larger than pinpoint and purpura as multiple, small 2 to 4 mm collections of extravasated blood. The same precipitating events can elicit either clinical presentation. Oral purpura/petechiae may develop as a consequence of trauma or viral or systemic disease . Petechiae secondary to platelet deficiencies or aggregation disorders are usually not limited to the oral mucosa but may occur concomitantly on the skin. Viral disease is more commonly associated with oral rather than cutaneous petechiae. 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.

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. Idiopathic, neonatal, blood transfusion, and heritable forms of this disease are recognized. Complications of hemochromatosis may include liver cirrhosis, diabetes, anemia, heart failure, hypertension, and bronzing of the skin.

Exogenous Pigmentation

Amalgam Tattoo

The single most common source of solitary or focal pigmentation in the oral mucosa is the 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. 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. If there is no radiographic evidence of amalgam, the lesion is not in proximity to any restored tooth, or the lesion suddenly appears, a biopsy is necessary. A typical differential diagnosis often includes melanotic macule, nevus, and melanoma.

Graphite Tattoos

Graphite tattoos are an unusual source of focal exogenous pigmentation. They are most commonly seen on the palate 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. Thus, a biopsy is often warranted.

Medicinal Metal-Induced Pigmentation

A variety of metallic compounds have been used medicinally for the treatment of various systemic diseases. With the exception of gold therapy (for rheumatoid arthritis), such medicaments are rarely or no longer in use. 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). 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 .

Generalized black pigmentation of the tongue has been attributed to the chewing of bismuth subsalicylate tablets, a commonly used antacid. This phenomenon is unlike black hairy tongue , which is associated with elongation of the filiform papillae, hyperkeratosis, and superficial colonization of the tongue by bacteria.

Heavy-Metal Pigmentation

Diffuse oral pigmentation may be associated with ingestion of heavy metals. It remains an occupational and health hazard for some individuals who work in certain industrial plants and for those who live in the environment in and around these types of facilities. Other relatively common environmental sources include paints, old plumbing, and seafood. 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 non–melanin-associated oral pigmentation.

Similar to tetracycline, minocycline can cause pigmentation of developing teeth. However, most patients are prescribed minocycline in early adulthood. When taken chronically, minocycline metabolites may become incorporated into the normal bone. Thus, whereas 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. There is no treatment necessary for minocycline-induced pigmentation. The discoloration often subsides within months after discontinuation of the medication. However, the bone pigment may persist for longer periods of time, if not indefinitely.

Reference: Burket's Oral Medicine, 12th edition ,2015