

6

PIGMENTED LESIONS OF THE ORAL MUCOSA

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▼ BLUE/PURPLE VASCULAR LESIONS

- Hemangioma
- Varix
- Angiosarcoma
- Kaposi's Sarcoma
- Hereditary Hemorrhagic Telangiectasia

▼ BROWN MELANOTIC LESIONS

- Ephelis and Oral Melanotic Macule
- Nevocellular Nevus and Blue Nevus
- Malignant Melanoma
- Drug-Induced Melanosis
- Physiologic Pigmentation
- Café au Lait Pigmentation
- Smoker's Melanosis
- Pigmented Lichen Planus
- Endocrinopathic Pigmentation
- HIV Oral Melanosis
- Peutz-Jeghers Syndrome

▼ BROWN HEME-ASSOCIATED LESIONS

- Ecchymosis
- Petechia
- Hemochromatosis

▼ GRAY/BLACK PIGMENTATIONS

- Amalgam Tattoo
- Graphite Tattoo
- Hairy Tongue
- Pigmentation Related to Heavy-Metal Ingestion

▼ SUMMARY

In the course of disease, the mucosal tissues can assume a variety of discolorations. Disease processes can culminate in the formation of pseudomembranes, in increased keratinization (white lesions), or in increased vascularization (red lesions). Blue, brown, and black discolorations constitute the pigmented lesions of the oral mucosa, and such color changes can be attributed to the deposition of either endogenous or exogenous pigments. Although there are many biochemical substances and metabolic products that are pigmented, only a few become deposited in the oral soft tissues although some accumulate in developing dentin during odontogenesis (eg, bilirubin pigment, porphyrins, and hemosiderin).

The endogenous pigmentation of the oral mucous membrane is most often explained by the presence of hemoglobin, hemosiderin, and melanin (Table 6-1). Hemoglobin imparts a red or blue appearance to the mucosa and represents pigmentation associated with vascular lesions; the coloration is rendered by circulating erythrocytes coursing through patent vessels. In contrast, hemosiderin appears brown and is deposited as a consequence of blood extravasation, which may occur as a consequence of trauma or a defect in hemostatic mechanisms. Hemochromatosis (generalized hemosiderin tissue deposition) may occur as a result of a variety of pathologic states.

Melanin is the pigment derivative of tyrosine and is synthesized in melanocytes, which subsequently transfer the melanin granules into adjacent basal cells to protect against the damaging effects of actinic irradiation. An increase in melanin pigment occurs when melanocytes oversynthesize or overpopulate. Overproduction (basilar melanosis) may be caused by a variety of mechanisms, including increased sun exposure, drugs, the pituitary adrenocorticotropic hormone (ACTH), and genetic factors (in association with certain syndromes). Melanocyte overpopulation occurs in benign nevi and in malignant melanomas.

TABLE 6-1 Endogenous Pigmentation in Oral Mucosal Disease

Pigment	Color	Disease Process
Hemoglobin	Blue, red, purple	Varix, hemangioma, Kaposi's sarcoma, angiosarcoma, hereditary hemorrhagic telangiectasia
Hemosiderin	Brown	Ecchymosis, petechia, thrombosed varix, hemorrhagic mucocele, hemochromatosis
Melanin	Brown, black or gray	Melanotic macule, nevus, melanoma, basilar melanosis with incontinence

The distribution of these various pigments in the oral mucosa is quite variable, ranging from a focal macule to broad diffuse tumefactions. The specific coloration, tint, location, multiplicity, size, and configuration of the pigmented lesion(s) are of diagnostic importance.

Exogenous pigments are usually traumatically deposited directly into the submucosa. However, some may be ingested, absorbed, and distributed hematogenously, to be precipitated in connective tissues, particularly in areas subject to chronic inflammation, such as the gingiva (Table 6-2). In the past, various metallic compounds were used medicinally, but currently, this therapy is rarely prescribed. For that reason, lesions attributable to heavy-metal therapy are no longer seen, with the exception of lesions caused by gold, which is still used systemically to treat arthritis. Lastly, exogenous pigment may be generated by chromogenic bacteria that colonize the keratinized surface of the tongue (hairy tongue).

In this chapter, the differential diagnosis of oral pigmentation is organized according to color, configuration, and distribution (Table 6-3).

▼ BLUE/PURPLE VASCULAR LESIONS

Hemangioma

Vascular lesions presenting as proliferations of vascular channels are tumorlike hamartomas when they arise in childhood; in adults (particularly elderly persons), benign vascular proliferations are generally varicosities. The hemangiomas of childhood are found on the skin, in the scalp, and within the connective tissue of mucous membranes. Approximately 85% of childhood-onset hemangiomas spontaneously regress after puberty.^{1,2}

TABLE 6-2 Exogenous Pigmentation of Oral Mucosa

Source	Color	Disease Process
Silver amalgam	Gray, black	Tattoo, iatrogenic trauma
Graphite	Gray, black	Tattoo, trauma
Lead, mercury, bismuth	Gray	Ingestion of paint or medicinals
Chromogenic bacteria	Black, brown, green	Superficial colonization

Depending on the depth of the vascular proliferation within the oral submucosa, the lesion may harbor vessels close to the overlying epithelium and appear reddish blue or, if a little deeper in the connective tissue, a deep blue. Angiomatous lesions occurring within muscle (so-called intramuscular hemangiomas) may fail to show any surface discoloration. Whereas most hemangiomas are raised and nodular, some may be flat, macular, and diffuse, particularly on the facial skin, where they are referred to as port-wine stains. The port-wine hemangioma of facial skin may concomitantly involve the oral mucosa, where the angioma may continue in macular fashion or become tumefactive. Thus, the clinical appearance of benign vascular hamartomas can be quite variable, ranging from a flat reddish blue macule to a nodular blue tumefaction.

Most oral hemangiomas are located on the tongue, where they are multinodular and bluish red. The multinodularity is racemose and diffuse. Tongue angiomas frequently extend deeply between the intrinsic muscles of the tongue. The lip mucosa is another common site for hemangiomas in children; these tumors are usually localized, blue, and raised. The aforementioned port-wine stain involves the facial skin and is flat and magenta in color. When there is a concurrent history of seizures, the condition represents encephalotrigeminal angiomatosis (Sturge-Weber syndrome). Vascular lesions occur in the brain as well as on the facial skin; skull radiography may disclose vessel wall calcifications that yield bilamellar radiopaque tracks referred to as "tram line" calcifications.

Hemodynamics in angiomas are perturbed, and stasis with thrombosis is commonly encountered. Most patent vascular lesions will blanch under pressure; indeed, placing a microscope glass slide over the pigmented area and adding pressure will often demonstrate this feature dramatically. Conversely, when intraluminal clots form, they become palpable and the lesion will usually not blanch. Thrombi in angiomas may eventually calcify, and such lesions will feel hard on palpation. The calcified nodules, or phleboliths, may be radiographically evident.

Microscopically, a hemangioma may comprise numerous large dilated vascular channels lined by endothelial cells without a muscular coat; such lesions are referred to as cavernous hemangiomas. Rarely, cavernous hemangiomas may show a media muscularis. Cellular- or capillary-type hemangiomas show significant endothelial proliferation, and the vascular lumina are very small. Both types may occur only in the subepithelial connective tissue or may extend deeply between muscle fibers (so-called intramuscular hemangiomas). This biologic feature is of clinical importance since intramuscular lesions may extend quite deeply and are more difficult to manage if treatment is required for functional or esthetic reasons.

Since many hemangiomas spontaneously involute during teenage years, treatment may be withheld in children. Patients who require treatment can undergo conventional surgery, laser surgery, or cryosurgery. Larger lesions that extend into muscles are more difficult to eradicate surgically, and sclerosing agents such as 1% sodium tetradecyl sulfate may be administered by intralesional injection. These agents result in postoperative pain, and the patient must be managed with a

TABLE 6-3 Clinical Classification of Oral Pigmentations

Color	Solitary		
	Focal	Diffuse	Multifocal
Blue/Purple	Varix Hemangioma	Hemangioma	Kaposi's sarcoma Hereditary hemorrhagic telangiectasia
Brown	Melanotic macule Nevus Melanoma	Ecchymosis Melanoma Drug-induced pigmentation Hairy tongue	Physiologic pigment Neurofibromatosis Hemochromatosis Lichen planus Addison's disease Drug-induced pigmentation Peutz-Jeghers syndrome Petechia
Gray/Black	Amalgam tattoo Graphite tattoo Nevus Melanoma	Amalgam tattoo Melanoma Hairy tongue	Heavy-metal ingestion pigmentation

moderate-level analgesic such as oxycodone or aspirin with codeine. Cutaneous port-wine stains can be treated by subcutaneous tattooing or by argon laser (see also Chapter 5, "Red and White Lesions of the Oral Mucosa").

Varix

Pathologic dilatations of veins or venules are varices or varicosities, and the chief site of such involvement in the oral tissues is the ventral tongue.³⁻⁵ Varicosities become progressively prominent with age; thus, lingual varicosities are encountered in elderly individuals. Lingual varicosities appear as tortuous serpentine blue, red, and purple elevations that course over the ventrolateral surface of the tongue, with extension anteriorly. Even though they may be quite striking in some patients, they represent a degenerative change in the adventitia of the venous wall and are of no clinical consequence. They are painless and are not subject to rupture and hemorrhage.

A focal dilatation of a vein or group of venules is known as a varix (Figure 6-1). These lesions also tend to occur in elderly persons and are primarily located on the lower lip, appearing as a focal raised pigmentation. They may be blue, red, or purple, and the surface mucosa is often lobulated or nodular. Whereas some can be blanched, others are not, due to the formation of intravascular thrombi. The varix resembles the hemangioma both clinically and histologically, yet it is distinguished by two features: (1) the patient's age at its onset and (2) its etiology. As previously mentioned, a hemangioma is usually congenital and has a tendency to spontaneously regress whereas a varix arises in older individuals and, once formed, does not regress. Alternatively, a varix has a finite growth potential; once a varix has formed, further enlargement is uncommon. Whereas hemangiomas are vascular hamartomas of unknown etiology, the varix represents a venous dilatation that may evolve from trauma such as lip or cheek biting. The traumatic event probably damages and weakens the vascular wall and culminates in dilation.

Microscopically, varices resemble cavernous hemangiomas. They may be represented by a single dilated vascular channel lined by endothelial cells lacking a muscular coat, or they may comprise numerous tortuous channels. Most show intraluminal thrombosis, and the thrombi show evidence of organization and canalization.

Varices of the lips and buccal mucosa may be unsightly and may interfere with mastication. The lesion can be excised or removed by other surgical methods, including electro-surgery and cryosurgery. Intralesional 1% sodium tetradecyl sulfate injection is effective as well, yet it is usually more painful than simple excision. This sclerosing agent should be injected directly into the lumina with a tuberculin syringe (depositing .05 to 0.15 mL/cm³).



FIGURE 6-1 Varix of the mucosal surface of the upper lip. The lesion appears as a blue nodule.

Angiosarcoma

Malignant vascular neoplasms, distinct from Kaposi's sarcoma, are not related to human immunodeficiency virus (HIV) and can arise anywhere in the body. Although the oral cavity is an extremely rare site for such tumors, those that occur will (if superficial) appear red, blue, or purple. They are rapidly proliferative and therefore present as nodular tumors. Angiosarcomas can arise from blood or lymph vessel endothelial cells or from pericytic cells of the vasculature. They have a poor prognosis and are treated by radical excision.

Kaposi's Sarcoma

A tumor of putative vascular origin, Kaposi's sarcoma (KS)^{6,7} was rarely encountered in the oral cavity prior to 1983. The classic form generally appeared in two distinct clinical settings: (1) elderly men (in the oral mucosa and on the skin of the lower extremities) and (2) children in equatorial Africa (in lymph nodes). The former is the classic form as originally described by Moritz Kaposi and is an indolent tumor with slowly progressive growth. Although classified as a malignancy, classic Kaposi's sarcoma does not show a great tendency for metastasis and probably has never caused the death of a patient. The oral and cutaneous tumors are considered to be of multifocal origin rather than metastases from a distant primary tumor. The oral tumors are red, blue, and purple, and the hard palate is the favored site; the skin tumors tend to localize in the dorsal aspect of the feet and great toe. The African form is characterized by lymph node enlargement and can progressively involve many node groups, being an aggressive and potentially lethal disease. Since it does not present with oral lesions, this form of KS is not discussed further.

After 1983, oral KS became much more prevalent, being the most common neoplastic process to accompany HIV infection. Indeed, the mere presence of KS lesions in HIV-seropositive subjects constitutes a diagnostic sign for acquired immunodeficiency syndrome (AIDS). The cutaneous lesions begin as red macules and enlarge to become blue, purple, and ultimately brown nodular tumefactions. The lower extremity shows no predilection over other cutaneous sites, and lesions may appear on the arms, face, scalp, or trunk. The oral lesions continue to show a predilection for the posterior hard palate, and they also begin as flat red macules of variable size and irregular configuration (Figure 6-2). Although they may appear as a focal lesion, typical oral KS lesions are multifocal, with numerous isolated and coalescing plaques. Eventually, these lesions increase in size to become nodular growths, and some will involve the entire palate, protruding below the plane of occlusion. The facial gingiva is the second most-favored oral site; in the early stages, the differential diagnosis includes pyogenic granuloma and giant cell granuloma. It is uncommon for AIDS-associated KS to arise in the buccal mucosa, tongue, and lips.

Laboratory studies have disclosed that the cell population is not transplantable into athymic nude mice as with most malignant tumors; rather, the human neoplastic cells secrete a variety of cytokines that induce KS lesions of mouse origin in



FIGURE 6-2 Multifocal reddish purple macules of the posterior palate, representing early-stage Kaposi's sarcoma in an HIV-seropositive patient.

the transplant recipient animals. Thus, even in the context of HIV infection, KS should be considered a low-grade sarcoma.

Microscopically, KS lesions show proliferating spindle cells with mild pleomorphism associated with plump endothelial cells oriented about small lumina. Typically, extravasation of erythrocytes is a prominent feature, and hemosiderin granules are commonly encountered. The more hemosiderin present, the browner the tumor will appear clinically. Overall, the pattern of growth in larger lesions is multinodular.

The early plaque or macular stage lesions are painless and do not require treatment. Nodular lesions may become unsightly and interfere with mastication; in this situation, therapy may be desirable. Surgical excision is not usually attended by severe hemorrhage, but electrocautery is recommended, either as a primary form of surgery or as a coagulative hemostatic adjunct to conventional excision. Intralesional injection of 1% sodium tetradecyl sulfate will result in necrosis of the tumefactions; however it is painful, and the patient should be prescribed a moderate-strength analgesic. Intralesional 1% vinblastine sulfate is also beneficial; because it is not a sclerosing agent, it is not associated with significant postinjection pain. Multiple biweekly injections of vinblastine can be given to eradicate the tumors.

Hereditary Hemorrhagic Telangiectasia

Characterized by multiple round or oval purple papules measuring less than 0.5 cm in diameter, hereditary hemorrhagic telangiectasia (HHT) is a genetically transmitted disease, inherited as an autosomal dominant trait^{8,9} (Figure 6-3). The lesions represent multiple microaneurysms, owing to a weakening defect in the adventitial coat of venules. The lesions are so distinct as to be pathognomonic. There may be more than 100 such purple papules on the vermilion and mucosal surfaces of the lips as well as on the tongue and buccal mucosa. The facial skin and neck are also involved. Examination of the



FIGURE 6-3 Multiple small purple papules of hereditary hemorrhagic telangiectasia.

nasal mucosa will reveal similar lesions, and a past history of epistaxis may be a complaint. Indeed, deaths have been reported in HHT attributable to epistaxis. The lesions may be seen during infancy but are usually more prominent in adults.

Although the differential diagnosis should include petechial hemorrhages with an attending platelet disorder, petechiae are macular rather than papular and (as foci of erythrocyte extravasation with breakdown to hemosiderin) red or brown rather than purple. Furthermore, HHT is genetic and should have been noticed in other family members. If any doubt exists, platelet studies can be ordered to rule out a blood dyscrasia.

Microscopically, HHT shows numerous dilated vascular channels with some degree of erythrocyte extravasation around the dilated vessels.

There is no treatment for the disease. If the patient would like to have the telangiectatic areas removed for cosmetic reasons, the papules can be cauterized by electrocautery in a staged series of procedures using local anesthesia.

▼ BROWN MELANOTIC LESIONS

Ephelis and Oral Melanotic Macule

The common cutaneous freckle, or ephelis,^{10,11} represents an increase in melanin pigment synthesis by basal-layer melanocytes, without an increase in the number of melanocytes. On the skin, this increased melanogenesis can be attributed to actinic exposure. Ephelides can therefore be encountered on the vermilion border of the lips, with the lower lip being the favored site since it tends to receive more solar exposure than the upper lip (Figure 6-4). The lesion is macular and ranges from being quite small to over a centimeter in diameter. Some patients report a prior episode of trauma to the area. Lip ephelides are asymptomatic and occur equally in men and women. They are rarely seen in children.

The intraoral counterpart to the ephelis is the oral melanotic macule.^{10,11} These lesions are oval or irregular in outline, are brown or even black, and tend to occur on the gingiva, palate, and buccal mucosa. Once they reach a certain size, they do not tend to enlarge further (Figure 6-5). The differential diagnosis includes nevus, early superficial spreading melanoma,



FIGURE 6-4 Ephelis of the lower lip, appearing as a brown macule.

amalgam tattoo, and focal ecchymosis. If such pigmented lesions are present after a 2-week period, hemosiderin pigment associated with ecchymosis can be ruled out, and a biopsy specimen should be obtained to secure a definitive diagnosis.

Microscopically, a normal epithelial layer is seen, and the basal cells contain numerous melanin pigment granules without proliferation of melanocytes. Melanin incontinence into the submucosa is commonly encountered. Rarely, melanin-containing dendritic cells are seen to extend high into a thickened spinous layer. Lesions of this nature are diagnosed as melanoacanthoma.

The oral melanotic macule is innocuous, does not represent a melanocytic proliferation, and does not predispose to melanoma. Once it is removed, no further surgery is required.

Nevocellular Nevus and Blue Nevus

Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi are due to benign proliferations of melanocytes.^{12,13} There are two major types, based on histology, and these two types tend to show differences clinically as well, particularly in tint and



FIGURE 6-5 Oral focal melanotic macule of the gingiva. This lesion is the oral counterpart of the ephelis.

coloration. Nevocellular nevi arise from basal-layer melanocytes early in life. In the evolutionary stages, the nevus cells maintain their localization to the basal layer, residing at the junction of the epithelium and the basement membrane and underlying connective tissue. Since proliferation is minimal, these nevi are macular and are classified as junctional nevi. In general, they are flat and brown and have a regular round or oval outline. With time, the melanocytes form clusters at the epitheliomesenchymal junction and begin to proliferate down into the connective tissue although they do not invade vessels or lymphatics. Such nevi assume a dome-shaped appearance (since more cells have accumulated) and are referred to as compound nevi. In late puberty, the melanocytes (now known as nevus cells) in compound nevi lose their continuity with the surface epithelium, and the cells become localized to the deeper connective tissues. They are then termed intradermal nevi when on skin and intramucosal nevi when in the mouth. On the skin, they are elevated brown nodules that often have hair protruding from them. Thus, in adults, junctional nevi should not exist. When a nevus shows microscopic evidence of junctional activity, premelanomatous change should be suspected.

The second type of nevus, not derived from basal-layer melanocytes, is the blue nevus. The blue nevus is blue on the skin because the melanocytic cells reside deep in the connective tissue and because the overlying vessels dampen the brown coloration of melanin, yielding a blue tint. The melanocytes of a blue nevus differ morphologically from those of a nevocellular nevus by being more spindle shaped while containing significant amounts of pigment. Such cells are neuroectodermally derived yet are believed to represent cells that failed to reach the epithelium. A rare cellular form of blue nevus also exists, and neither the ordinary nor the cellular form has the potential to become a melanoma.

In the oral mucosa, both nevocellular and blue nevi tend to be brown and may be macular or nodular (Figure 6-6). They may be seen at any age and are found most frequently on the palate and gingiva but may also be encountered in the buccal mucosa and on the lips. Once they reach a given size, their growth ceases, and the lesions remain static. Biopsy is necessary for diagnostic confirmation since the clinical diagnosis includes many other focal pigmentations, such as melanotic macule, melanoma, and amalgam tattoo. Simple excision is the treatment of choice.

Malignant Melanoma

On the facial skin, the malar region is a common site for melanoma^{14,15} because this area of the face is subject to significant solar exposure. In fact, cutaneous melanoma is most common among white populations that live in sunbelt regions of the world. Facial cutaneous melanomas may appear macular or nodular, and the coloration can be quite varied, ranging from brown to black to blue, with zones of depigmentation. An important difference is that unlike common nevi that exhibit smooth outlines, melanomas show jagged irregular margins. These lesions are more common among elderly



FIGURE 6-6 Nevocellular nevus of the palate. The nevus is raised and gray brown.

patients and show a male predilection. The term “lentigo maligna melanoma” or “Hutchinson’s freckle” has been applied to these facial skin lesions that exhibit atypical melanocytic hyperplasia or melanoma in situ. The melanocytic tumor cells spread laterally and therefore superficially; this pattern has been referred to as a radial growth phase. These lesions have a good prognosis if they are detected and treated before the appearance of nodular lesions, which indicates invasion into the deeper connective tissue (ie, a vertical growth phase). The level of invasion is determined by the Breslow method, by which millimeter depths of invasion are measured (depth correlating with prognosis).

Mucosal melanomas are extremely rare. Their prevalence appears to be higher among Japanese people than among other populations. Melanomas arising in the oral mucosa tend to occur on the anterior labial gingiva and the anterior aspect of the hard palate. In the early stages, oral melanomas are macular brown and black plaques with an irregular outline. They may be focal or diffuse and mosaic, and the differential diagnosis should include nevi, melanotic macules, and amalgam tattoo. Any pigmented oral lesion with an irregular margin or with a history of growth should be suspect, and a biopsy of it should be performed without delay. Eventually, melanomas become more diffuse, nodular, and tumefactive, with foci of hyper- and hypopigmentation.

Microscopically, oral mucosal melanomas (like cutaneous melanomas) may exhibit a radial or a vertical pattern of growth. The radial or superficial spreading pattern is seen in macular lesions; clusters and theques of nevus cells showing nuclear atypia and hyperchromatism proliferate within the basal cell junctional region of the epithelium, and many of the neoplastic cells invade the overlying epithelium as well as the submucosa. Once vertical growth into the connective tissue progresses, the lesions can become clinically tumefactive. The vertical growth phase connotes a poor prognosis because of the likelihood of lymphatic and hematogenous metastasis, and

grading systems are based on the quantitation of vertical penetration of the submucosa. The Breslow classification has not been applied to oral melanomas, principally because they are generally quite advanced and invasive when biopsy specimens are initially obtained.

Excision with wide margins is the treatment of choice; once nodularity has evolved, however, the lesion has probably already metastasized. Computed tomography and magnetic resonance imaging studies should be undertaken to explore regional metastases to the submandibular and cervical lymph nodes. A variety of chemo- and immunotherapeutic strategies can be used once metastases have been identified.

Drug-Induced Melanosis

A variety of drugs can induce oral mucosal pigmentation.^{16–18} These pigmentations can be large yet localized, usually to the hard palate, or they can be multifocal, throughout the mouth. In either case, the lesions are flat and without any evidence of nodularity or swelling. The chief drugs implicated are the quinoline, hydroxyquinoline, and amodiaquine antimalarials. These medications have also been used in the treatment of autoimmune diseases. Minocycline, used in the treatment of acne, can also produce oral pigmentation. The pigment is not confined to oral mucosa and is also encountered in the nail bed and on the skin. Last, oral contraceptives and pregnancy are occasionally associated with hyperpigmentation of the facial skin, particularly in the periorbital and perioral regions (Figure 6-7). This condition is referred to as melasma or chloasma. Endocrine disease should be excluded by appropriate laboratory studies when oral or facial nonphysiologic melanosis is encountered.

The cause is unknown, and the pigment may remain for quite some time after withdrawal of the incriminated drug. Microscopically, basilar melanosis without melanocytic proliferation is observed, and melanin incontinence is commonly seen.

Physiologic Pigmentation

Black people, Asians, and dark-skinned Caucasians frequently show diffuse melanosis of the facial gingiva.^{19,20} In addition, the lingual gingiva and tongue may exhibit multiple, diffuse, and reticulated brown macules. Although other causes of hyperpigmentation are possible, racial pigmentation, representing basilar melanosis, evolves in childhood and usually does not arise *de novo* in the adult. Therefore, any multifocal or diffuse pigmentation of recent onset should be investigated further to rule out endocrinopathic disease.

Café au Lait Pigmentation

In neurofibromatosis, an autosomal dominant inherited disease, both nodular and diffuse pendulous neurofibromas occur on the skin and (rarely) in the oral cavity. A concomitant finding is the presence of “café au lait” pigmentation.^{21,22} As the term implies, these lesions have the color of coffee with cream and vary from small ephelis-like macules to broad diffuse lesions. They tend to appear in late childhood and can be multiple; many overlie the neurofibromatous swellings on the skin.



FIGURE 6-7 Perioral melanosis (melasma) in a young woman taking birth control pills.

Rarely, oral pigmentation is encountered. Importantly, the patient will manifest cutaneous signs as the predominant feature of the disease.

Microscopically, café au lait spots represent basilar melanosis without melanocyte proliferation.

Smoker's Melanosis

Diffuse macular melanosis of the buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers^{23,24} (Figure 6-8). Although no cause-and-effect relationship has been proven and although most smokers (even heavy smokers) usually fail to show such changes, those who do are said to exhibit smoker's melanosis. Thus, it is probable that in certain individuals, melanogenesis is stimulated by tobacco smoke products. Indeed, among dark-skinned individuals who normally exhibit physiologic



FIGURE 6-8 Diffuse melanosis of the buccal mucosa in a cigarette smoker (smoker's melanosis).

pigmentation, studies have disclosed that tobacco use stimulates an increase in oral pigmentation. The lesions are brown, flat, and irregular; some are even geographic or maplike in configuration. Histologically, basilar melanosis with melanin incontinence is observed, and the lesions have no premalignant potential.

Pigmented Lichen Planus

Lichen planus (discussed in detail in Chapter 5) is a disease that generally presents as a white lesion, with variants showing red and desquamative lesions. Rarely, erosive lichen planus can be associated with diffuse melanosis. In such instances, the classic lesions of lichen planus remain recognizable, usually in the buccal mucosa and vestibule.²⁵ Reticulated white patches, with or without a red erosive component, overlie or are flanked by diffuse brown macular foci (Figure 6-9). This increase in melanogenesis may be stimulated by the infiltrate into the basal layer of T lymphocytes that contribute to basal cell degeneration. Histologically, the usual features of lichen planus are observed, along with basilar melanosis and melanin incontinence.

Endocrinopathic Pigmentation

Bronzing of the skin and patchy melanosis of the oral mucosa are signs of Addison's disease and pituitary-based Cushing's syndrome.²⁶ In both of these endocrine disorders, the cause of hyperpigmentation is oversecretion of ACTH, a hormone with melanocyte-stimulating properties. In Addison's disease, adrenocortical insufficiency evolves as a consequence of granulomatous infection of the cortex or autoimmune cortical destruction. As steroid hormones decrease, the feedback loop is stimulated with excess secretion of ACTH by the neurohypophysis. With a decrease in mineralocorticoids and glucocorticoids, the patient develops hypotension and hypoglycemia, respectively.

In Cushing's syndrome, adrenocortical hyperactivity is observed, and if such activity is caused by a cortical secretory adenoma or cortical hyperplasia of adrenal origin, ACTH secretion will be shut down. Alternatively, if the hypercorticism is the consequence of a pituitary ACTH-secreting tumor that secondarily induces an adrenal hypersecretion, then melanocyte-stimulating effects may evolve. Patients with Cushing's syndrome may be hypertensive and hyperglycemic and may show facial edema ("moon face").

In both cases, the skin may appear tanned, and the gingiva, palate, and buccal mucosa may be blotchy. These changes in pigmentation are due to an accumulation of melanin granules as a consequence of increased hormone-dependent melanogenesis. Endocrinopathic disease should be suspected whenever oral melanotic pigmentation is accompanied by cutaneous bronzing. Serum steroid and ACTH determinations will aid the diagnosis, and the pigment will disappear once appropriate therapy for the endocrine problem is initiated.

HIV Oral Melanosis

HIV-seropositive patients with opportunistic infections may have adrenocortical involvement by a variety of parasites,



FIGURE 6-9 White speckled foci, plaques, and striae, seen overlying diffuse brown melanosis in pigmented lichen planus.

which manifests signs and symptoms of Addison's disease.²⁷⁻²⁹ Such patients undergo progressive hyperpigmentation of the skin, nails, and mucous membranes. In actuality, most HIV-seropositive patients presenting with diffuse multifocal macular brown pigmentations of the buccal mucosa show no features of adrenocortical disease. The oral pigmentation cannot be attributed to medications in this population because cases have been recorded in individuals who have not received any medications that could be so implicated. Thus, the etiology remains undetermined. As mentioned, the pigmentation resembles most of the other diffuse macular pigmentations discussed so far; the buccal mucosa is the most frequently affected site, but the gingiva, palate, and tongue may also be involved.

Like all diffuse melanoses, HIV-associated pigmentation is microscopically characterized by basilar melanin pigment, with incontinence into the underlying submucosa.

Peutz-Jeghers Syndrome

In Peutz-Jeghers syndrome (discussed more fully in Chapter 7), oral pigmentation is distinctive and is usually pathognomonic.^{30,31} Multiple focal melanotic brown macules are concentrated about the lips while the remaining facial skin is less strikingly involved. The macules appear as freckles or ephelides, usually measuring < 0.5 cm in diameter (Figure 6-10). Similar lesions may occur on the anterior tongue, buccal mucosa, and mucosal surface of the lips. Ephelides are also seen on the fingers and hands.

Lesions on the perioral areas are essentially pathognomonic although in individuals who have diffuse cutaneous ephelides (such as red-haired light-complected individuals), an erroneous diagnosis could be made.

Histologically, these lesions show basilar melanogenesis without melanocytic proliferation.



FIGURE 6-10 Multiple labial brown melanotic ephelides, characteristic of Peutz-Jeghers syndrome.

▼ BROWN HEME-ASSOCIATED LESIONS

Ecchymosis

Traumatic ecchymosis^{32,33} is common on the lips and face yet is uncommon in the oral mucosa. 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 (Figure 6-11). The differential diagnosis must include other focal pigmented lesions. If the patient recalls an episode of trauma, however, the lesion should be observed for 2 weeks, by which time it should have resolved if it represents a focus of ecchymosis.

When multiple brown macules or swellings are observed and ecchymosis is included in the differential diagnosis, a hemorrhagic diathesis should be considered. Certainly, patients taking anticoagulant drugs may present with oral ecchymosis, particularly on the cheek or tongue, either of which can be traumatized while chewing. Coagulopathic ecchymosis of the skin and oral mucosa may also be encountered in hereditary coagulopathic disorders and in chronic liver failure. A coagulation panel including prothrombin time and partial thromboplastin time should be ordered in instances of unprovoked ecchymoses to explore defects in the extrinsic and intrinsic pathways, respectively. The clotting time will also be prolonged.

Petechia

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 secondary to platelet deficiencies or aggregation disorders are usually not limited to the oral mucosa but occur concomitantly on skin.³³ Autoimmune or idiopathic thrombocytopenic purpura (ITP), HIV-related ITP, disorders of platelet aggregation, aspirin toxicity, myelophthistic lesions, and myelosuppressive chemotherapy all will lead to purpura, with petechiae being the major lesions. Alternatively, most oral petechiae are not associated

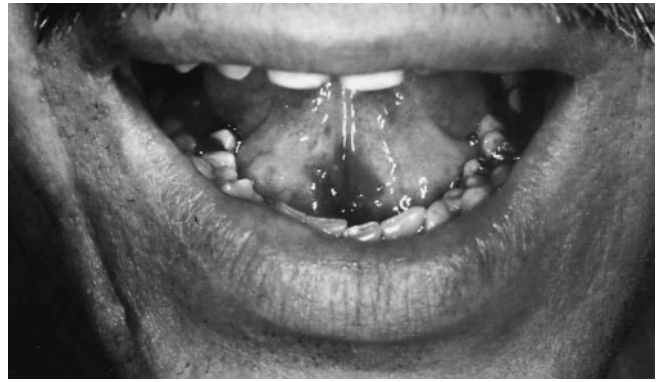


FIGURE 6-11 Ecchymosis in the floor of the mouth, secondary to trauma.

with thrombocytopenia or thrombocytopathia; rather, they are usually confined to the soft palate, where 10 to 30 petechial lesions may be seen and can be attributed to suction. Excessive suction of the soft palate against the posterior tongue is self-inflicted by many patients who have a pruritic palate at the onset of a viral or an allergic pharyngitis; they simply “click” their palate. Palatal petechiae can also appear following fellatio. When traumatic or suction petechiae are suspected, the patient should be instructed to cease whatever activity may be contributing to the presence of the lesions. By 2 weeks, the lesions should have disappeared. Failure to do so should arouse suspicion of a hemorrhagic diathesis, and a platelet count and platelet aggregation studies must be ordered.

Hemochromatosis

The deposition of hemosiderin pigment in multiple organs and tissues occurs in a primary heritable disease with a prominent male predilection or may evolve secondary to a variety of diseases and conditions, including chronic anemia, porphyria, cirrhosis, postcaval shunt for portal hypertension, and excess intake of iron.^{34,35} The oral mucosal lesions of hemochromatosis are brown to gray diffuse macules that tend to occur in the palate and gingiva. Although these pigmentations are predominantly the result of iron deposition in the submucosa, basilar melanosis is also observed microscopically and may be the result of a secondary Addisonian complication, whereby hemosiderin deposition within the adrenal cortex may lead to hypocorticism and ACTH hypersecretion.

When hemochromatosis is suspected, an oral biopsy may be helpful in the diagnosis. The tissue can be stained for iron by using Prussian blue; iron levels will be elevated in the serum if hemochromatosis is present. Since the condition can be the consequence of a variety of disease states, medical referral is recommended.

▼ GRAY/BLACK PIGMENTATIONS

Amalgam Tattoo

By far, the most common source of solitary or focal pigmentation in the oral mucosa is the amalgam tattoo.³⁶ The

lesions are macular and bluish gray or even black and are usually seen in the buccal mucosa, gingiva, or palate (Figure 6-12). Importantly, they are found in the vicinity of teeth with large amalgam restorations or crowned teeth that probably had amalgams removed when the teeth were being prepared for the fabrication of the crown. Such lesions are the consequence of an iatrogenic mishap whereby the dentist's bur, loaded with small amalgam particles that accumulate during the removal of amalgam, accidentally veers into the adjacent mucosa and traumatically introduces the metal flecks. The metallic particles are quite fine, but in some instances (when large enough), they are identifiable on radiographs of the area. Amalgam fragments can also be deposited in oral tissue during multiple tooth extractions. Metal particles may fall unnoticed into extraction sockets, and during the healing phase, the amalgam becomes entombed within the connective tissue while re-epithelialization occurs. In these instances, radiography almost always demonstrates the presence of the metal.

Microscopically, amalgam tattoos show a fine brown granular stippling of reticulum fibers, particularly around vessel walls, and in many instances, large chunks of black metallic particles can be seen. A giant cell reaction is uncommon; however, a mononuclear inflammatory cell infiltrate is often noted.

Since amalgam tattoos are innocuous, their removal is not required, particularly when they can be documented radiographically. Alternatively, biopsy is recommended when a gray pigmented lesion suddenly appears or when such a lesion arises distant from any restored teeth; the differential diagnosis must include nevi and melanoma in such instances.

Graphite Tattoo

Graphite tattoos tend to occur on the palate and represent traumatic implantation from a lead pencil.³⁷ The lesions are usually macular, focal, and gray or black. Since the traumatic event usually occurred in the classroom during grade school,

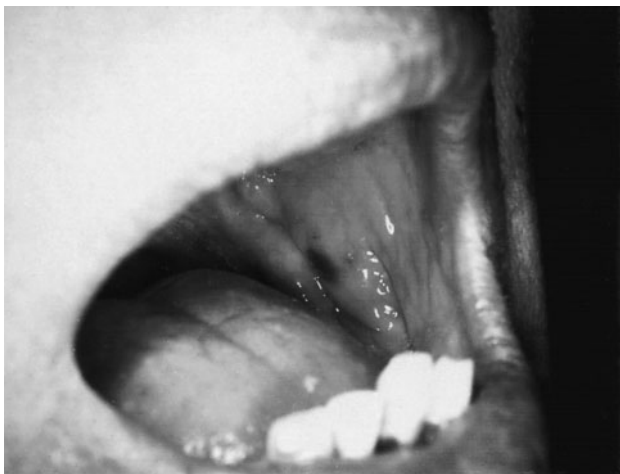


FIGURE 6-12 Amalgam tattoo of the buccal mucosa. The lesion appears gray black.

many patients may not recall the injury. Microscopically, graphite resembles amalgam in tissue although special stains can segregate the two.

Hairy Tongue

Hairy tongue is a relatively common condition of unknown etiology.^{38,39} The lesion involves the dorsum, particularly the middle and posterior one-third. Rarely are children affected. The papillae are elongated, sometimes markedly so, and have the appearance of hairs. The hyperplastic papillae then become pigmented by the colonization of chromogenic bacteria, which can impart a variety of colors ranging from green to brown to black. Various foods, particularly coffee and tea, probably contribute to the diffuse coloration.

Microscopically, the filiform papillae are extremely elongated and hyperplastic with keratosis. External colonization of the papillae by basophilic microbial colonies is a prominent feature. Otherwise, there are no pathologic findings in the remaining epithelium or in the connective tissue. The condition is so classic in its clinical presentation that biopsy is not required, and a clinical diagnosis is appropriate.

Treatment consists of having the patient brush the tongue and avoid tea and coffee for a few weeks. Since the cause is undetermined, the condition can recur.

Pigmentation Related to Heavy-Metal Ingestion

Many years ago, a variety of metallic compounds were used medicinally, but such medicaments are either no longer or rarely still in use. Ingestion of heavy metals or metal salts can be an occupational hazard since many metals are used in industry and in paints. Lead, mercury, and bismuth have all been shown to be deposited in oral tissue if ingested in sufficient quantities or over a long course of time.^{40,41} These ingested pigments tend to extravasate from vessels in foci of increased capillary permeability such as inflamed tissues. Thus, in the oral cavity, the pigmentation is usually found along the free marginal gingiva, where it dramatically outlines the gingival cuff, resembling eyeliner. This metallic line has a gray to black appearance. The heavy metals may be associated with systemic symptoms of toxicity, including behavioral changes, neurologic disorders, and intestinal pain. This condition is now rarely seen.

▼ SUMMARY

Oral pigmentations may be focal, diffuse, or multifocal. They may be blue, purple, brown, gray, or black. They may be flat or tumefactive. Importantly, some are harbingers of internal disease; some are localized harmless accumulations of melanin, hemosiderin, or exogenous metal; and some can be highly lethal. The differential diagnosis can be lengthy, particularly when the pigmentation is macular and diffuse or multifocal. Although biopsy is a helpful aid to diagnosis for localized lesions, the more diffuse lesions will require a thorough history and laboratory studies in order to arrive at a definitive diagnosis.

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