



Oral Pigmented Disorders: A Review

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[Review Article](#)

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ABSTRACT

Oral pigmentations are common conditions which involve any part of the oral cavity. Color changes in oral mucosa can serve as a marker of local or systemic changes in our body. The pigmentations can be endogenous or exogenous, benign or malignant, physiological or pathological. Their diverse clinical picture and its presence anywhere around the oral cavity make it difficult to differentiate. As dentists are the first to identify any of the oral changes, the knowledge of aetiology, clinical features, and treatment is considered important for prompt diagnosis and treatment. This review discusses various pigmentations of the oral cavity.

Keywords: Melanin, Endogenous, Exogenous, Oral mucosa.

Introduction

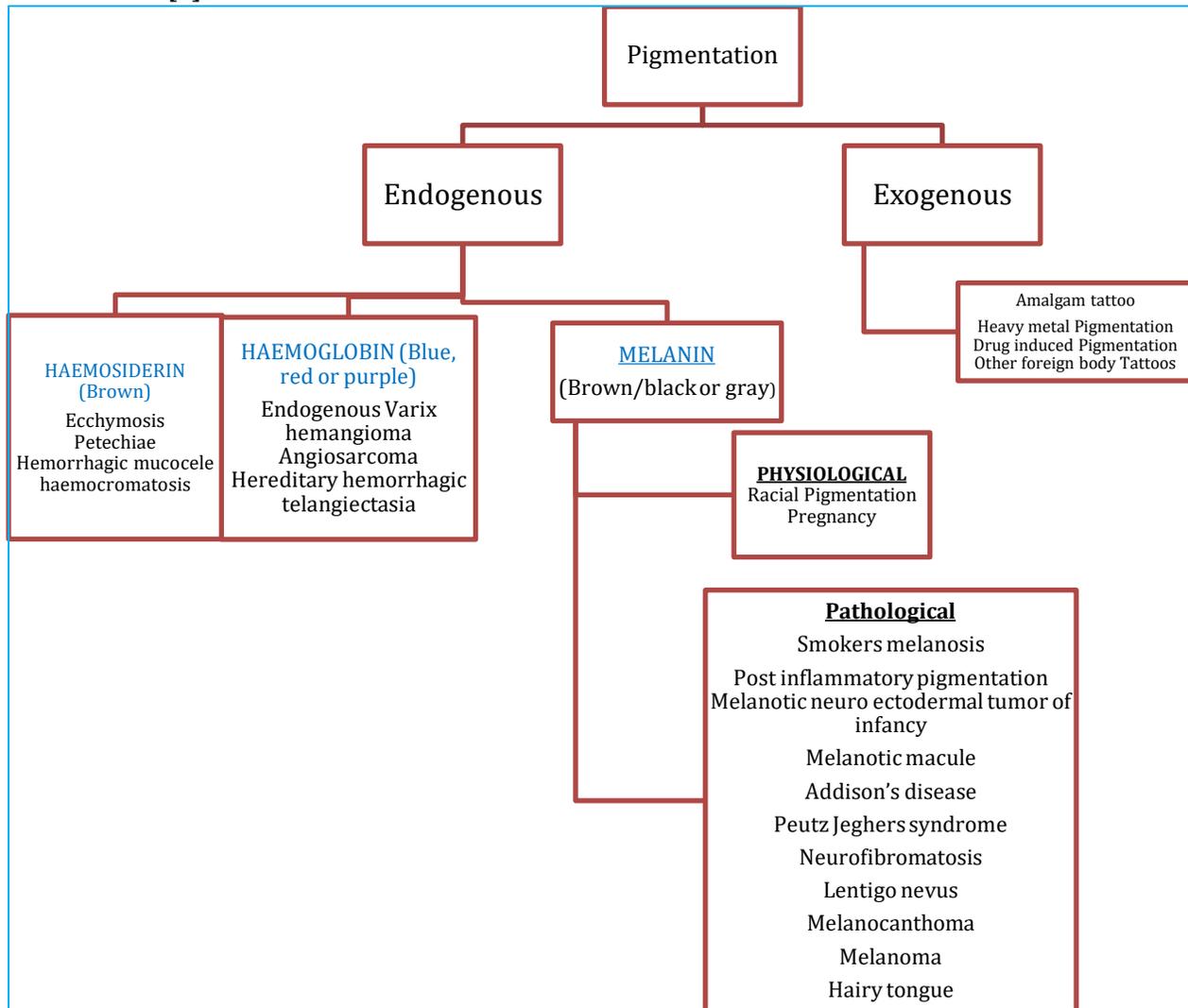
Pigmentations of Oral Cavity

Pigmentations are commonly found in the mouth. It represents a variety of clinical entities, ranging from physiologic changes (such as racial pigmentation) to manifestations of systemic illnesses (like Addison's disease) and malignant neoplasms (e.g., melanoma and Kaposi's sarcoma). It's a requirement that proper understanding of the cause of mucosal pigmentations and evaluation of the patient is essential.¹

Pigmented lesions of the oral cavity are due to the augmentation of melanin production and increased number of melanocytes (melanocytosis) or it could originate from the deposition of accidentally introduced exogenous materials.²

The colour of oral pigmentation varies depending on the quantity, depth, and location of pigments. Colour varies from brown (on the surface) to black or blue (deeper).³ It can be due to exogenous or endogenous in origin. Exogenous is due to implantation of a foreign body to the oral mucosa and endogenous due to pigments like melanin, haemoglobin, hemosiderin, and carotene.⁴

Classification [5]



Endogenous

There are four pigments which contribute to the normal color of the skin and mucosa. Melanin, Carotenoids, Reduced HBO, and oxygenated Hb. Among these four pigments, melanin plays a major role.²

Melanocytes, the melanin-producing cells, derived from neural crest cells, migrate to the epithelium and resides among the basal cells. They have dendritic processes that extend to the keratinocytes.^{1,6,7}

Pigment production depends on the light, hormones, and genetic constitution. Due to the low level of pigment production, they go unnoticed in the oral mucosa even though there is a numerous number of melanocytes.¹

In histopathology, they appear clear due to their non-staining cytoplasm. Based on the production they may be responsible for different entities ranging from physiologic pigmentation to malignant neoplasia.¹



Nevus cell is responsible for pigmented nevi. These cells are morphologically different from melanocytes but they possess the same enzyme, tyrosinase which converts tyrosine to melanin in melanosome organelle.⁸

Physiologic Racial

It is a diffuse bilateral pigmentation, with no alteration in the normal architecture and seen in any age group without any gender predilection. Physiologic pigmentation is mainly due to increased melanin production rather than an increase in the number of melanocytes. It is found to be common in Africans, Asians, and the Mediterranean population. The degree of intraoral pigmentation may not correspond to the degree of cutaneous coloration. Pigmentation may be found in any location with gingiva being the most commonly affected intraoral tissue. The color of pigmentation can vary from light brown to black.^{1,9} Histopathologically melanin is found in surrounding basal keratinocytes and subjacent connective tissue macrophages.¹

Physiologic pigmentation is clinically diagnosed easily, but if any atypical clinical feature present, a biopsy can be used for justification purposes. As it is asymptomatic, no treatment is required.¹

Pregnancy

Pregnancy and aging can alter the body and lead to skin dysfunction. Skin becomes more sensitive to Melanocyte-Stimulating hormone (MSH) and tyrosinase and produces hyperpigmentation. Melasma - the mask of pregnancy is commonly seen post-pregnancy. Multiple melanotic macules are visualized on the oral mucosa and facial skin, usually on the upper lip, cheeks, and forehead.²

Pathological

Smoking Associated Melanosis/ Smoker's Melanosis

An abnormal melanin pigmentation of the oral mucosa, seen along with cigarette smoking. Pathogenesis is related to components in tobacco smoke that stimulates melanocytes.¹ Female sex hormones are believed to be modifiers of this pigmentation, hence has their predominance in women.^{1,10} Discrete or coalescing multiple brown macules are commonly located in the attached labial mandibular gingiva. Pigmentation of the palate and buccal mucosa has also been associated with pipe smoking.¹¹ Pigmentation in children can be due to passive smoking.¹²

Smoking associated with melanosis is due to an increase in melanin production by melanocytes and its deposition within the basal cell layer and lamina propria, and microscopic appearance holds similarities to physiologic pigmentation or melanotic macules.¹

Generally, with the cessation of smoking improvement is expected over the course of months to years, but if the pigmentation is in an unusual location or if ulcerations and elevations present, a biopsy is necessary.¹³

Post-inflammatory Pigmentation

Inflammation associated hyperpigmentation develops commonly in dark-complexioned individuals. This is found in patients with clinical evidence of lichenoid inflammation within the oral cavity. The pigment may be brown in colour and focal, diffuse, or patchy, found regional to the lichenoid reaction. Histopathologically in addition to lichenoid features, there is melanin pigmentation in the basal cell layer with melanin incontinence. Treatment is aimed at the resolution of lichenoid inflammation.⁹



Oral Melanotic Macule

A small, well-circumscribed, brown-to-black pigmentation that occurs commonly on the vermilion borders of lips and gingiva, palate and buccal mucosa⁽¹⁴⁾. Some systemic conditions associated with oral melanotic macules are Peutz-Jeghers syndrome, intestinal polyposis, autosomal dominant inheritance, Addison's disease, macule and diffuse bronzing, Adrenal cortical insufficiency-weakness, hypotension, weight loss, nausea oral subgenual and skin macule.¹

Microscopically number of melanocytes is normal and melanin accumulation is seen in the basal keratinocytes.¹⁵ Melanin is also seen in the melanophage in the upper portion of lamina propria. Biopsy is recommended to distinguish it from other oral melanocytic lesions.¹⁶

Café-au-lait Macule

Discrete melanin pigmented patches of skin with irregular margins and brown coloration. Treatment is not required, but they are indicative of several syndromes. Individuals with six or large lesions (greater than 1.5cm diameter) should be suspected of neurofibromatosis or Albright syndrome.¹ In oral cavity, neurofibrotic café au lait spots are commonly seen on tongue may present along with nodules and fissuring.¹⁷

Pigmented Neuroectodermal Tumor of Infancy

A rare, benign neoplasm of early infancy, composed of primitive pigment producing cell like melanocytes nevus cell which have their origin in neural crest cell.¹⁸

Usually found in infants less than 1 year of age, with rapid growth and recurrence and most commonly seen in maxilla. Other sites involved are mandible, skull and epididymis.¹⁹ Clinically it presents as a non-nucleated and rarely dark pigmented mass which is due to melanin production by tumor cells. Radiographically it appears as an ill-defined radiolucency that may contain developing teeth. Surgical excision is the treatment of choice.¹

Histopathology shows nests of tumor cells with small amount of intervening connective tissue. Nests are of round to oval cells found within a well-defined connective tissue margin. Centrally located cells within the neoplastic nests are dense and compact, resembling neuroendocrine cell and the peripheral cells are often larger.¹

Nevomelanotic Nevus

Also called as nevocellular nevus, melanotic nevus or pigmented nevus. The nevi of the skin are acquired popular lesion, usually appears shortly after the birth and throughout the childhood. Intraoral nevi are rare lesion occur at any age.¹

Melanocytic nevi constitute benign neoplasms of cutaneous melanocytes, which harbour oncogenic serine/threonine-protein kinase B-Raf (BRAF) or, less commonly, neuroblastoma RAS viral oncogene homolog (NRAS) mutations. Oncogenic mutations drive the initial hyperproliferation that results in the formation of the nevi, while a subsequent growth-arrest response with the features of oncogene-induced cellular senescence accounts for the cessation of further growth.^{1,16,20}

Histopathologically these are a collection of nevus cells that are round or polygonal and are typically seen as a nested pattern. They may be found in the epithelium or the connective tissue or both.¹



Clinically oral nevi are small, well-circumscribed macules but commonly appear as slightly raised papules. They can be brown, bluish grey, or almost black. It may be difficult to differentiate clinically between a nevus and an early lesion of mucosal melanoma, in the palate, the most common site for both lesions. It is believed that nevi may represent precursor lesions to oral mucosal melanoma.^{16,20}

The blue nevus is second most common type and seen most commonly in the palate.²¹ The blue nevus is a benign, acquired melanocytic lesion that typically presents as an asymptomatic, slate-blue, or blue-black smooth-surfaced macule or papule and usually measures less than 6 mm in diameter.¹⁶ Blue nevi are characterized by the proliferation of dermal melanocytes within deep connective tissue at some distance from the surface epithelium, which accounts for the blue colour.²²

Oral Melanoacanthoma

A rare benign pigmented lesion, brown to brown-black, well-circumscribed and similar to cutaneous melanoacanthoma, characterized by hyperplasia of spinous keratinocytes and dendritic melanocytes. Lesions usually develop after trauma, and are most commonly seen on the buccal mucosa, and are more frequently unilateral. Other common intraoral sites are the lip, palate, and gingiva. The average age of presentation is 28 years, mainly in blacks, with a strong female predilection.¹⁶ The pathogenesis remains uncertain, although its clinical behavior is suggestive of a reactive origin.²³

Histopathology shows acanthosis, basal layer hyperpigmentation, and many dendritic melanocytes distributed through all layers of the epithelium without atypia. Lesions regress spontaneously after removal of traumatic irritants or following incisional biopsy.²⁴

Melanoma

Melanoma is a malignant neoplasm of the epidermal melanocytes. Benign lesions like common acquired nevus, congenital nevus, dysplastic nevus, and cellular blue nevus are said to undergo a malignant transformation to melanoma. Acral lentiginous and mucosal lentiginous melanoma commonly occur in the oral cavity. The hard palate is the most commonly involved site where it presents as a brown to black macule with irregular borders.²

HIV Associated

In human immunodeficiency virus (HIV) the immune system is dysregulated, which leads to an increase in inflammatory mediators like interleukin (IL)-1, (IL)-6, tumor necrotic factor (TNF) α which in turn cause a febrile response, as a result of which α melanocytes stimulating hormone (MSH) is released from the anterior pituitary. The α MSH is a potent stimulator of melanocytes, and IL-1 upregulates MSH receptor expression by melanocytes. The body's natural mechanism for controlling fever and inflammation leads to the release of α MSH, which contributes to pigmented lesions in HIV patients.² HIV manifests in the oral cavity clinically as single or multiple brownish or brown-black macules or ill-defined areas of melanin hyperpigmentation, most frequently seen in the buccal mucosa.²⁵

Aspergillus and Mucormycosis Infection

Fungal infections, if left untreated, these infections can lead to necrotic palatal perforation that is seen as a black ulcer, especially in immunocompromised patients.²⁶



Hairy Tongue

Brown or black discoloration of the tongue may be caused by poor oral hygiene, general debilitation, radiation therapy, tobacco smoking, oxidizing mouthwashes or antacids, fungal or bacterial organisms, or broad-spectrum antibiotic usage.^{26,27} Hypertrophy of the filiform papillae with an accumulation of bacteria and yeast occurs with discoloration and furring of the tongue.²⁶ Treatment consists of any removal of predisposing factors, with good oral hygiene. Retin-A gel may be applied to the tongue.²⁸

Ephelides and Lentigines

Ephelides are common, uniform, small, light brown macules localized on sun-exposed areas of skin, including perioral skin and lips. They are more frequent in childhood. Histological examination shows increased melanin pigmentation of the basal layer without an increased number of melanocytes.²⁸

Lentigines are ultraviolet (UV) induced pigmented lesions and may be seen in the perioral region. They are common in older individuals. Histopathological examination shows hyperplasia of basal melanocytes with elongated rete ridges. Non-sun-induced pigmentations are also present.²⁸

Endocrine Disease

Primary adrenocortical insufficiency, also referred to as Addison's disease. This results in a diffuse dark pigmentation of the skin and the oral mucosa. In one-third of cases, pigmentation is an initial sign of the disease. Cutaneous pigmentation is commonly seen in areas of friction or pressure such as the palms and soles and flexures. Similar patterns of pigmentation seen in Cushing's disease, Nelson's syndrome, hyperthyroidism, McCune-Albright syndrome, and acromegaly.^{6,27}

Haemoglobin Pigmentation

Varix

A dilated, tortuous vein which is subjected to increased hydrostatic pressure but poorly supporting connective tissue,²⁸ that appears as multiple bluish purples, irregular soft elevations (2-4mm), mainly seen on the ventral surface of the tongue.²⁹ This can be either excised or removed by electrosurgery or cryosurgery.³⁰

Haemangioma

Haemangioma is a proliferation of endothelial vascular channels.³ One of the common aetiologies is suggested to be estrogen signalling. These pigments appear as flat reddish-blue macule to a nodular blue tumefaction.³¹ Rare in the oral cavity but may be seen on the tongue, lips, buccal mucosa, gingiva, palatal mucosa, salivary glands, alveolar ridge, and jawbones. Treated by surgery, false lamp pulsed laser, intralesional injection, and electrocoagulation.³²

Hereditary Haemorrhagic Telangiectasia (Osler Weber Randu syndrome)

It is characterised by multiple, round or oval papules measuring less than 0.5 mm, seen in conditions like ataxia telangiectasia, pregnancy, chronic liver disease. Treatment is removal by electrocautery.³³

Angiosarcoma

Angiosarcoma is a malignant mesenchymal tumor with a differentiation into vascular endothelium.^{34,35} In oral cavity, it appears as a poorly demarcated nodular tumor that is red-blue to purplish in color.³⁶ It is seen in lips, tongue, floor of the mouth, cheek and palate.³⁷ Treated by surgery or combined with post-operative radiotherapy.³⁶



Hemosiderin Pigmentation Ecchymosis (Bruises)

It is seen as a little larger than pinpoint spots and larger than petechiae.³⁷ The application of ice or epinephrine is used to prevent ecchymosis formation.³⁸

Petechiae

These are minute pinpoint haemorrhages, seen most commonly on soft plate, can also be seen on any mucosal site.²⁹

Haemochromatosis

It is an autosomal recessive disease with increased iron absorption, resulting in cirrhosis, hyperpigmentation, diabetes, and cardiac failure characterized by excessive iron deposition in the liver and other organs and tissue which leads to organ toxicity. Oral findings are present in 25% of patients and seen as bluish-grey pigmentation of the hard palate and attached gingiva. Generalized bronze or slate grey discoloration of the skin is also seen in 70% cases.^{39,40} The pigment can be treated by phlebotomy.⁴¹

Exogenous

Drug-induced Oral Pigmentation

Many drugs induce pigmentary changes in the oral mucosa. Some of these drugs are Phenolphthalin, Minocyclin, Chlorpromazine, Chloroquine, Hydroquine, Quinidine, Quinacrine, Doxorubicin, Busulfan, Cyclophosphamide, 5-Flurouracil, Zidovudine, Ketoconazole Clofazimine.⁴²

Usually drug-induced oral pigmentation is not directly related to dose or duration of medication. Most agents produce a diffuse melanosis but some drugs may be localized to one mucosal surface. The pathogenesis varies depending on the causative drug.⁴²

Mucosal discoloration associated with Chloroquine and other quinine derivatives appears as a blue-grey or blue-black, and in most cases only the hard palate is involved. Studies have shown that these drugs may produce a direct stimulatory effect on the melanocytes.⁴³

Minocycline can cause pigmentation of the alveolar bone, which can be seen through the thin overlying oral mucosa. Especially the maxillary anterior alveolar mucosa as a grey discoloration. Minocycline has also cause pigmentation of the tongue mucosa. In addition to mucosal changes, teeth in adults and children may appear to be bluish grey owing to minocycline/tetracycline use.^{2,3}

Heavy Metal Exposure

Heavy metals capable of producing oral pigmentation are arsenic, bismuth, lead, mercury, silver, gold, and platinum.⁴⁰

Amalgam tattoo is the most common causes of intraoral pigmentation. Clinically it presents as a localized flat, blue-grey lesion of variable dimensions. The gingiva and alveolar mucosa are the common sites of involvement, but these lesions may also see on the floor of the mouth and the buccal mucosa. No signs of inflammation are present at the periphery of the lesion. When the amalgam particles are large enough, they can be seen in intraoral radiographs as fine radiopaque granules. In some cases, biopsy is required for the diagnosis.⁴²



Graphite may be introduced into the oral mucosa through accidental injury with the graphite pencil. The lesion occurs most frequently in the anterior palate in young children, appearing as an irregular grey to black macule.²

Gold and bismuth can cause slate-grey gingival hyperpigmentation; silver can produce a permanent diffuse bluish-grey pigmentation, most frequently of the hard palate. Systemic symptoms and signs associated with chronic exposure may occur, depending on the type of metal implicated.^{9,40}

Lead, which produces characteristic generalized cutaneous 'lead hue' (described as a combination of pallor and lividity), and 'lead lines' on the gingiva (grey areas of discoloration below the gingival margins).^{9,40}

Investigations

They are

- History
- Dermoscopy
- Binocular stereo microscope
- Pigmentations
- Biopsy [44]

Conclusion

Although most of the oral diseases are not problematic, early detection and timely biopsy can lead to the diagnosis of malignant lesions and also associated systemic diseases. And it requires knowledge of wide variety of oral pigmentations.

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