INTRODUCTION

Oral mucosa is deeply colored when compared to skin. Color reflects the clinical state of the mucosa; inflamed tissues are red, because of the increase in number and dilation of blood vessels, whereas normal healthy tissues are pale pink. This coloration is the net result of many factors, one of which is pigmentation. Pigment is any coloring matter in the living tissues. Pigments are present throughout the human body including the oral cavity.

Oral pigmentation is a relatively common condition that may involve any part of the oral cavity.

These pigmentation may arise from intrinsic and extrinsic factors and can be physiological or pathological. If pathological, it may represent a localized anomaly of limited significance or the presentation of potentially life-threatening disease.

As dental professionals encounter a number of pigmented conditions in the oral cavity it is important to differentiate between normal and pathological pigmentation. Pigmentation is of two types - exogenous and endogenous.

Endogenous refers to arise from within the tissues and exogenous, caused by foreign material introduced into the body.²

The color of the oral mucosa is due to two main endogenous pigments namely- Melanin and hemoglobin.

MELANOCYTES

Melanin is produced by a specialized pigment producing cell called ‘Melanocyte’ situated in the epidermis and basal layer of the epithelium and are developed from the neural crest cells.

LIGHT MICROSCOPIC APPEARANCE

In hematoxylin-eosin(H&E) stained sections, melanocytes appear as randomly dispersed cells...
wedged between the basal cells of the epidermis, having a small, dark staining nucleus and a clear cytoplasm, largely as a result of shrinkage. It is also called as low level clear cells.

The average number of melanocytes in H&E stained sections is 1 of 10 cells in the basal layer. Because only 10 percent of the cells in the basal layer is melanocytes, each melanocyte supplies several keratinocytes with melanin, forming with them an Epidermal- Melanin unit.²

SPECIFIC METHODS OF IDENTIFICATION
- Silver staining by Masson-Fontana method
- Treatment with strong oxidizing agents like hydrogen peroxide and potassium permanganate.
- DOPA reaction.
- Immunohistochemically by antibodies directed against S-100 and HMB-45.

MELANOGENESIS
Melanin formation begins by tyrosinase dependant hydroxylation of tyrosine to Dihydroxy-phenyl alanine (DOPA) and the oxidation of DOPA to dopa quinone, which is subsequently polymerized into melanin.

Melanin is synthesized within the rER of melanocytes from where it is transferred to the Golgi apparatus where it is modified and packed into as small membrane bound structures called melanosomes. These melanosomes gradually move from the cytoplasm of the melanocyte to the dendritic processes. As the content of melanin increases in the melanosomes the concentration of melanogenic enzyme decreases.

The development of the melanosomes takes place in four stages.

Stage I melanosomes are round, measure about 0.3 mm in diameter and possess very intense enzyme activity concentrated along filaments. They contain no melanin.

Stage II melanosomes are ellipsoid and measure approximately 0.5 mm in length, as do the melanosomes of stage III and IV. They contain longitudinal filaments that are cross-linked with one another. Enzyme activity is present both on the enveloping membrane and on the filaments. Melanin deposition on the cross-linked filaments begins at this stage.

Stage III melanosomes have only little tyrosinase activity but show continued melanin deposition, partially through non enzymatic polymerization.

Stage IV melanosomes no longer possess tyrosinase activity. Melanin, which is formed entirely by nonenzymatic polymerization, fills the entire organelle and obscures its internal structure.²

MELANIN TRANSFER
Formed melanin is transferred to the keratinocytes takes place by exocytosis, cytophagocytosis, plasma membrane fusion or transfer by membrane vesicles.

PIGMENTED ORAL LESIONS
- Developmental Disorders
  - Pigmented cellular nevus
  - Labial and Oral melanotic macule
  - Forbes-Albright syndrome
  - Polyostotic fibrous dysplasia
  - Neurofibromatosis
  - Peutz-Jeghers syndrome
- Functional/Physiologic Variants
  - Racial pigmentation
  - Chloasma
- Specific Agents
  - Dental Amalgam
  - Chewing/Smoking of Tobacco
  - Betel nut chewing
  - Lead
  - Silver
- Drugs
**PIGMENTATION DUE TO DEVELOPMENTAL DISORDERS**

**Pigmented cellular nevus**

Nevus is also called birth mark. Pigmented cellular nevus is benign proliferation of the nevus cells either in the epithelium or connective tissue and is categorized as hamartoma or developmental malformation. Melanocytic nevi can be congenital or acquired. Congenital melanocytic nevi are classified into two types according to their size: Giant congenital melanocytic nevi (also called as the ‘Garment nevus’, ‘Bathing trunk nevus’ or ‘Giant hairy nevus’) are greater than 20 cm in diameter and Small congenital nevi, which are usually less than 1.5 cm in their greatest dimension.3

Acquired melanocytic nevus, commonly referred to as the ‘mole’ is seen occurring frequently on the skin. Intra orally, they occur on the hard palate. Histologically, they are classed as junctional, intradermal or intramucosal, and compound nevi based on the location of the nevus cells.4 Junctional nevi are at and dark brown in colour because the nevus cells proliferate at the tips of the rete pegs close to the surface. Intramucosal and compound nevi are typically light brown, dome-shaped lesions.

**Blue nevi** are characterized by proliferation of dermal melanocytes within the deep connective tissue at some distance from the surface epithelium, which accounts for the blue colour. Although transformation of oral pigmented nevi to melanoma has not been well documented, it is believed that nevi represent precursor lesions to oral mucosal melanoma. It is therefore recommended that these lesions be excised and submitted for histopathologic examination.5

**Labial Melanotic Macule (labial lentigo)**

The labial melanotic macule occurs in the lips, more commonly in the lower lip. It shows a predilection for occurrence in women but can also occur in males.5 The lesion appears as a solitary well-defined, oval, brownish-black, flat patch ranging from 1 to 8 mm in diameter. Exposure to UV radiation is thought to be the most important etiologic factor in the pathogenesis of the lesion7 (Fig 1).

**Oral Melanotic Macule**

Macule is a non elevated discoloration. The oral melanotic macule is a flat, brown mucosal discoloration produced by a focal increase in melanin deposition along with an increase in the number of melanocytes. They may appear as solitary or multiple macules and can involve the gingiva, lip, palate, buccal mucosa, and alveolar ridge. Microscopically, the melanin deposition is seen mainly in the basal cell layers.4

**Polyostotic Fibrous Dysplasia**

Fibrous dysplasia principally affects the bone wherein bone is replaced by a dysplastic fibrous tissue. It is classified according to the number of bones affected as monostotic (single bone) and polyostotic (multiple bones). The polyostotic form is associated sometimes with syndromes like Jaffe-Lichtenstein and McCune Albright, where Café au lait pigmentation is a common clinical presentation.8

**Neurofibromatosis**

Neurofibromatosis (NF) is an autosomal dominant disorder with a high degree of penetrance and variable expressivity. Two sub types are known Neurofibromatosis 1 (NF1) and Neurofibromatosis 2 (NF2). NF 1 is commonly associated with Café au lait pigmentation.
pigmentation of the skin. They appear as oval-shaped light brown patches greater than 0.5 cm in diameter. It is also known as Von Recklinghausen’s disease of the skin.9

**Peutz-Jeghers Syndrome**

Peutz-Jeghers syndrome is an autosomal dominant disorder with a high degree of penetrance and is commonly associated with benign intestinal polyposis, most commonly in the jejunum and ileum.10 The typical presentation is irregular pigmented patches of dark brown or black up to five millimeters in diameter on the buccal mucosa and perioral region. The lesions may also be found on the gingiva and palate.11

**Physiologic (Racial) Pigmentation:**

Physiologic pigmentation occurs due to an increased melanocytic activity rather than an increase in the number of melanocytes. The colour ranges from light to dark brown. The attached gingiva is the most common intraoral site of such pigmentation. It appears as a bilateral, well demarcated, ribbon-like, dark brown band. The marginal gingiva is usually not affected. The buccal mucosa, hard palate, lips and tongue may also be affected. This pigmentation is asymptomatic which requires no treatment.5 (Fig 2)

**PIGMENTATION DUE TO SPECIFIC AGENTS**

**Amalgam Tattoo and Other Foreign-Body Pigmentation**

Amalgam tattoo is one of the most common causes of intraoral pigmentation. Amalgam tattoos are twice as common as melanotic macules and ten times as common as oral nevi.12 The gingiva and alveolar mucosa are most commonly involved, it may also occur in the floor of the mouth and buccal mucosa. It presents clinically as a localized, blue–grey lesion. In periapical view radiographs the amalgam particles are usually seen as radiopaque granules. In case of doubt, a biopsy should be performed to demonstrate the presence of amalgam particles in the connective tissue.

Sometimes, graphite may be incorporated into the oral mucosa through accidental injury with a graphite pencil. This type of lesion occurs frequently in children especially in the anterior palate. Clinically, it appears as an irregular grey to black macule. It is mandatory to differentiate this lesion from melanoma since it commonly occurs on the palate.5

**Smoker’s Melanosis**

Smoking may cause oral pigmentation with increased production of melanin. It may provide a biologic defence against the noxious agents present in tobacco smoke. Smoker’s melanosis occurs in up to 21.5 percent of smokers. The intensity of the pigmentation is related to the duration and amount of smoking. Women are more commonly affected than men, which suggest a possible synergistic effect between the female sex hormones and smoking. The brown–black lesions most often involve the anterior labial gingiva followed by the buccal mucosa. Smoker’s melanosis usually disappears within three years of smoking cessation. Biopsy should be performed if there is surface elevation or increased pigment intensity or if the pigmentation is in an unexpected site.13 (Fig 3)

**Heavy Metal Pigmentation**

Increased levels of heavy metals (e.g., lead, bismuth, mercury, silver, arsenic and gold) in the blood are commonly known to cause oral mucosal discoloration. In adults, the most common cause is occupational exposure to heavy metal vapors. Treatment with drugs containing heavy metals, such as arsenicals for syphilis, was a common cause in the past.

In children, exposure to lead-contaminated water or paint and mercury or silver-containing drugs represents a common cause. For example, pigmentation due to lead poisoning appears as a blue–black line along the marginal gingiva known as Burtonian line.5

**Drug-Induced Pigmentation**

Oral mucosal pigmentation may occur as a side effect of drug therapy. Drugs commonly associated
with oral mucosal pigmentation include Zidovudine, estrogen, cyclophosphamide, ketoconazole, chloroquine and minocycline. This pigmentation occurs due to synthesis of melanin under the influence of the drug, deposits of the drug or one of its metabolites. These drugs commonly cause pigmentation of the hard palate where it commonly produces a blue-grey or blue-black discoloration. Laboratory studies have shown that these drugs may produce a direct stimulatory effect on the melanocytes.

Minocycline, a synthetic tetracycline causes pigmentation of the alveolar bone, which can be seen through the thin overlying oral mucosa as a grey discolouration.

**Post inflammatory Pigmentation**

Mucosal diseases in particular lichen planus can cause mucosal pigmentation which is clinically seen as multiple brown–black-pigmented areas adjacent to reticular or erosive lesions of lichen planus. Histologically, there is increased production of melanin by the melanocytes and accumulation of melanin-laden macrophages in the superficial connective tissue.

**PIGMENTATION DUE TO ENDOCRINE DISORDERS**

**Addison’s Disease**

Addison’s disease, or primary hypoadrenalism, is due to progressive bilateral destruction of the adrenal cortex by autoimmune disease, infection or malignancy. The increased production of ACTH induces melanocyte-stimulating hormone, which results in diffuse pigmentation of the skin and oral mucosa. Oral involvement presents as diffuse brown patches which affects the gingiva, buccal mucosa, palate and tongue.

Cushing’s syndrome, acromegaly and hyperthyroidism also show pigmentation similar to Addison’s disease.

**COLOURED LESIONS OF VASCULAR ORIGIN**

**Hemangioma and Vascular Malformation**

Hemangiomia is a benign proliferation of the endothelial cells, endothelial lined vessels or spaces. Vascular malformation is a structural anomaly of blood vessels without endothelial proliferation. Vascular malformation occurs during birth and regresses as the patient ages. The lesion may be at or slightly raised and varies in color from red to bluish purple depending on the type of vessels involved (capillaries, veins or arteries) and the depth of the lesion in the tissues. The most commonly affected site is the lip, although any region in the oral cavity may be involved.

**Varix and Thrombus**

Varices are abnormally dilated veins. The most common intraoral location is the ventral surface of the tongue, where varices appear as multiple bluish purple, irregular, soft elevations that blanch on pressure. If the varix contains a thrombus, it presents as a bluish purple nodule that does not blanch on pressure. Thrombi are more common on the lower lip and buccal mucosa.

**Hemorrhagic Lesions**

Petechiae, purpurae and ecchymoses are sub mucosal hemorrhages. They all have the same mechanism of presentation and differ only in size. Telangiectasia is a small, red, macular lesion that is composed of dilated capillaries under the epithelium. Petechial and ecchymotic patches are usually seen at the junction of hard and soft palate.

**Kaposi’s Sarcoma**

Kaposi’s sarcoma (KS) is a multifocal vascular malignancy seen predominantly in HIV-infected individuals. The development of this tumor is considered diagnostic of AIDS progression. A human herpes virus (HHV-8, also called Kaposi’s sarcoma-associated herpes virus) has been implicated as the cause. KS in the oral mucosa most commonly affects the hard palate, gingiva and tongue. Early lesions appear as at or slightly elevated brown to purple lesions that are often bilateral. Advanced lesions appear as dark red to purple plaques or nodules that may exhibit ulceration, bleeding and necrosis. Definitive diagnosis requires biopsy, which shows a proliferation of spindle-shaped cells surrounding poorly formed vascular spaces or slits with numerous extravasated red blood cells.
PIGMENTATION DUE TO SUN EXPOSURE

**Actinic Lentigo (Solar lentigo)**

Actinic lentigo is a benign, brown macule that occurs due to chronic ultra violet damage to the skin. It commonly occurs on the dorsum of the hands and face. (Fig 5)

**Melasma**

It is an acquired, symmetric hyperpigmentation of the sun exposed skin of face and neck. It is seen on the upper lip.

PIGMENTATION DUE TO HYPERPLASTIC PROCESS

**Lentigo simplex**

It is a benign cutaneous melanocytic hyperplasia of unknown cause. It usually occurs on skin not exposed to sunlight. Oral lesions are also seen. The lesions appear as sharply demarcated macule less than five millimeters in diameter.

**Oral Melanoacanthoma**

Oral melanoacanthoma is an uncommon benign pigmented reactive lesion of the oral mucosa with no malignant potential. The buccal mucosa is the most common site of occurrence. Clinically, the lesion appears at or slightly raised and is hyperpigmented, the colour ranging from dark brown to black. It is characterized by proliferation of dendritic melanocytes scattered throughout the thickness of an acanthotic and hyperkeratotic surface epithelium. This lesion, in contrast to most of the benign pigmented lesions has a tendency to enlarge rapidly, which raises the possibility of a malignant process in the clinical differential diagnosis.

PIGMENTED MALIGNANT LESION

**Malignant melanoma**

Melanoma is a malignant neoplasm of the epidermal melanocytes. Certain lesions are said to be precursor lesions of melanoma, including the common acquired nevus, dysplastic nevus, congenital nevus and cellular blue nevus.

**Criteria for clinical diagnosis of melanoma (ABCDE-rule)**

- Asymmetry- in which one half does not match the other half
- Border irregularity- with blurred, notched or ragged edges
- Colour irregularity- pigmentation is not uniform. Brown, black, tan, red, white and blue can all appear in a melanoma.
- Diameter- greater than 6 mm. Growth in itself is also a sign.
- Elevtaion- a raised surface can also be a sign.

**Types of melanoma:**

1. Superficial spreading
2. Nodular melanoma
3. Lentigo maligna melanoma
4. Acral lentiginous melanoma
5. Mucosal lentiginous melanoma

Of these, Acral lentiginous and Mucosal lentiginous melanoma commonly occur in the oral cavity. Most frequently seen in the hard palate, where it appears as a brown to black macule with irregular borders. (Fig 6)

**CONCLUSION**

It is clear that oral pigmentation is a relatively common condition that can occur in any portion of the oral cavity and arises from intrinsic and extrinsic factors and can be physiological or pathological. The dentist may be the first health care professional to observe the colour changes in the oral cavity which may be a manifestation of the underlying pathological process.

**REFERENCES**


Fig 1: Labial melanotic macule of the lower lip

Fig 2: Physiologic racial pigmentation of the gingiva.

Fig 3: Smoker’s melanosis

Fig 4: Ecchymotic patch of the hard palate

Fig 5: Solar lentigo of the lower lip

Fig 6: Malignant melanoma of the hard palate.