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Gingival pigmentation: A review of literature

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Abstract

A beautiful smile surely enhances the individual's self-confidence. The harmony of smile is attributable to the shape, colour, and position of the teeth in conjunction with the gingival tissue. Gingival pigmentation occurs in all races of man and it varies from one race to another. It results from melanin granules which are produced by melanoblasts. Excessive gingival pigmentation is considered as a one of the major esthetic concern for many patients. This article aims at reviewing briefly about melanin synthesis and classification, indices and etiology of gingival pigmentation.

Keywords: gingival pigmentation, melanin, melanocytes, gingiva

1. Introduction

A beautiful smile surely enhances the individual's self-confidence. The harmony of smile is attributable to the shape, colour, and position of the teeth in conjunction with the gingival tissue [1]. Gingival health and appearance are essential components for an attractive smile and removal of unsightly pigmented gingiva is the need for a pleasant and confident smile [2].

Gingival colour is generally described as "coral pink". Gingival pigmentation is presented as a diffuse deep purplish discoloration or as irregularly shaped brown and light brown or black patches, striae or strands [3].

Melanin, carotene, reduced haemoglobin and oxy-haemoglobin are the prime pigments contributing to the normal colour of the gingiva, out of which melanin shows the maximum incidence rate [4]. Excessive deposition of melanin located in the basal and supra-basal cell layers of the epithelium will result in gingival hyperpigmentation (Dummett, 1979) [5].

The name "melanin" comes from the Greek word "melanos", meaning "dark," and the term was first applied by the Swedish chemist Berzelius in 1840 to call a dark pigment extracted from eye membranes [6].

2. Physiology of melanin pigmentation

The gingival color depends primarily upon

- The number and size of vasculature
- Epithelial thickness
- Degree of keratinization
- Pigments within the gingival epithelium

Melanin is the end-product of complex multistep transformations of L-tyrosine, are polymorphous and multifunctional biopolymers, represented by [7]

- Eumelanin
- Pheomelanin
- Neuromelanin

2.1 Melanocytes

Melanocytes constitute a heterogeneous group of cells. These unicellular dendritic cells reside in the basal cell layer of the epidermis and oral epithelium. Primitive melanocytes originate from neural crest of ectoderm. Melanocytes have a round nucleus with a double nucleus membrane and clear cytoplasm lacking desmosomes or attachment plates, but possess long dendritic processes [8].

2.2 Melanosomes

Melanocytes synthesize melanin in organelles called melanosomes. There are four stages in melanosome development^[9]

Stage I Premelanosomes: They are round, small vesicles with an amorphous matrix.

Stage II Melanosomes: They have an organized, structured fibrillar matrix and tyrosinase is present but pigment synthesis has not been noted.

Stage III: The beginning of melanin production takes place at this stage, where pigment is deposited on protein fibrils.

Stage IV: At the last, pigment fills the whole melanosome.

Fully melanized melanosomes lose tyrosinase activity and are transported to surrounding keratinocytes by elements of the cytoskeletal system.

2.3 Melanoid

Melanoids are granules of melanoid pigment and are scattered in the stratum lucidum and stratum corneum of the skin. Melanoid imparts a clear yellow shade to the skin^[9].

2.4 Melanogenesis

Melanin is synthesized by a process called melanogenesis. It takes place in cytoplasmic organelles called melanosomes of melanocytes. As a result two types of melanin are produced – pheomelanin and eumelanin. They differ in color and in the pathway of synthesis^[10].

2.4.1 The process of pigmentation consists of three phases

- Activation of melanocytes
 - Synthesis of melanin
 - Expression of melanin
- The activation phase occurs when the melanocytes are stimulated by factors like stress hormones, sunlight etc. leading to production of chemical messengers like melanocyte stimulating hormone^[11].
 - In synthesis phase, melanocytes make granules called melanosomes. Tyrosinase (TYR) carries out tyrosine hydroxylation to L-3, 4-dihydroxy phenylalanine (DOPA) which is rapidly oxidized to DOPA quinone. In the presence of cysteine, DOPA quinone react with it, yielding 3- or 5-cysteinyl DOPAs, which then oxidize and polymerize and giving rise to yellow-red soluble

melanin called pheomelanin^[12]. In the absence of thiols (cysteine, glutathione or thioredoxin) brown-black eumelanin is synthesised. DOPA quinone spontaneously undergoes cyclization to DOPAchrome. The DOPAchrome spontaneously loses carboxylic acid and generates 5, 6-dihydroxyindole (DHI), which rapidly oxidizes and polymerizes to form dark brown-black, insoluble DHI-melanin. However, if DOPAchrome tautomerase (TYRP2/DCT) is present, DOPAchrome will form DHI-2-carboxylic acid (DHICA). Tyrosinase and TYRP1 catalyze further conversions and finally result in a production of lighter brown color DHICA-melanin. DHI and DHICA are further oxidized and polymerized to form eumelanin^[13].

- In expression phase, melanosomes are transferred from the melanocytes to the keratinocytes which are the skin cells located above melanocytes in the epidermis. After this, melanin color eventually becomes visible on the surface of skin^[14].

3. Classification

Pigmented lesions of the oral cavity are of multiple origin. Different classifications are used at this time.

3.1 Dummet *et al.* (1967)^[15].

- Primary oral melanin pigmentations
- Secondary oral melanin pigmentations
- Oral non-melanin pigmentations
- Oral melanoclasias.

3.2 Brocheriou (1985)^[16].

- Non tumoral pigmentations
- Non-melanin pigmented tumors or tumor-like lesions
- Benign melanin pigmented tumors
- Malignant melanomas.

3.3 Meleti (2008)^[17]

- Melanin-associated lesions (e.g.- Racial pigmentations, melanotic macules, melanocytic nevi, and malignant melanoma).
- Non melanin-associated lesions (e.g.- Blood-related pigmentations, metallic pigmentations).

3.4 Kuzman *et al.* (2004) classified pigmented lesions into different groups^[18].

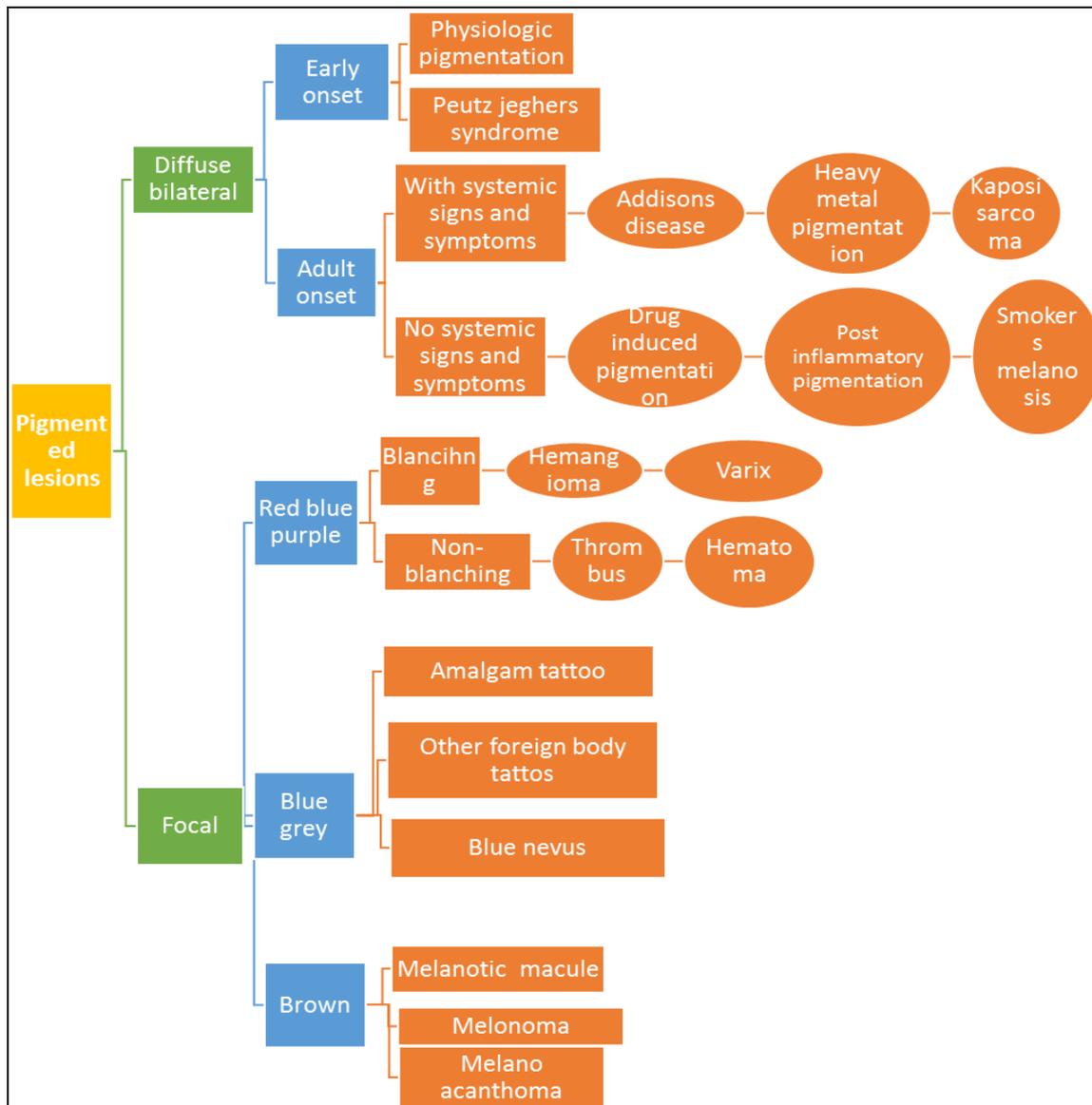


Fig 1: Classification of pigmented lesion (Kauzman *et al* in 2004)

3.5 Peeran *et al.* (2014) proposed a new improved classification for gingival pigmentation and pigmented lesions [19].

Table 1: Classification of gingival pigmentation (Peeran *et al* 2014)

Class	Criteria of classifications
I	Coral pink/salmon pink colored gingiva
II	Localized/Isolated spots/areas of gingival melanin pigmentation which does not involve all the three parts of gingiva, that is, attached, free, and papillary gingiva Mild to moderate pigmentation Severe/intense pigmentation
III	Localized/Isolated unit/s of melanin pigmentation which involve all the three parts of gingiva, that is, attached, free, and papillary gingiva Mild to moderate pigmentation Severe/intense pigmentation
IV	Generalized diffuse pigmentation which involve all the three parts of gingiva that is, attached, free and papillary gingiva. Mild to moderate pigmentation Severe/intense pigmentation
V	Tobacco associated pigmentation like smoker's melanos and chewing tobacco
VI	Gingival pigmentation due to exogenous pigments eg:-Amalgam tattoos, Cultural gingival tattooing, Drinks, Food colors, Habitual betelnut/khat chewing, Lead-Burtonian line, Mercury, Silver, Arsenic, Bismuth, Graphite, Other foreign bodies, Topical medications, Idiopathic
VII	Gingival pigmentation due to endogenous pigments like Bilirubin, Blood breakdown products, Ecchymosis, Petechiae, Hemochromatosis, Hemosiderin.
VIII	Drug-induced gingival pigmentation like ACTH, Antimalarial drugs, Chemotherapeutic agent busulfanb and doxorubicin, Minocycline, Oral contraceptives, Phenothiazines.
IX	Gingival pigmentation associated with systemic diseases and syndromes like Addison's disease, Albright's syndrome, Basilar melanosis with incontinence, Beta thalassemia; Healed mucocutaneous lesions-Lichen planus, Pemphigus, Pemphigoid; Hereditary hemorrhagic telangiectasia; HIV-associated melanos, Neurofibromatosis, Peutz-Jeghers and other familial hamartoma syndromes, Pyogenic granuloma/Granulomatous epulis
X	Pigmented benign and malignant lesions involving the gingival like Angiosarcoma, Hemangioma, Kaposi's sarcoma, Malignant melanoma, Melanocytic nevus, Pigmented macule

3.6. Patil S *et al.* (2015) classified pigmented lesions into different groups [20].

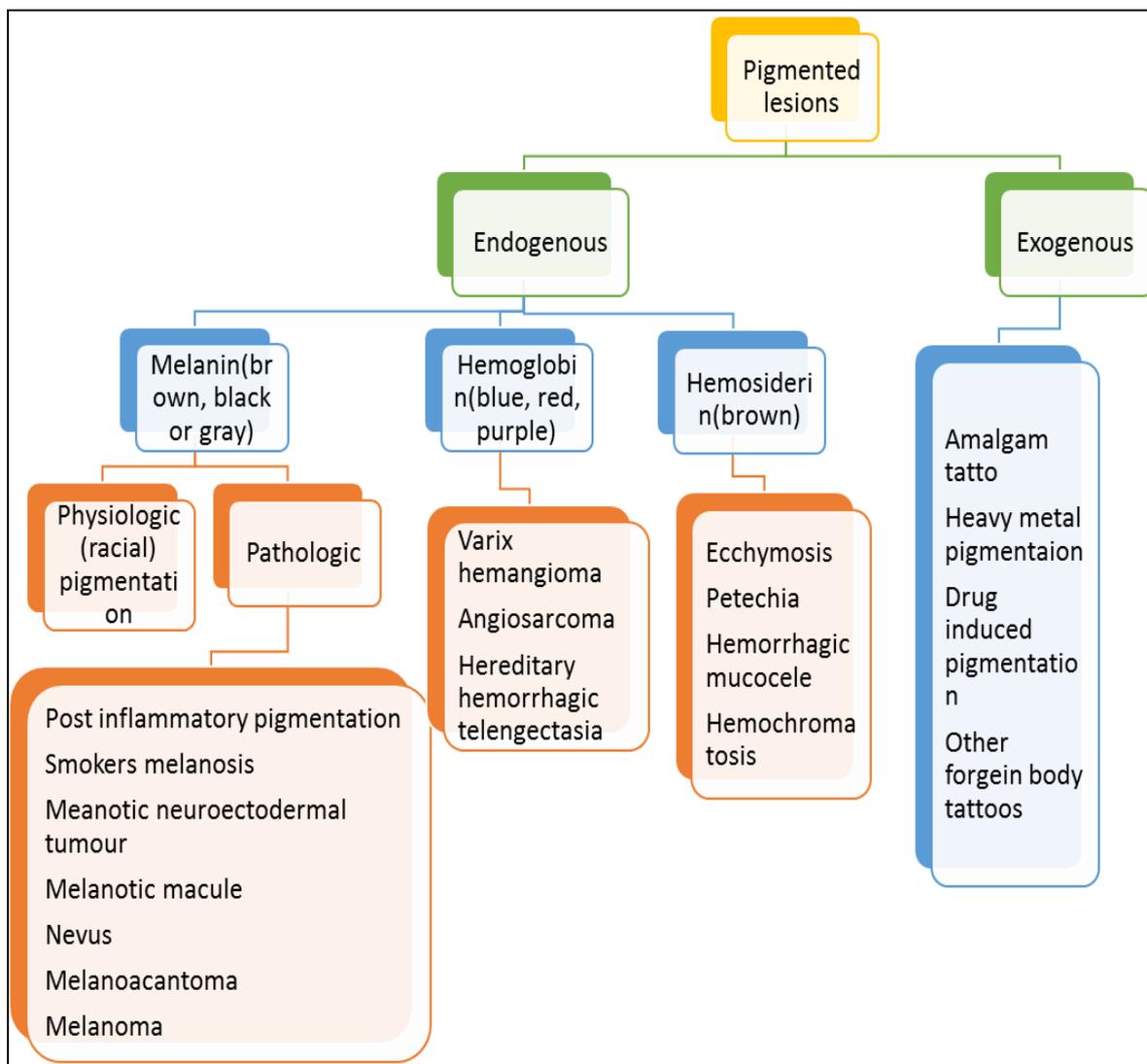


Fig 2: Classification of pigmented lesion (Patil S, *et al* -2015)

4. Review of current indices

Gingival pigmentation has three dimensions: etiology, distribution, and severity. The existing indices on gingival pigmentation are as follows.

4.1 Oral pigmentation index (DOPI) [21, 22]

Dummet proposed the oral pigmentation index (DOPI assessment) in 1964. This index of oral pigmentation is the commonly used index due to its simplicity and ease of use.

The gingivae of the maxillary and mandibular arches are each divided into 32 unit spaces, sixteen on the lingual aspect and sixteen on the buccal and labial surfaces. Each unit space approximates the area of the marginal gingiva, and extends from the gingival crest apically about 4 or 5 mm up to the level of the attached gingiva. The unit spaces correspond to the buccal and lingual gingival areas which normally invest the human adult dentition. In cases in which there are either partially or completely edentulous areas, this division into 32 unit spaces is still maintained since the oral pigmentation is independent of the presence or absence of teeth.

The method consists of assigning a numerical oral pigmentation estimate to each one of these 32 unit spaces. The assigned estimate is based upon the following scale: -

The scores are as follows:

Score 0 - No clinical pigmentation (pink-colored gingiva)

Score 1 - Mild clinical pigmentation (mild light brown color)

Score 2 - Moderate clinical pigmentation (medium brown or mixed pink and brown color)

Score 3 - Heavy clinical pigmentation (deep brown or bluish black color)

$$\text{DOPI assessment} = \frac{\text{Sum of assigned estimates of components}}{32 \text{ unit spaces}}$$

The DOPI assessment is scaled according to following designations

0	No clinical pigmentation of the gingiva
0.031-0.97	Mild gingival pigmentation
1.0-1.9	Medium gingival pigmentation
2.0-3.0	Heavy gingival pigmentation

4.2 Melanin index: [HEDIN 1997] [23]

This index has classified pigmentation as follows:

- No pigmentation
- One or two solitary unit(s) of pigmentation in papillary gingiva without the formation of a continuous ribbon between solitary units
- More than three units of pigmentation in papillary gingiva without the formation of a continuous ribbon

- One or more short continuous ribbons of pigmentation
- One continuous ribbon including the entire area between canines

4.3 Melanin pigmentation index [24]

Takashi *et al.* in 2005 have proposed another index to measure gingival melanin pigmentation.

The index is as follows:

- Score 0: No pigmentation
- Score 1: Solitary unit(s) of pigmentation in papillary gingiva without extension between neighboring solitary units
- Score 2: Formation of continuous ribbon extending from neighboring solitary units

This index is not equipped to describe the degree of melanin pigmentation.

4.4 Gingival pigmentation index [25]

- Score 0: Absence of pigmentation
- Score 1: Spots of brown to black color or pigments.
- Score 2: Brown to black patches but not diffuse pigmentation
- Score 3: Diffuse brown to black pigmentation, marginal, and attached gingiva.

4.5 Gingival melanin pigmentation and pigmented lesions index by Peeran *et al.* (2014) [19]

Table 2: Gingival melanin pigmentation and pigmented lesions index by Peeran *et al.* (2014)

Score 0	Coral pink-colored gingiva, no gingival pigmentation, and/or pigmented lesions
Score 1	Mild, solitary/diffuse, gingival melanin pigmentation involving anterior gingiva, with or without the involvement of posterior gingiva
Score 2	Moderate to severe, solitary or diffuse, gingival melanin pigmentation involving anterior gingiva with or without the involvement of posterior gingiva
Score 3	Gingival melanin pigmentation only in posterior gingiva
Score 4	Tobacco-associated pigmentation: Smoker’s melanosis, chewing tobacco
Score 5	Gingival pigmentation due to exogenous pigments-Amalgam tattoos arsenic, bismuth, chewing betel nut, cultural gingival tattooing, drinks, food colors, lead-burtonian line, mercury, silver, topical medications, idiopathic etc
Score 6	Gingival pigmentation due to other endogenous pigments: Bilirubin, blood breakdown products, ecchymosis, hemochromatosis, hemosiderin, petechiae etc
Score 7	Drug-associated gingival pigmentation: Antimalarial drugs, minocycline, oral contraceptives etc
Score 8	Gingival pigmentation associated with other causes: Addison’s disease, Albright’s syndrome, basilar melanosis with incontinence, hereditary hemorrhagic telangiectasia, HIV patients, lichen planus, neurofibromatosis, Peutz-Jeghers syndrome, pyogenic granuloma/granulomatous epulis etc
Score 9	Pigmented benign lesions: Hemangioma, melanocytic nevus, pigmented macule
Score 10	Pigmented malignant lesions: Angiosarcoma, Kaposi’s sarcoma, malignant melanoma

5. Etiology of pigmentation

The causes of pigmentation mainly classified into endogenous and exogenous.

5.1 Endogenous pigmentation

5.1.1 Physiologic pigmentation or Racial pigmentation

Oral pigmentation occurs in all races of man and it varies from one race to another. There are no significant differences in oral pigmentation between males and females. The intensity and distribution of racial pigmentation of the oral mucosa varies between the races, between different individuals of the same race and within different areas of the same mouth. Attached gingiva represents the most common intraoral pigmented area. Other less common sites include hard palate, lips and tongue [26].

Physiologic pigmentation develops during the first two decades of life but may not come to the patients notice until later. Color variation may be uniform, unilateral, bilateral, mottled, macular or blotched and may involve the gingival papillae alone or extend throughout the gingiva and into other oral tissues [27].

5.1.2 Pathological pigmentation

5.1.2.1 Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (intestinal polyposis) is a genetic disorder characterized by mucocutaneous pigmentation and hamartomas of the intestine. It manifests itself as freckle like macules about the hands, perioral skin, and intraorally to include the gingiva, buccal, and labial mucosa. Pigmented spots are particularly found on the lower lip and buccal mucosa but rarely on the upper lip, tongue, palate, and

gingiva [28].

5.1.2.2 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 lack of adrenocortical hormones in the blood stimulates production of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland. The increased production of ACTH induces melanocyte-stimulating hormone, which results in diffuse pigmentation of the skin and oral mucosa [29].

Oral involvement presents as diffuse brown patches on the gingiva, buccal mucosa, palate and tongue, which may resemble physiologic pigmentation [30].

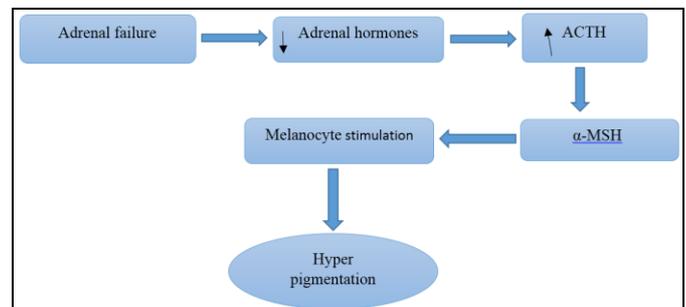


Fig 3: mechanism of hyperpigmentation in Addison’s disease

5.1.2.3 Kaposi’s Sarcoma

Kaposi’s sarcoma (KS) is a multifocal vascular malignancy seen predominantly in HIV-infected individuals. KS in the

oral mucosa most commonly affects the hard palate, gingiva and tongue [31]. Early lesions appear as flat 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 [32].

5.1.2.4 Post inflammatory pigmentation

Oral post-inflammatory pigmentation (OPP) is a discoloration of the oral mucosa caused by an excess of melanin production and deposition within the basal layer of the epithelium and connective tissue of areas affected by chronic inflammation.³³ Clinically OPP appears as a localized or diffuse, black to brown pigmentation. OPP may persist for many years even though the disappearing of the pigmentation after the resolution of the inflammatory state has been reported [34].

5.1.2.5 Smoker's Melanosis

Smoking may cause oral pigmentation in light-skinned individuals and accentuate the pigmentation of dark skinned patients. There is increased production of melanin, which may provide a biologic defense against the noxious agents present in tobacco smoke. Smoker's melanosis occurs in up to 21.5% of smokers [35].

5.1.2.6 Pigmented Nevi

Pigmented nevi of the oral cavity are uncommon. The clinical features include brownish black to blue elevated papules with a well-defined border. Nevi can be classified based on time of occurrence as congenital and acquired. Congenital nevi, can be sub-classified as giant nevus and small nevus. An acquired nevus is also called as a mole, occurs most commonly in the sun exposed regions. Nevus represents a benign proliferation of melanocytes [36].

5.1.2.7 Oral Melanoacanthoma

Oral melanoacanthoma is an uncommon benign pigmented lesion of the oral mucosa characterized by proliferation of dendritic melanocytes scattered throughout the thickness of an acanthotic and hyperkeratotic surface epithelium [37].

5.1.2.8 Oral Melanoma

Oral mucosal melanoma is rare, accounting for less than 1% of all oral malignancies. It is characterized by proliferation of malignant melanocytes along the junction between the epithelial and connective tissues, as well as within the connective tissue.

The most common site is the palate, which accounts for about 40% of cases, followed by the gingiva (30%), which accounts for one third of cases. Other oral mucosal sites may also be affected [38].

5.1.2.9 HIV Infection

In patients infected with human immunodeficiency virus (HIV), progressive hyperpigmentation of the skin, oral mucosa, fingernails, and toenails have been reported being related to primary adrenocortical deficiency and to zidovudine (Azidothymidine) therapy in some cases. Clinically, oral pigmentation appears as irregular macules with brown or dark brown color. The tongue, buccal mucosa, and palate are the most commonly affected sites [39].

5.1.2.10 Laugier hunziker syndrome

LHS is an acquired, benign skin condition characterized by hyperpigmented macules on the lips and buccal mucosa associated with longitudinal melanonychia of nails. The

buccal mucosa and the lips (usually the lower lip) are the most commonly involved sites, but gingiva, tongue, soft palate, and the hard palate can also be involved. The pigmentation is in the form of smooth-surfaced brown-, black-, or slate-colored macules measuring 1-5 mm in size [40].

5.1.2.11 Hemangioma and Vascular Malformation

Hemangioma is a benign proliferation of the endothelial cells that line vascular channels. Vascular malformation is a structural anomaly of blood vessels without endothelial proliferation. Both lesions are developmental abnormalities, characterized by onset during infancy. Hemangioma regresses as the patient ages, but vascular malformation persists throughout life. The mouth, the tongue is the most common site of occurrence [41].

5.1.2.12 Angiosarcoma

Angiosarcoma is a malignant mesenchymal tumor with a differentiation into vascular endothelium. In oral cavity involves lips, tongue, and floor of mouth, cheek and palate [42].

5.1.2.13 Hereditary hemorrhagic telangiectasia (HHT)

Hereditary hemorrhagic telangiectasia (HHT) is an unusual bleeding disease which is clinically characterized by numerous angiomatous lesions (telangiectasia), hereditary incidence and hemorrhagic diathesis [43].

The lesions generally involve the skin or mucous membranes (or both) and tend to bleed spontaneously after slight trauma. Overt lesions may be found on the lips, tongue, buccal mucosa, nasal mucosa; less common locations include ears, nail-beds, scalp; rare sites are the mucosa of the palate, the gingiva, and the remaining oral mucosa [44].

5.1.2.14 Haemochromatosis

Hemochromatosis is a chronic disease characterized by the deposition of excess iron (ferritin and hemosiderin) in the body tissues, resulting in fibrosis and functional insufficiency of the involved organs. Gingival or mucosal pigmentation is reported to occur in 15 to 25 per cent of patients with hemochromatosis [45].

5.1.2.15 Ecchymosis

Ecchymosis commonly known as bruises, frequently occur after injury. Traumatic ecchymosis is common on the lips [46].

5.1.2.16 Petechiae

Petechiae are submucous or subcutaneous minute pinpoint hemorrhages. In most cases, the petechiae are identified on the soft palate, although any mucosal site may be affected [47].

5.2 Exogenous pigmentation

5.2.1 Heavy Metal Pigmentation

Increased levels of heavy metals (e.g., lead, bismuth, mercury, silver, arsenic and gold) in the blood represent a known cause of oral mucosal discoloration. In adults, the most common cause for such increased levels is occupational exposure to heavy metal vapours. In adults, the most common cause for such increased levels is occupational exposure to heavy metal vapours [48].

Lead results in a bluish red or deep blue linear pigmentation of the gingival margin (Burtonian line). Exposure to silver causes a violet marginal line, often accompanied by a diffuse bluish-grey discoloration throughout the oral mucosa [49].

5.2.2 Drugs associated with oral mucosal pigmentation

A number of medications may cause oral mucosal pigmentation. The pathogenesis of drug-induced pigmentation depends upon the causative drug. It can involve accumulation of melanin, deposits of the drug or one of its metabolites, production of pigments under the influence of the drug or deposition of iron after damage to the dermal vessels^[50].

- Amiodarone
- Amodioquine
- Azidothymidine
- Bleomycin
- Chloroquine
- Chlorpromazine
- Clofazamine
- Gold
- Hydroxychloroquine
- Hydroxyurea
- Imipramine
- Ketoconazole
- Mepacrine

Mucosal discolouration associated with antimalarial like chloroquine is described as blue–grey or blue–black, and in most cases only the hard palate is involved. Laboratory studies have shown that these drugs may produce a direct stimulatory effect on the melanocytes.

Minocycline is a synthetic tetracycline used in the long term treatment of refractory acne vulgaris. It 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 discolouration. Minocycline has also been reported to cause pigmentation of the tongue^[51].

5.2.3 Amalgam Tattoo

Amalgam tattoo is one of the most common causes of intraoral pigmentation, the etiology being embedded metallic silver. It presents clinically as a localized flat, blue–grey lesion of variable dimensions^[52].

Amalgam may be introduced in several ways during restorative and surgical procedures:

1. It may be condensed in abraded gingiva during routine amalgam restorative work.
2. It may enter mucosa lacerated by rotary instruments during removal of old amalgam fillings or crown and bridge preparation of teeth with large amalgam restorations.
3. Broken pieces may be introduced into a socket or beneath the periosteum during extraction of teeth.
4. Particles may enter a surgical wound during root canal treatment with a retrograde amalgam filling.

The gingiva and alveolar mucosa are the most common sites of involvement, but these lesions may also involve the floor of the mouth and the buccal mucosa and the mandibular region being affected more than the maxillary region^[53].

5.2.4 Graphite tattoo

Graphite may be noticed in the oral mucosa through accidental injury with a graphite pencil. The graphite tattoo occurs predominantly in women and youngsters from age 5 to 21 years. The size is variable, generally from 1 to 15 mm, and macules are blue–gray in color. Graphite tattoos occur most frequently on the anterior palate of young children, appearing as an irregular grey to black macule. A history of injury confirms the diagnosis; otherwise, a biopsy should be performed to exclude the possibility of the other conditions

^[54].

Graphite tattoos may be often confused with the more commonly seen amalgam tattoos. One differentiating factor may be the radiographic appearance of the lesion: whereas amalgam may (but not always) produce radio opacities near the area in question, graphite is radiolucent. Microscopically, the special stains can segregate the two^[55].

6. Conclusion

Gingival pigmentation though not a major complication, yet it greatly affects the facial appearance. The patient's medical history is important in determining its cause whether physiological or pathological, but the histopathological examination is conclusive. Accordingly, treatment of the pigmentation is determined either surgically or chemically.

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