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Classification of oral pigmented lesions: A review

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Abstract
Mouth reflects the health status of an individual. There are various pigmented lesions present widely in an around the oral cavity which depicts whether they are benign or malignant. Therefore, classification has been made to quantify the size, color, location of the lesion. And also proper management can be made depending on the lesion. Dental professionals deal with the lesions pertaining to oral cavity, so classification made eases their quality of their work and also in treating the patient.

Keywords: Pigmented lesions, endogenous, exogenous, physiological

Introduction
It is said "mouth is mirror of body" because many dermatological lesions have their manifestation in oral cavity.

There forms a strong link between the skin and oral mucosa: The skin arises by the juxtaposition of two major embryological elements: the prospective epidermis, which originates from a surface area of the early gastrula, and the prospective mesoderm, which is brought into contact with the inner surface of the epidermis during gastrulation .The neural crest also makes an important contribution to the skin, namely the pigment cells so called as melanin, although their bulk is small whereas the primitive oral mucosa is lined by ectoderm and is separated from the gut by the buccopharyngeal membrane [1]. The color of the oral mucosa is the net result of a number of factors, one of which is pigmentation. The pigments most commonly contributing to the color of the oral mucosa are melanin and hemoglobin. Melanin is produced by specialized pigment cells, called melanocytes, situated in the basal layer of the oral epithelium. Melanocytes arise embryologically from the neural crest ectoderm and enter the epithelium at about 11 weeks of gestation. In the epithelium they divide and maintain themselves as a self reproducing population. Melanocytes possess long dendritic (branching) processes that extend between the keratinocytes, often passing through several layers of cells. Melanin is synthesized within the melanocytes as small structures called melanosomes [2]

We know that there are gradations in skin colour i.e During slavery, lighter-skinned African-Americans were perceived as more intelligent, cooperative, and beautiful than do blacks and this prevailed in India too and this led to the discriminations between "Blacks & Whites"----------Lightly and darkly pigmented individuals have the same number of melanocytes in any given region of skin or oral mucosa; color differences result from the relative activity of the melanocytes in producing melanin and from the rate at which melanosomes are broken down in the keratinocytes. In persons with heavy melanin pigmentation, cells containing melanin may be seen in the connective tissue. Light-skinned persons rarely show any oral melanin pigmentation [3].

Human skin pigmentation is a complex trait that evolved as an adaptation to local environmental conditions. The distribution of human skin colour is highly correlated with the intensity of incident ultraviolet radiation. Although pigmentation of the skin is 0influenced by pigments such as carotene, reduced haemoglobin and oxyhaemoglobin, the main determinant is however the pigment melanin. Melanin is a complex mixture of biopolymers, whose synthesis takes place within the melanosomes, specialized lysosomal organelles typical of melanocytes [4].

Oral Pigmentations generally occur as diffuse lesions throughout the oral cavity or as an isolated focal lesion. The word *"*Pigment*"* is derived from the Latin word meaning

*"*Color or Coloring*"* and so pigmented lesions of oral mucosa may be applied to a wide range of entities caused by the accumulations of one or more pigments and featuring a change in color of the tissues. Pigmented lesions may represent a localized anomaly of limited significance or the presentation of potentially life threatening multisystem disease [2]

Oral mucosa is deeply colored when compared to skin which denotes that discoloration of the oral mucosa by pigment occurs with many different conditions, which may be otherwise totally unrelated in many other respects. The color of oral mucosa depends upon the epithelial thickness, the keratin status, the vascularity, and the density of the underlying fibrous tissue/hard tissue. Lesions like erosions (shallow ulcers) will lead to epithelial thinning and the red color of the vascularized tissues. 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 and so oral pigmentation is likely to have a multifactorial etiology[3].

Oral pigmentations can be endogeneous, exogeneous, depigmentation or hemoglobin and iron-associated pigmentation or idiopathic.

a) Endogeneous pigmentation: includes oral melanotic macule which is a flat, brown mucosal discoloration produced by a focal increase in the number of melanocytes and it accounts for 85% of all solitary melanocytic lesions diagnosed. Oral melanoacanthoma is a rare, ill-defined macular or popular like lesions with only approximately fewer than 100 cases reported. Melanomas are common cancers arising from the pigment cells of the skin and it accounts for 4%-6% per annum. Certain drugs also induces oral pigmentation and melanosis and it has been estimated that 10-20% of all cases of acquired melanocytic pigmentation may be drug induced[5]. Smokers melanosis condition may be due to the physical effect of tobacco smoke on the oral tissues by heat and/or the direct effect of nicotine stimulating melanocytes located along the basal cells of the epithelium to produce more melanosomes, thus resulting in increased deposition of melanin and the prevalence ranges from 21-90% [6]. Melasma is an acquired increased pigmentation of the skin,a symmetric hypermelanosis, characterized by irregular light to gray brown macules and the prevalence rate suggests between melasma and pregnancy since 50-70% of pregnant women seem to develop melasma whereas women receiving oral contraceptives seem to develop melasma in about 38% of the cases [7]. Genetically associated pigmentation such as Addison's Disease exibits brown macular pigmentation of local or diffuse quality and affects 110 to 144 of every 1 million people in developed countries [8]. Peutz-Jeghers syndrome (PJS) is an autosomal dominant syndrome characterized by multiple hamartomatous polyps with an estimated prevalence of 1:8000 to 1:200,000 births. Males and females are equally affected [9]. Café au lait spots are macules varying from light brown to dark brown with smooth or irregular borders [10].
b) Exogenous pigmentation: such as amalgam tattoo or any heavy metal deposits is an iatrogenic entity defined as a bluish, black or grey lesion of the oral mucous membrane caused by accidental implantation of silver amalgam into the tissue during tooth restoration or extraction with prevalence rate as 0.26%.
c) Depigmentation: includes vitiligo which is a chronic stigmatizing disease, already known for millennia, which mainly affects melanocytes from epidermis basal layer, leading to the development of hypochromic and achromic patches. Its estimated prevalence is 0.5% worldwide [11].
d) Hemoglobin or iron associated pigmentation: such as ecchymosis is a lesion which will assume a brown coloration after the hemoglobin degraded to hemosiderin. When multiple brown macules or swellings are observed and ecchymosis is included in the differential diagnosis, a hemorrhagic diathesis or coagulation disorder should be considered, certain patients taking anti-coagulant drugs may be present with oral ecchymosis. Capillary hemorrhages such as purpura or petechiae will appear red initially and turn brown in a few days once the extravasated red cells have lysed and have degraded to hemosiderin. Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition in the liver and the other organs and the tissues and this cutaneous pigmenatation is seen in and over 90% of all affected patients [12].
e) Idiopathic: Pigmentation such as Laugier- Hunziker pigmentation (Laugier- Hunziker Syndrome) was initially described as an acquired, idiopathic, macular hyperpigmentation of the oral mucosal tissues specifically involving the lips and buccal mucosa. Upto 60% of affected patients also may have usually are in the form of longitudinal melanotic streaks and without any evidence of dystrophic change [12]

Many oral pigmentations have widespread manifestations and is quite variable ranging from focal, multifocal, or diffuse or blue, purple, brown, gray, or black or macular or tumefactive. The precipitating factors affecting melanogenesis can be sunlight, drugs,hormones,genetic constitution or racial factors [6] Here the oral pathologist plays a very important role in detecting such diseases at the very initial stage.

The incidence of Peutz-Jeghers syndrome reported is 1, 087 people in USA and 4260 people in INDIA. Furthermore oral melanin pigmentation reported is with 30% and 98% among Asians; Arsenic consumption reports (13 million people) in USA and 42.7 million in INDIA. Patients with Smoker's melanosis is found to be 4.1% in India and lastly 0.5% is reported with oral melanoma in India.

Oral pigmentation may be physiologic or pathologic.[13] Pigmentations in the oral cavity vary from color to color and also in shape and size. They may spread as diffusely or remain consolidated in one particular site. They can occur either under normal conditions.

Classification

Oral pigmentation has been associated with variety of lesions and conditions. Oral pigmentation is a relatively common condition that may involve any part of the oral cavity. A dental professional can encounter a number of pigmented conditions in the oral cavity in day to day practice. It is therefore important to differentiate between normal and pathological pigmentations. Broadly, pigmentation is classified into endogenous, exogenous, and idiopathic and heme related pigmentations. However various classifications have been suggested in the literature to elaborate as well as simplify their diagnosis [14].

Classification Proposed By Faizan Alawi [12]:

This classification system groups the orofacial pigmentations

in to 4 broad categories including endogenous and exogenous pigmentation, idiopathic and heme-associated pigmentation. It provides an easy and simplified reference point for the study of the pigmented lesions.

A) Endogenous Pigmentation:
1. Focal Melanocytic Pigmentation
a) Freckle/Ephelis
b) Oral/Labial Melanotic Macule
c) Oral Melanoacanthoma
d) Melanocytic Nevus
e) Malignant Melanoma

2. Multifocal/Diffuse Pigmentation
a) Physiologic Pigmentation
b) Drug-induced Melanosis
c) Smoker's Melanosis
d) Post-inflammatory Hyperpigmentation
e) Melasma(Chloasma)

3. Melanosis Associated With Systemic Or Genetic Disease
a) Hypoadrenocorticism (Adrenal Insufficiency/Addison's Disease)
b) Cushing's Syndrome/Cushing's Disease
c) Hyperthyroidism (Graves' Disease)
d) Primary Biliary Cirrhosis
e) Vitamin B12 (Cobalamin) Deficiency
f) Peutz-Jeghers Syndrome
g) Café au Lait Pigmentation
h) HIV/AIDS-Associated Melanosis

B) Idiopathic Pigmentation
Laugier-Hunziker Pigmentation

C) Hemoglobin And Iron-Associated Pigmentation:
1. Ecchymosis
2. Purpura/Petechiae
3. Hemochromatosis

D) Exogenous Pigmentation
1. Amalgam Tattoos
2. Graphite Tattoos
3. Ornamental Tattoos
4. Medicinal Metal-induced Pigmentation
5. Drug-induced Pigmentation
6. Hairy Tongue

According To Thibodeau Ea *et al*[15]:
This system of classification is grouped into five sub-categories which includes endogenous, exogenous, drug-related, oral & perioral and miscellaneous. This is an elaborate form of classification.

A) Endogenous Pigmentation:
1. Melanin
2. Blood and bile pigments
3. Carotene
4. Lipofuscin

B) Exogenous Pigmentation:
1. Accidental impregnation
2. Iatrogenic impregnation
3. Increased exogenous deposition

C) Drug Related Pigmented Lesions
1. Naproxen
2. Minocycline
3. Chloroquine
4. Cis platinium
5. Cyclophosphamide

D) Syndromes Associated With Oral And Perioral Pigmentation:
1. Peutz-Jeghers Syndrome
2. Laugier-Hunziker Syndrome
3. Addison's Disease
4. Albright Syndrome
5. Neurofibromatosis

E) Miscellaneous Lesions:
1. Varicosities
2. Hemangiomas
3. Black Hairy Tongue
4. Pigmented Fibroma
5. Nevus

According To Pramod John Classification[16]:
This form of classification is basically formed of two broad categories such as endogenous and exogeneous pigmentations. It provides an easy access to understand from this point of reference.

A) Endogenous Pigmentation:
a) Melanin
a) Normal racial variation
b) Addison's disease
c) Peutz-Jeghers Syndrome
d) Albright's Syndrome
e) Hyperfunction of the pituitary gland
f) Pregnancy and female sex hormones
g) Von-Recklinghausen's disease(neurofibromatosis)

b) Bilirubin
a) Jaundice

3. Iron
c) Haemochromatosis

B) Exogenous Pigmentation:
1. Systemically introduced metallic substances
a) Mercury
b) Bismuth
c) Lead
d) Silver
e) Mercury
f) Gold
g) Arsenic

2. Locally introduced pigments
a) Amalgam Tattoo
b) Graphite

3. Miscellaneous Conditions
a) Black Hairy Tongue
b) Carotenaemia
c) Stains from tobacco etc.

According to Amit Parate *et al*[17]:
This form of classification includes provides a descriptive discussion about each lesion and thus provides an enhance idea regarding each lesion in toto.

A) According To Color

1. Color:
a) Blue/Purple
b) Brown
c) Gray Black

2. Focal:
a) Varix/ Hemangioma
b) Melanotic Macule /Nevus / Melanoma
c) Amalgam Tattoo/Graphite tattoo/nevus/melanoma

3. Diffuse:
a) Hemangioma
b) Ecchymosis/melanoma/drug induced/hairytongue/petechiae
c) Amalgam Tattoo/hairy tongue

4. Multifocal:
a) Kaposi Sarcoma/Hereditary hemorrhagic telangiectasia
b) Hereditary hemorrhagic telangiectasia
c) Physiologic pigmentation
d) Neurofibromatosis
e) Lichen Planus
f) Addison's disease
g) Drug induced
h) Peutz- Jeghers Syndrome
i) Metal Ingestion

B) Second Classification
1. Diffuse and bilateral:
Early Onset - Physiological pigmentation
Peutz –Jeghers syndrome
Predominantly adults onset- Addisons's disease
Kaposi sarcoma
Heavy metal pigmentation
No systemic signs and symptoms – Smoker's Melanosis
Drug-induced pigmentation
Post inflammatory pigmentation

2. Focal
Red blue purple blanching: Hemangioma
Varix
Non- Blanching: Thrombus
Hematoma
Blue-gray: Amalgam Tattoo
Other foreign body tattoo
Blue Nevus
Brown: Oral melanotic macule
Pigmented nevus
Melanoacanthoma
Melanoma

C) Endogeneous Pigmentation

Pigment	Colour	Disease Process
Hemoglobin	Blue, Purple, Red	Varix, Hemangioma, Kaposi's sarcoma, Angiosarcoma, Hereditary Hemorrhage telengiectasia
Hemosiderin	Brown	Ecchymosis, Petechiae, Varix, Hemorrhage Mucocele, Hemochromatosis
Melanin	Brown, Black, Gray	Melanotic macule, Nevus Melanoma, Basilar melanoma

According To Sr Prabhu *et al*. [18]:
Classification of Pigmented Lesions of the Oral Mucosa based on the source or origin of Pigment:

Lesions caused by endogeneous pigmentation:
1. Physiological, racial pigmentation (melanoplakia)
2. Ephelis (freckle)
3. Oral melanotic macule
4. Smoking-associated melanosis
5. Lentigo
6. Naevus
7. Melanoma
8. Neuroectodermal tumour of infancy
9. Drug-induced pigmentation
10. Drug-induced pigmentation.
11. Pigmentation associated with systemic disease for example Addison's Disease, Peutz-Jeghers syndrome, Albright's Syndrome, HIV/AIDS

Lesions produced by exogeneous pigmentation:
1. Amalgam Tattoo (Focal Agyrosis)
2. Heavy-metal pigmentation.
3. Tattoos-cultural and social.

Classification of Pigmented Lesions of the oral mucosa Based on Clinical Presentation of Lesions

Localized
1. Amalgam and other tattoos
2. Ephelis(freckle)
3. Melanotic macule
4. Naevus
5. Malignant melanoma

Generalized
1. Genetic
a) Racial(physiological)
b) Peutz-Jeghers syndrome

2. Drug-Related
a) Smoking
b) Heavy metals for example arsenic,bismuth,lead
c) Anti-malarials
d) Tetracyclines
e) ACTH
f) Zidovudine
g) Clofamazine
h) Methyldopa
i) Busulphan
j) Menthol
k) Contraceptive pills
l) Endocrine
m) Addisons disease (hypoarenocorticism)
n) Albright's syndrome
o) Pregnancy
p) Other
q) Incontenentia pigmenti
r) Generalized neurofibromatosis
s) Wilson's disease
t) Gaucher's disease
u) HIV disease

Compiling all the above classifications into consideration, we have proposed our own classification. This classification is

chiefly grouped broadly into 4 categories such as colour, shape & size, location or site and syndromes associated.

A) According To Color:

1. BROWN: Ecchymosis, Petechiae, Varix, Hemorrhage, Mucocele, Hemochromatosis.
2. BLACK: Melanotic Macule, Nevus, Melanoma, Basilar melanoma.
3. GRAY: Foreign Body Tattoo
4. BLUE/PURPLE: Kaposi Sarcoma, Angiosarcoma, Amalgam Tattoo
5. RED: Hemorrhage telangiectasia

B) According to Shape & Size

1. SMALL: Freckle, Oral Melanotic Macule, Melanocytic Nevus, Petechiae
2. MEDIUM: Amalgam Tattoo, Graphite Tattoo, Lichen Planus.
3. LARGE: Melasma, Post-inflammatory Pigmentation

C) According to Location/Site

1. Focal:

a) Unifocal: Hemangioma, Melanotic Macule, Nevus, Amalgam Tattoo

b) Multifocal: Kaposi sarcoma, Hereditary hemorrhagic telangiectasia, Physiologic pigmentation, Neurofibromatosis, Lichen Planus

2. Diffuse: Hemangioma, Ecchymosis, hairy tongue

D) According To Syndromes Associated

1. Generalized: Addisons Syndrome, Nelsons Syndrome, Albright Syndrome
2. Localized: Peutz-Jeghers Syndrome, Laugier-Hunziker Syndrome

Discussion

Pigmented lesions are those lesions which are either endogenous or exogenous in origin. It is multifactorial in nature. Pigmented lesions either present orally or in general which occurs due to deposition of melanocytes in the tissues. Solitary melanocytic pigmented lesions on the oral mucosa are infrequent, representing only 0.9% of cases evaluated in oral and maxillofacial pathology services. Most affected individuals are in their 30s or 40s [20]

According to Alawi *et al*, this classification system groups the orofacial pigmentations in to 4 broad categories including endogenous and exogenous pigmentation, idiopathic and heme-associated pigmentation. It provides an easy and simplified reference point for the study of the pigmented lesions [12].

THIBODEAU EA *et al* stated that classification is grouped into five sub-categories which includes endogenous, exogenous, drug-related, oral & perioral and miscellaneous. This is an elaborate form of classification [15]

Another author named JOHN *et al*. classified is basically formed of two broad categories such as endogenous and exogeneous pigmentations. It provides an easy access to understand from this point of reference [16].

PARATE *et al* in his studies formed a classification includes provides a descriptive discussion about each lesion and thus provides an enhance idea regarding each lesion in toto.[17]

By this author SR PRABHU *et al***,** Classification of Pigmented Lesions of the Oral Mucosa was based on the source or origin of Pigment [18]

These above mentioned authors shows the various locations or sizes concerned with that of the various lesions. But, in our study we have compiled all the above classifications into consideration, we have proposed our own classification. This classification is chiefly grouped broadly into 4 categories such as colour, shape & size, location or site and syndromes associated. Each lesion is sub-divided into small, medium and large. Also the lesions are divided into unifocal, multifocal and diffuse locations.

This classification proposes the entire entities at one particular place which eases our difficulties in studying the classification.

Conclusion

The diagnosis of oral pigmentation is difficult. Thus, biopsy is indeed essential for each and every lesion, so that histopathological evaluation confirms the diagnosis. Thus, classification is made to differentiate the various lesions according to shape, size, color and location of the particular lesion. This classification in lesions would rather provide benefit for the evaluation, prognosis and management in treating the lesion.

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