Normal and Pathological Pigmentation of Oral Mucosa
A Review

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ABSTRACT:
Oral mucous membrane pigmentation refers to both normal and pathological discolouration. The causes of pigmentation are multifaceted. The majority of pigmentation is physiologic, however occasionally it might be a sign of serious disorders. Oral tissues' abnormal melanin pigmentation and colour changes may be important diagnostic indicators of both local and systemic illness. The current literature is reviewed, along with the differential diagnostic, clinical, etiological, and histological characteristics of pigmentation.

KEYWORDS: Endogenous pigmentation, exogenous pigmentation, melanogenesis, melanin, oral pigmentation, Peutz-jeghers syndrome

INTRODUCTION:
Pigmentation, which results from a wide range of disorders and conditions, is a darkening of the gingiva or oral mucosa. Many endogenous and external etiologic factors have been linked to oral pigmentation. [1,2] Five main pigments are primarily responsible for pigmentation. They include carotene, oxyhemoglobin, decreased haemoglobin, melanin, and melanoid. [3] Others are brought on by iron and bilirubin. The buildup of one or more pigments in the oral cavity may be the root of the pigmentation, which then affects the tissues' colour. Both normal and pathologic situations exhibit chromatic variegation in varying degrees. [4] Normal oral mucosa tissues are a light pink tint, however when there is inflammation, the colour changes from pink to red.

Pigmentation is one of the variables that contribute to this colouring. [5] Gingiva, buccal mucosa, tongue, hard palate, soft palate, and mouth floor all exhibit typical geographical differences in oral pigment, ranging from greatest to least. [6]

CLASSIFICATION OF ORAL PIGMENTATION:
Many lesions and illnesses have been linked to oral pigmentation. The following circumstances are taken into consideration while making a differential diagnosis of oral pigmentation, as stated in Table 1. [7]

<table>
<thead>
<tr>
<th>Pigment</th>
<th>Color</th>
<th>Disease process</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemoglobin</td>
<td>Blue, red, purple</td>
<td>Varix, hemangioma, Kaposi's sarcoma, angiosarcoma, hereditary hemorrhage telangiectasia</td>
</tr>
<tr>
<td>2. Hemosiderin</td>
<td>Brown</td>
<td>Ecchymosis, petechiae, thrombosed varix, hemorrhagic mucocele, hemochromatosis</td>
</tr>
<tr>
<td>3. Melanin</td>
<td>Brown, black or gray</td>
<td>Melanosis macule, nevus, melanoma, basilar melanosis with incontinence</td>
</tr>
</tbody>
</table>

EPIDEMIOLOGY:
There is oral pigmentation throughout all human races. Males and females did not exhibit any appreciable differences in oral pigmentation. [8,9] Racial pigmentation of the oral mucosa varies in intensity and distribution not just between races but also within the same race, as well as in different regions of the same mouth. [10] While Dummett suggested, [11] that the degree of pigmentation is in part influenced by mechanical, chemical, and physical stimuli, physiological pigmentation is likely genetically predetermined. There is no difference in the quantity of melanocytes between fair-skinned and dark-skinned people, although oral pigmentation rises in darker skinned people. The variation is linked to variations in melanocyte activity. [10] Regarding the connection between age and oral pigmentation, there is significant debate. All different types of oral pigmentation are present in young children, according to Steigmann and Amir et al. Contrarily, Prinz [12] asserted that physiologic pigmentation did not develop in children and became clinically apparent only after puberty.
DIFFERENTIAL DIAGNOSIS:

The following circumstances are taken into consideration while making a differential diagnosis of oral mucous membrane pigmentation:

A. Localized Pigmentations:
- Amalgam tattoo, graphite or other tattoos, nevus, melanotic macules, melanoacanthoma, malignant melanoma, Kaposi’s sarcoma, epithelioid oligomatosis, verruciform xanthoma

B. Multiple or Generalized Pigmentations:
1. Genetics: Idiopathic melanin pigmentation (racial or physiologic pigmentation), Peutz-Jegher’s syndrome, Laugier-Hunziker syndrome, complex of myxozomas, spotty pigmentation, endocrine overactivity, Carney syndrome, Leopard syndrome, and lentiginosis profuse
2. Drugs: Smoking, betel, anti-malarials, antimicrobials, minocycline, amiodarone, clorpromazine, ACTH, zidovudine, ketoconazole, methyldopa, busulphan, menthol, contraceptive pills, and heavy metals exposure (gold, bismuth, mercury, silver, lead, copper)
3. Endocrine: Addison’s disease, Albright’s syndrome, Acanthosis nigricans, pregnancy, hyperthyroidism
4. Postinflammatory: Periodontal disease, postsurgical gingival repigmentation

Endogenous pigmentation:

The body's internal metabolic processes are what cause the mouth mucosa to have endogenous pigmentations. They consist of hemosiderin, hemosiderin, and melanin. Melanin, which is produced by melanocytes in the basal epithelial layer and subsequently transported to keratinocytes, is the most significant of them all.

Melanin:

The most prevalent endogenous pigment is melanin, a brown pigment not generated from haemoglobin, which is produced by melanocytes found in the basal layer of the epithelium. [10,13]

Although the number of melanocytes in the mucosa is numerically equal to that of the skin, their activity is lower there. Melanin production at the mucosal level can be stimulated by a variety of factors, including trauma, hormones, radiation, and medicines. [2]

Synthesis of melanin:

Starting with the amino-acid tyrosine, which, with the enzyme tyrosinase, is a fundamental prerequisite, the successive steps in the production of melanin are as follows:

```
Tyrosine
  ↓
Dopa
  ↓
Dopa-quinone
  ↓
Dihydroxy-indole
  ↓
Dopa-chrome
  ↓
Leuco-dopa-chrome
  ↓
Indole 5, 6- quinone
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When tyrosine is oxidized by tyrosinase, dopaquinone is produced as the immediate product. In the absence of cysteine, dopaquinone undergoes the intramolecular addition of the amino group giving leukodopachrome. The redox exchange between leukodopachrome and dopaquinone then gives rise to dopachrome. Dopachrome gradually decomposes to give mostly 5,6-dihydroxyindole (DHI), and to a lesser extent DHI-2-Carboxylic acid (DHICA). This latter process is catalyzed by tyrosinase-related protein-2, now known as dopachrome tautomerase. Finally, these DHI are oxidized to eumelanin. tyrosinase-related protein-1 is believed to catalyze the oxidation of DHICA to eumelanin. On the other hand, in the presence of cysteine, dopaquinone rapidly reacts with cysteine to give 5-S-cysteinyl dopa and to a lesser extent 2-scysteinyldopa. Cysteinyldopas are then oxidized to give benzothiazine intermediates and finally to produce pheomelanin.

1. Oral melanotic macule

A benign pigmented lesion of the oral cavity has been referred to as a melanotic macule. It shows an increase in basal cell layer melanocytes' production of melanin pigments without an increase in the total number of melanocytes. As a result, it develops on the lower lip's vermillion border and is thought to be caused by actinic exposure. It is a consistent size of around 1 cm, brown or brown black colouring. It is an asymptomatic illness. [1] There is no need of additional therapy once diagnosis got established.

2. Nevus

Nevus refers to the pigmented lesion composed of nevus cells. The pigment cells that migrate from the neural crest to the epithelium give rise to the nevus cells. They might appear as flat or barely elevated lesions, tumours, or both. Nevus can range in hue from bluish grey to brown to practically black, or they may not be pigmented at all. Most oral nevi may have a maximum diameter of less than 1 cm in about 80% of cases. [17] Any intraoral pigmented nevi should be surgically removed.

3. Malignant melanoma

A neoplasm of epidermal melanocytes is melanoma. These are posterior tumours and make up less than 1% of all mouth cancers. They are frequently discovered on the hard palate, then on the gingiva. [18] It might be brown, black, or blue in colour. It manifests in the oral cavity as brown or black plaques with uneven borders on the anterior labial gingiva and the anterior portion of the palate. [16]

Having incontinence and basilar melanosis The research has placed increased attention on the direct impact of smoking on oral mucosal pigmentation. It is well known that basilar melanosis causes excessive melanin pigmentation. The activation of melanin may be a defensive mucosal reaction to either the heat of the smoke or to an irritant included in the cigarette. [19] It can be found on the lateral tongue, palate, buccal mucosa, etc. The diagnosis can be made by biopsy of the lesion. It usually disappears within 3 years of smoking cessation. [20]

Oxyhemoglobin and Reduced Hemoglobin-

Oxyhemoglobin and reduced hemoglobin are pigments resulting from hemosiderin deposits. The skin color is affected by the capillary and venom plexuses shining through the skin.

1. Varix A

A varix is a dilated, convoluted vein that is typically subjected to high hydrostatic pressure but is not well supported by the tissue around it. The ventral surface of the tongue is the primary location for this sort of pigmentation. It appears as numerous, erratic, gentle elevations that are bluish purple in colour. [17] If a thrombus is present, pressure does not cause it to blanch. It typically has a diameter between 2 and 4 mm. Electrosurgery or cryosurgery can be used to eliminate the lesion or excise it. [16]

2. Hemangioma

Endothelial cells in vascular channels are growing rapidly. It could have traumatic and congenital roots. Although there is no established cause, one theory puts the growth of hemangiomas down to oestrogen signalling. [22] They can develop on the tongue, lips, buccal mucosa, gingiva, palatal mucosa, salivary glands, alveolar ridge, and jaw bones but are uncommon in the oral cavity. It can take the form of a nodular blue tumefaction to a flat reddish blue macule (port-wine stain). [16] Surgery, flash lamp pulsed laser, intralesional fibrosing agent injection, and electrocoagulation are among the available treatments. [21]

3. Kaposi sarcoma

It is a multicentric proliferation of vascular and spindle cell components. HIV/AIDS is implicated with this tumour. Kaposi's sarcoma has a strong association with immunosuppression. [23] The tongue, gingiva, and posterior hard palate are all affected by oral lesions. Rarely, the patient has just one cutaneous lesion, which frequently occurs on the head or neck. It starts out as a flat,
c crimson macule that is varied in size and irregular in shape. Nodular lesions may become unattractive and hinder chewing; in this case, electrocautery and excision may be desired forms of therapy. Very active anti-retroviral medication is helpful for controlling AIDS-related Kaposis sarcoma.

4. Hereditary hemorrhagic telangiectasia

It is also known as Osler Weber Randu syndrome. Papules are not purple, but rather red or brown. When pressed, the lesions turn white; when released, they return to their original hue. It is characterised by numerous, round or oval papules typically <0.5 cm in diameter. A cherry-red macule with a diameter of 1 to 3 mm is the early oral lesion. It can happen during pregnancy, chronic liver illness, ataxia-telangiectasia, and other diseases. Electrocautery under local anaesthetic is the method of treatment for telengectatic regions that need to be eliminated.

5. Angiosarcoma

A malignant mesenchymal tumour called angiosarcoma differentiates into vascular endothelium. It is also referred to as intravascular endothelioma, angioblastoma, malignant hemangoendothelioma, and hemangiosarcoma. Angiosarcoma is a fairly aggressive tumour in general. encompasses the tongue, lips, floor of the mouth, cheeks, and palate. It presents as a red-blue to purplish nodular tumour with poorly defined borders. There is no preference based on gender. The mainstay of treatment is still surgery. Post-operative radiation may be utilised as part of a combination therapy regimen.

Hemosiderin-

1. Ecchymosis

Ecchymosis, also referred to as bruises, typically develops following injury. On the lips, traumatic ecchymosis is typical. Anytime there is damage, the erythrocytes leak into the submucosa and show as brilliant red macules. After a few days, the lesion turns brown as hemosiderin breaks down the haemoglobin. They are larger than petechiae and larger than pin-point dots (1-3 mm). The administration of epinephrine or the application of cold is used to stop the development of ecchymosis.

2. Petechiae

Petechiae are tiny, pinpoint haemorrhages under the skin or in the mucous membrane. Capillary haemorrhages start out red and change to brown over the course of a few days after the extravasated red cells have lysed and been broken down to hemosiderin. Although any mucosal site may be impacted, the soft palate is where the petechiae are most frequently found. Prior to identifying and treating the issue, surgery should not be done.

3. Hemochromatosis

Excessive iron deposition in the liver and other organs and tissue characterises hemochromatosis, a chronic, progressive illness that can cause organ damage. Also known as bronze diabetes. Hemochromatosis is brought on by an abnormality in the genetic code that causes an excessive intake of iron. The most often impacted areas of the oral cavity are the palate and gingiva. The oral pigmentation is frequently widespread and appears brown to grey. It is handled with phlebotomy.

Exogenous pigmentation:

Typically, traumatically deposited exogenous pigments are placed right in the submucosa. Some, though, may be consumed, absorbed, and distributed hematogenously, precipitating in connective tissues, especially in regions prone to persistent inflammation, like the gingiva.

1. Amalgam tattoo-

The amalgam tattoo is the most prevalent kind of focused pigmentation in the oral mucosa. Large amalgam restorations contain them. The mandibular region is more frequently impacted than the maxillary region, with the gingiva and alveolar mucosa being the most frequent sites. Blue-black pigmentation is the colour. A biopsy is required if there is no radiographic indication of amalgam, the lesion is not close to any restored teeth, or it abruptly manifests.

2. Graphite tattoo -

Sometimes pencil points break off in the gingival tissue, and if they are not entirely removed, they can leave a permanent stain like a graphite tattoo. The lesion may be grey or black in colour. Since both melanoma and graphite tattoos frequently appear on the palate, it is imperative to distinguish between the two. The particles in graphite mimic those in amalgam.

3. Hairy tongue-

The filiform papillae's improper desquamation causes hairy tongue. It affects the dorsum of the tongue, especially the middle and back third. Filiform papillae in hairy tongues can reach lengths of up to 15 mm. Depending on the exact etiology, it can be brown, white, or green in hue. You can get rid of the filiform papillae by simply brushing your tongue with a toothbrush.
4. Pigmentation Related to Heavy Metal Ingestion-

Different types of heavy metal pigmentation are as following:

- Bismuthism
- Plumbism
- Mercurialism
- Argyriosis
- Arsenism Auric stomatitis

A) Bismuthism

It is a result of bismuth poisoning brought on by the use of bismuth-containing products for medical purposes. Hydrogen sulphide reacts with the component of bismuth to form this pigment. Patients frequently express discomfort in the oral cavity and a metallic taste. In the cheek mucosa in the molar region, large, excruciatingly painful, superficial ulcerations can occasionally be detected. On gingival papillae, the "blue black" bismuth line appears to be clearly defined. Its impact can be reduced by practising good dental hygiene, quitting bismuth use, and other lifestyle changes. [34]

B) Plumbism

Lead in paints, glazes, cooking utensils, batteries, ointment, and containers is to blame. Through both direct contact with ingested lead and the release of lead in saliva, oral tissues are exposed to lead. An unpleasant metallic taste, increased salivation, and dysphagia are present. The "burtonian line," which is seen along the gingival margin, is evident when lead exposure is very high and dental hygiene is very bad. Chelating agents can be used to eliminate lead from the body. [34]

C) Mercurialism

It could be acute or persistent. Acrodynia and pink sickness are other names for it. It is a rare disease brought on by a mercury toxicity reaction, which may result from genuine mercury poisoning or, more often, from a metal sensitivity. The patient will show a lot of salivation. Pain makes mastication difficult. The gums have a darker shade than usual. To reduce salivation, a doctor may give atropine or belladonna. [34]

D) Argyriosis

The condition, also known as argyrosis, is brought on by repeated exposure to a silver compound. The nail beds and other exposed body surfaces have a severe discoloration. The skin is slate grey, violet, or cyanotic, and there may even be a hint of metallic shine in some cases. The gingival and mucosal tissue has a widespread distribution of pigmentation. Eliminating the point of contact is necessary. [34]

E) Arsenism

It happens as a result of arsenic poisoning brought on by purposeful usage, industrial exposure, or therapeutic use. Oral tissues experience excruciating pain, significant inflammation, and the potential for severe gingivitis. It has a dry mouth. The colour of tissues is a rich crimson. Ulceration is a common side effect of arsenic trioxide local exposure. It is recommended to administer surface anaesthetic ointments or rinses such lidocaine or dylonine solution. [34]

F) Auric stomatitis

Leprosy, lupus erythematosus, and rhesus arthritis can all be treated with gold. Its overuse leads to the oral mucosa developing vesiculations and ulcers. That is the patient's most frequent complaint when receiving gold therapy. It causes a slight tint of blue or purple. Alkaline mouthwashes and stopping gold therapy will lessen its impact. [16]

Idiopathic pigmentation-

One such pigmented lesion, the Laugier-Hunziker syndrome, may raise more red flags. Increased melanosomes and their migration to the epithelium's basal cell layer are the aetiology of this lesion. [15] It is more frequent for Caucasians or those with light complexion to get this illness. It is lenticular, asymptomatic, and less than 5 mm in diameter. Most commonly, the lips, hard palate, and buccal mucosa will exhibit this lesion. The lesion can be treated with laser therapy and cryotherapy. [7]

Peutz-Jeghers Syndrome-

A genetic condition known as Peutz-Jeghers syndrome (intestinal polyposis) is characterised by mucocutaneous pigmentation and intestinal hamartomas. [36] It appears as macules that resemble freckles on the palms, perioral skin, and intraorally in the labial, gingiva, and buccal mucosa. [37] Diameters of pigmented patches range from 1 to 0 mm. The lower lip and buccal mucosa are particularly prone to pigmented patches, whereas the upper lip, tongue, palate, and gingiva are far less frequently affected.
Smoker’s Melanosis-
A benign localised pigmentation of the oral mucosa is known as smoker's melanosis. With cigarette use, it typically rises dramatically. [38] Oral surfaces of smokers are noticeably more pigmented than those of non-smokers. Clinically, the lesion often appears as many brown pigmented macules less than 1 cm in diameter, mostly located in the mandibular interdental papillae and the connected labial anterior gingival. Females are more likely to develop Smoker's Melonosis, mainly after their third decade of life. [36]

Antimalaria Drug Use-
It is known that a number of antimalarial medications might cause intraoral melanin pigmentation. Quinacrine, chloroquine, and hydroxychloroquine are some of these medications. [39,40] The oral mucosa may become pigmented with prolonged use. The oral mucosa's pigmentation is described as slate-grey in tone and resembling pigmentation brought on by silver arspleamine to some extent. [41]

Minocycline Use-
Acne vulgaris is frequently treated with minocycline, a synthetic tetracycline. [1,42] Although tetracycline pigments bones and teeth, soft tissue pigmentation is also brought on by minocycline alone. [43] Brown melanin deposits are typically visible on the tongue, gingiva, hard palate, and mucous membranes. [1,43]

Addison’s Disease-
Adrenocortical injury and hypofunction are the causes of Addison's disease, also known as primary adrenocortical hypofunction. There may be skin bronzing as well as enhanced pigmentation of the lips, gingivae, buccal mucosa, and tongue. [44,45] The condition may first manifest as oral pigmentation. In cells of the stratum germinativum, a biopsy of the oral lesions reveals acanthosis with silver-positive granules. The basal layer contains melanin. [49]

Periodontal Diseases-
The oral mucosa frequently becomes discoloured as a result of periodontal disorders. Since gingivitis increases vascular permeability and gives heavy metals access to the soft tissues, it exacerbates pigmentation. Re-pigmentation of the melanin is associated to surgical injury. [46]

HIV Infection-
Progressive hyperpigmentation of the skin, oral mucosa, fingernails, and toenails has been linked to primary adrenocortical insufficiency and, in certain circumstances, zidovudine (azidothymidine) therapy in individuals with human immunodeficiency virus (HIV). [47] Oral pigmentation manifests clinically as irregular macules that are brown or dark brown in colour. The most often impacted areas are the palate, buccal mucosa, and tongue. [36]

INVESTIGATIONS:
Various investigations required in diagnosis of oral pigmentation are as following:

- History
- Dermoscopy
- Binocular stereo microscope
- Pigmentations
- Biopsy

History-
The patient's complete medical and dental history is included in the history of the pigmented lesion. After that, laboratory testing as well as extraoral and intraoral examinations should be carried out. The history of a pigmented lesion comprises the start and duration of the lesion, as well as the existence of any concomitant hyperpigmentation. [36]

Dermoscopy-
A non-invasive diagnostic method called dermoscopy is used to examine pigmented lesions and find cutaneous melanoma early. Also, it aids in preventing pointless oral cavity procedures and large excisional biopsies. [48]

Binocular stereo microscope-
The ability of this diagnostic method to distinguish between benign and malignant melanocytic processes and melanocytic lesions has been demonstrated. [7]
Pigmentations-
It is common to find abnormal insoluble deposits that are not clearly stained with H or E and are yellow, brown, or black in colour. An crucial role for pigments in illness diagnosis. Color, size, and form can be used to identify pigments, as well as chemical tests.

Biopsy-
Oral biopsies are thought to be necessary for accurate and conclusive diagnosis of disorders of the oral mucosa as well as for planning the best course of treatment.

CONCLUSION:
A vast range of intricate elements, some of which are reliant on appropriate nutrition, work together to preserve the integrity of the oral mucous membrane. In the past, a wide range of ailments have been linked to the lack or depletion of key nutritional components, particularly vitamins. One should always pay attention to how different oral tissues appear from their typical colour because some of these alterations could be signs of underlying pathology. Even epidemiology may be of some assistance in guiding practitioners because it can be challenging to diagnose pigmented lesions in the oral cavity and surrounding tissues. Typically, a biopsy and histopathologic study of the lesion are necessary for the final diagnosis. Therefore, for accurate patient evaluation, diagnosis, and therapy, it is crucial to have a thorough grasp of the numerous diseases and drugs that can cause oral and perioral pigmentation.

REFERENCES


