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PHYSIOLOGICAL AND PATHOLOGICAL DARK PIGMENTATION IN ORAL MUCOSA

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Abstract. *The presence of melanocytes in the oral epithelium is a well established fact but their physiological functions are not well defined. milline provides protection from environmental stressors such as ultra violet radiation and reactive oxygen and melanocyte function as a stress sensors having capacity to react and to produce variety of micro-inveremental cytokines, and growth factors modulating immune inflammatory and antibacterial responses. There is wide range of normal and pathological variations in melanin pigmentations of the oral mucosa. Oral pigmentation can be physiological or pathological and endogenous and exogenous. Such lesions represent a variety of clinical entities, ranging from physiologic changes to manifestation of systemic illnesses and malignant neoplasms.The color of oral mucose depend upon the epithelial thickness, the keratin status, the vascularity and the density of the underlying fibrous tissue. Dark or black pigmented lesions can be focal, multifocal or diffuse macules. The pigmented lesions including entiteties such as physiological pigmentation, smokers melanosis, melanotic macule, drugs pigmentation, Peutz-Jeghers syndrome, Kaposi`s sarcoma, pigmentation related to heavy-metal ingestion (lead, mercury, bismuth amalgam), endocrinopathic pigmentation, and melanoma malignum.*

1. INTRODUCTION

Oral mucose is not uniformly colored. the color varies in different physiological or pathological conditions[1,2,3,4,5,6]. physiological pigmentation is frequent in asians, africans and mediterranean people[3].

These lesions represent a width variety of clinical entities, ranging from physiological changes to manifestation of systemic illnesses and malignant neoplasm. It can be important symptoms, sometimes the first symptom or accompanied symptom in some diseases. Therefore oral pigmentation needs to be assessed carefully by a medical professional.

Pigmentation of oral mucose membrane may be endogenous or exogenous in origin. Endogenous pigments included melanin, hemoglobin, hemosiderin and carotene. Melanin is produced by melanocytes in the basal lear of the epithelium and its transferred to adjacent keratinocytes via membrane-bound organelles called melanosomes. Melanin is also synthesized by nevus cells, which are derived from the neutral crest and are found in the skin and mucosa [7] Pigmented lesions caused by increased melanin deposition may be brown, blu, grey or black, depending of amount and location of melanin in the tissues [8]. Exogenous pigmentation (heavy metals, drugs, foreign bodies), may also promote pigmented lesions, which can vary in intensity and extension and can occur in any sites in the oral cavity.

2. PHYSIOLOGICAL PIGMENTATION

Physiologic pigmentation is common in darker skinned individuals, African, Asian and Mediterranean population, is due to greater melanocyte activity rather than a greater number of melanocytes [3]. The color of physiological pigmentation can range from light brown to almost black. Microscopical examinations of physiological pigmented oral mucosa show increased melanin in the basal cell types and sometimes in the upper portion in lamina propria with him melanophages or simply as extracellular melanin particles [9]. This microscopical features are very similar to those found in melanotic maculae and smokers melanosis [3]. Physiological oral pigmentation and pathological oral pigmentation that may be similar in appearance should be differentiator. deceases that may be confuced with physiological oral pigmentation include Adison decease neurophybromatosis oral melanotic maculae ray mucosal mellanoma, drug-induced oral mucosa pigmentation, and too as much lesser extended Kaposi sarcoma, vascular malformation and angioma of the oral mucosa [10]. The pigmentation is symmetrically distributed, especially on the gingival [Fig. 1] and buccal mucosa, on the hard palate, lips and tongue may also be seen as brown patches with well-defined borders.

Physiological melanin pigmentation of the oral mucosa affects males and females equally, as asymptomatic, solitary or multiple brown maculae with well-defined borders [Fig. 1] [11]. It may involve any part of the oral mucosa but most frequently the gingiva [3, 11, 13]. Oral pigmentation gradually appears during the first two decades od life.[11] but affected subject maybe unaware of it. [11,13]. The extend and intensity of oral pigmentation increase with age [13,14] concurrently with increase of the number of melanocytes, perhaps because of the effects of potential melanogenic stimuli such recurrent minor functional injury inflammatory conditions medication, or tobacco smoke cumulative [15]. Physiological pigmentation increases with age and color intensity, and can be influenced by smoking, hormones and systemic medication [16]. The attached gingiva is the most common location, but physiological pigmentation can be noted anywhere in the oral cavity (buccal mucosa, hard palate, lips and tongue). This pigmentation is asymptomatic and no treatment is required [17]. Pathological oral melanin pigmentation are divided in two group benign, malign and hereditary. Most common benign oral mucosa pigmentation.

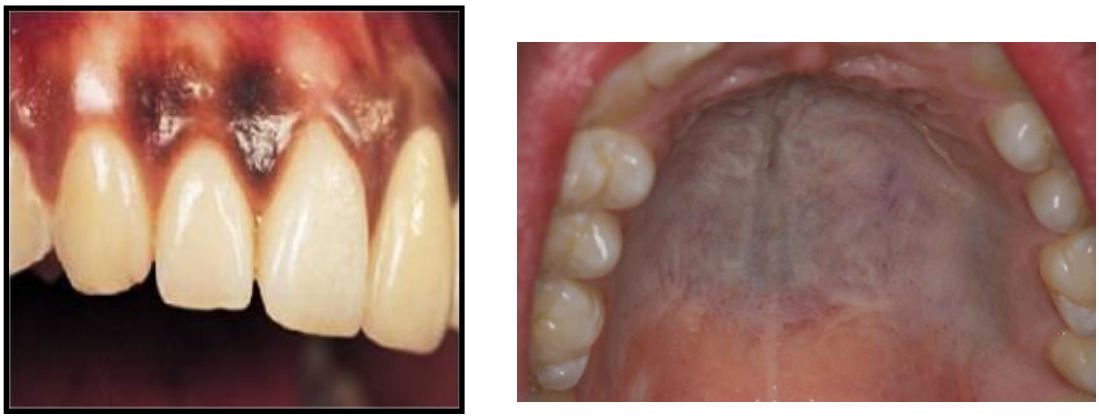

Figure 1. Physiologic pigmentations in gingiva

3. DRUG INDUCED PIGMENTATION

A variety of drugs can induce oral mucosa pigmentation [13, 14]. This pigmentation can be localized, usually to the hard palate, or they can be multifocal throughout the mouth. The pathogenesis of drug-induced pigmentation varies, depending on the causative drug. It can involve accumulation of melanin, deposit of the drug or one of its metabolites, synthesis of pigments under the influence of the drug deposition on iron after damage to the dermal on mucosal vessels. Chloroquine and other quinine derivates are used in the treatment of malaria, cardiac arrhythmia and a variety of immunoglobulin's diseases including systemic and discoid lupus erythematosus and rheumatoid arthritis. Mucosal discoloration associated with this group of drugs is described as blue-grey or blue-black, and in most case only the hard palate is involved [25,26]. [Fig.2] female patient with typical discoloration of the teeth after prolong use of tetracycline.

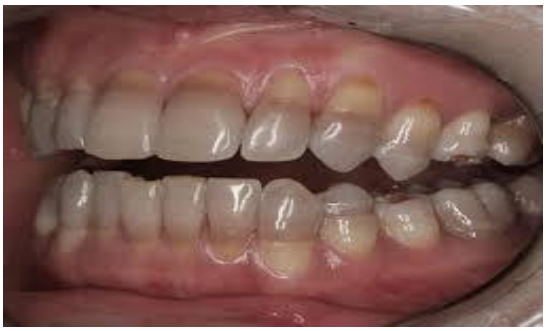

Figure 2. Tetracycline discoloration of teeth

In predisposed patients, drugs may cause inflammatory reaction and subsequently induce post inflammatory hyper-pigmentation, a non-specific reaction that is the basis of pigmentary change seen in fixed drug reaction [27]. Drugs such as arsenic can directly induced pigmentation by combining with sulfhydryl groups in the epithelial cells causing promotion of the action of tyrosine. Other such as the phenothiazines and minocycline may be deposited in mucosa and directly react with melanin to from a drug-pigment complex. Cortimozole was the most common drug associated to oral pigmentation followed by tetracycline: however, many others have been implicated, including colchicines, ketoconazole, pyrimethamine and barbiturates [28]. Fixed drug eruptions are more commonly seen in people with dark skin and often present as a slate brown color due to pigmentary incontinence of melanophages in the upper dermis. Pigmented macules of the tongue have also been described, occurring as a result of a fixed drug eruption [29].

4. MELATONIC MACULE

The oral melanotic macule is a small, well-circumscribed, brown-to-black that occurs commonly on the lips and gingiva, followed by palate and buccal mucosa [18,19]. Melanotic maccules are usually smaller than 1 cm in diameter and show a well demarcated smooth border [Fig.3].

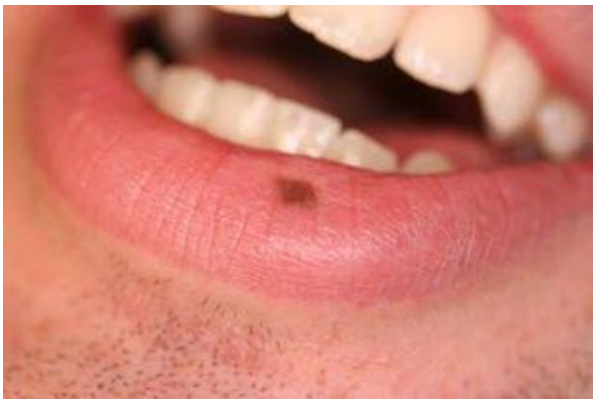

Figure 3. Melanotic macule

They usually occur as single lesions, but multiple lesions are sometimes seen [10]. The color may be light or dark-brown and is homogenous within each lesion. Melanotic macules are more common in women and yang adults. These are benign pigmented lesions and are not know to transform into melanoma [20]. Biopsy may be indicated to rule out melanoma and no treatment in otherwise indicated.

5. HEAVY METAL PIGMENTATION

Increase in heavy metal (e.g. lead, bismuth, mercury, arsenic and gold) levels in the blood leads to oral mucosal discoloration. It is mostly seen in individuals exposed to heavy metal occupational, or patients taking drugs containing heavy metals such as arsenic, mercury or silver.[7]. The pigmentation appears as a blue-black line along the gingival margin and seems to be proportional to the amount of gingival inflammation as stated by Esen et al. [8,30]. Other oral mucosal sites may also be involved [Fig. 4].

A variety of systemic signs and symptoms may be seen depending on the type of heavy metal exposure [8]. Malignant transformation of oral pig- mentation due to heavy metal pigmentation has not been reported. Yet care should be taken regarding severe systemic toxicity.

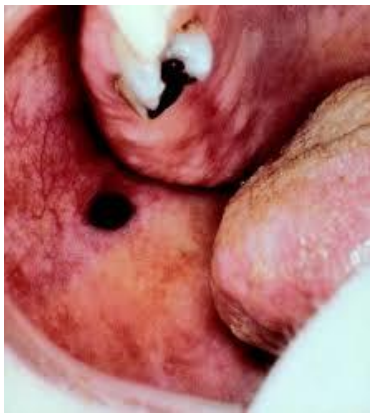

Figure 4. Heavy metal pigmentation

6. SMOKERS'S MELANOSIS

Smoking may cause oral pigmentation in light-skinned individuals. Smoker's melanosis occurs in 25-31% of tobacco users. There is increased production of melanin which may provide a biologic defense against the noxious agents present in tobacco smoke [21]. Lesions are brown-black and most often on the anterior labial gingiva, followed by the buccal mucosa. There are irregular, some are even geographic or map like on configuration. The intensity of the pigmentation is the related to the duration and amount of smoking [21, 22]. Women are more commonly affected than man, which suggest a possible synergistic effect between the female sex hormones and smoking [21]. Biopsy should be performed if there is surface elevation or increased pigment intensity or if the pigmentation is in an unexpected site [23].

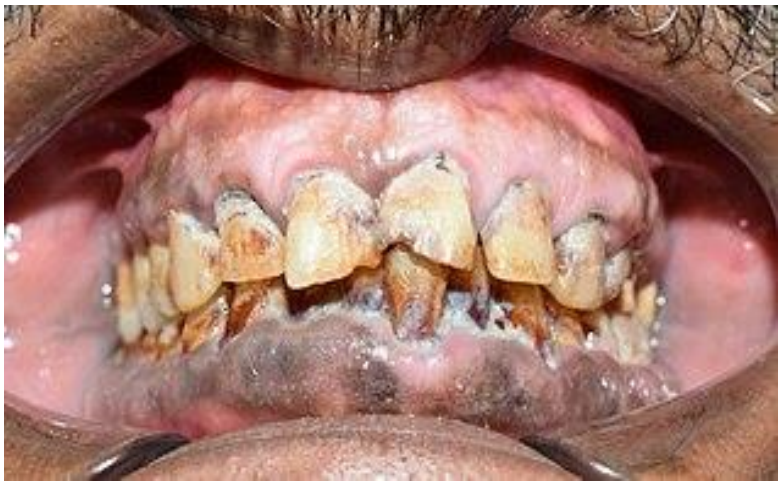

Figure 5. Smoker`s melanosis

7. AMALGAM TATTOO AND OTHER FOREIGN-BODY PIGMENTATION

Many metals have been implicated in the production of pigmentation in oral mucose. Lead, mercury and bismuth have all been shown to be deposited in oral tissue if ingested in sufficient quantities or over a long course of time [31, 32]. These ingested pigments tend to extravagate from vessels in foci of increased capillary permeability such as inflamed tissue. Thus in the oral cavity, the pigmentation is usually found along the free marginal gingiva, where it dramatically outlines the gingival cuff, resembling eyeliner. The metallic line has a gray to black appearance.

Graphite may be introduced into the oral mucosa through accidental injury with graphite pencil. The lesion occurs most frequently in the anterior palate of yang children, appearing as an irregular grey to black macule [23].

An amalgam tattoo is a localized, blue-gray lesion of variable dimensions most commonly cited on the gingiva or alveolar mucose, or less commonly of the floor of mouth or buccal mucosa. Amalgam tattoo is one of the most common causes of intraoral pigmentation. The lesion does not disappear with pressure, and there are no signs of inflammation at the periphery of the lesion. If the deposits of amalgam in the tissues are large enough, they may be show up radiographically as radiopaque debris in the soft tissues or superimposed on hard tissue.

a history of injures confirms the diagnosis otherwise a biopsy should be performed to exclude the possibility of melanoma. as amalgam filings still are ubiquitous and amalgam tattoos remain one of the most common causes of intramural pigmentation, we consider amalgam tattoos to be an important differential diagnosis consideration, when assessing patients suspect for mucosal melanoma of oral cavity. information regarding previous prosthetic dental work should be included in the patient medical history and x ray showing metal deposits in the mucosa

As amalgam fillings still are ubiqui- tous and amalgam tattoos remain one of the most common causes of intraoral pigmentation, we consider amalgam tattoos to be an important differential diagnosis considera- tion, when assessing patients suspected for mucosal mela- noma of the oral cavity. Information regarding previous prosthetic dental work should be included in the patient's medical history, and an X-ray showing metal deposits in the mucosa can safely rule out mucosal melanoma. But when in doubt, we recommend a diagnostic biopsy for histopathological examination [10]. This lesion is just a localized reaction to metal deposition in the mucosa.

8. ENDOCRINOPATHIC PIGMENTATION

Patchy melanosis on the oral mucose and bronzing of the skin are signs of Adison`s diseases and Cusing`s syndrome. In both of these endocrine disorders, the cause of hyperpigmentation is over secreting of ACTH, a hormone with melanocyte-stimulating properties.

Primary hypoadrenalism is due to progressive bilateral destruction of the adrenal cortex by autoimmune disease, infection or malignancy. A decreased level of adrenocortical hormones in the blood stimulates ACTH production in the anterior pituitary. Increased ACTH induces melanocyte-stimulating hormone, resulting in diffuse pigmentation of the skin and oral mucose. Intraorally, this presents as a brown patches on the gingiva, buccal mucosa, palate and tongue [Fig.6] These lesions may resemble racial pigmentation, but they developed during adult life and are progressive. Oral pigmentation may be the first, sign and oral biopsy show acanthosis with silver positive intracellular granules in the stratum germinatuvum and melanin in basal layer. Addisons may give systemic manfestations such as weakness, nausea, vomiting, abdominal pain, constipation or diarrhea, weight loss and hypertension. Management is cause related and corticosteroid replacement therapy.

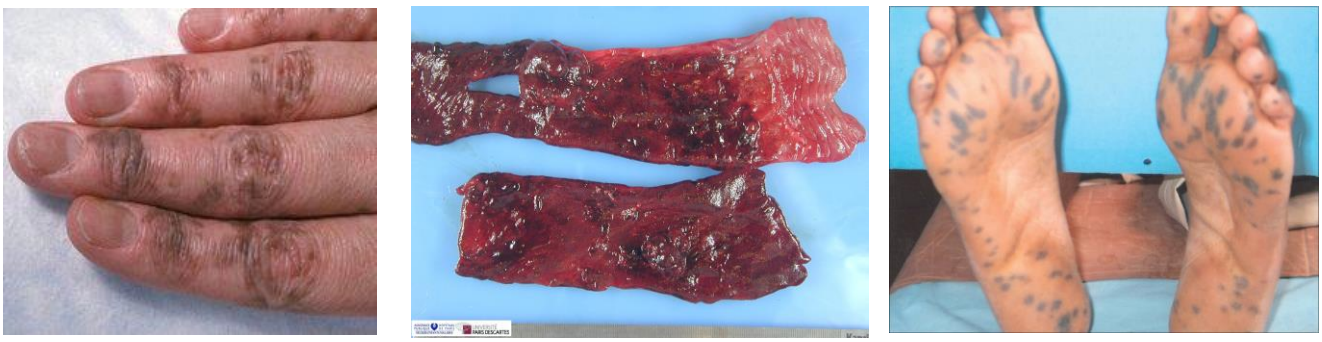

Figure 6. Addison disease

In Chushing`s syndrome, adrenocortical hyperactivity is observed, and if such activity is caused by a cortical secretory adenoma or cortical hyperplasia of adrenal origin, ACTH secretion will be shut down. Patients with Cushing`s syndrome may be hypertensive and hyperglycemic and may show facial edema “moon face”. Oral pigmentation may be the first sign on the gingiva, palate and bucall mucose. These changes in pigmentation are due to an accumulation of melanin granules, as a consequence of increased hormone dependent melanogenesis.

9. MUCOCUTANOUS MELATONIC PIGMENTATION AND GASTROINTESTINAL POLYPOSIS (PEUTZ-JAGHERS SYNDROME)

The hereditary intestinal polyposis syndrome is an unusual condition which is of the interest to the dentist because, pigmentation in oral cavity is usually patognomic sign, for these syndrom. The cause of human herpes virus 8, and the lesion most commonly occurs on the hard palate present from birth and appears as a small brown macules. On the lips, especially the lower and oral mucosa can be seen round, oval, or irregular, rarely confluent macules of blush-gray pigment of variable intensity. They vary of size from 1 to 12 mm, in general, larger than those on the cutaneus surface, which diameter is 1 to 5 mm. Intraorally the buccal mucosa is most frequently involved, with the gingival and hard palate next. Selom does the tangue show this pigmentation. On the face the spots tend to be grouped around the eyes, nostrils and lips.
Histologically, these lesions show basilar melanogenesis without melanocytic proliferation. The melanotic spots do not require treatment and are not associated with increased risk of melanoma. Such oral lesions help in early diagnosis and should alert the clinician to prompt the patient to screen for cancers in organs implicated in this syndrome.

Figure 7.Peutz-Jeghers syndrome

10. KAPOSI'S SARCOMA

This is a multifocal malignancy seen mostly in HIV infected patients. Appearance of Kaposi`s sarcoma is considered a heralding event for progression to AIDS [Fig.8a]. The cause is human herpes virus 8, and the lesion most commonly occurs on the hard palate, gingival and tang. Early lesions are macular, brown to purple and often bilateral[fig.8]. Advanced lesions are dark red to purple plaques or nodules with or without ulceration, bleeding and necrosis. Biopsy shows a proliferation of spindle shaped cells surrounding poorly formed. Vascular spaces or slits with numerous extravagated erythrocytes.

a) Typical Kaposi`s sarcoma* *b) Kaposi`s sarcoma attached to gingiva

Figure 8. Kaposi`s sarcoma

11. ORAL MELANOACANTHOMA

Oral melanoacanthoma is uncommon benign pigmented lesion of the oral mucosa, characterized by proliferation of dendritic melanocytes dispersed throughout the thickness of an acanthotic and hyperkeratotic surface epithelium [15,33]. Clinically, the lesion appears hyper pigmented black or brown, flat or slightly raised. 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 [34]. Howeverits tendency to occur in young black females distinguishes it from melanoma, which is uncommon in this age and racial group. Goode et al. stated that the buccal mucosa is the most common site of occurrence, which may be related to greater frequency of trauma in this area [33]. Oral melanoacanthoma appears to be a reactive lesion with no malignant potential. In some cases, the lesion disappears after incisional biopsy or removal of the offending stimulus [34].

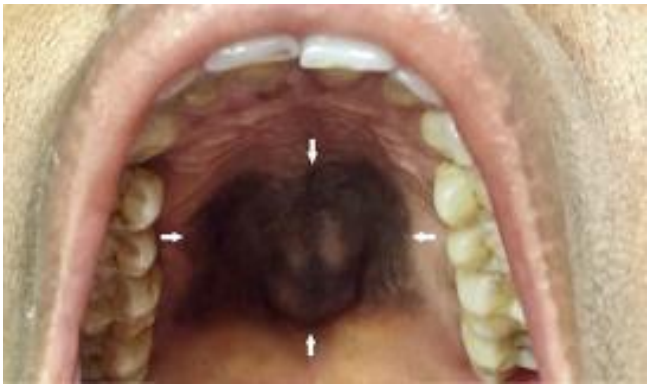

Figure 9. Oral melanoacanthoma

11. ORAL MELANOME

Oral mucosal melanoma is rare, accounting for less than 1% of all oral malignancies. Clinically, oral melanoma may present as an asymptomatic, slow-growing brown or black patch and bone destruction. In approximately one-third of the cases, oral manifestations are characterized by a prolonged radial growth phase followed by a vertical growth phase, whereas others exhibit a faster progression into a vertical growth phase [35]. The most common site it's the hard palate, with 30%, followed by gingival, which account for 1/3 of case [36]. Oral mucosa melanoma is generally encountered between fourth and seventh decade of life, with a greater incidence in man than in women. Histologically, the radial growth phase represents in situ and superficial melanoma and the vertical growth phase represent the modular or invasive melanoma [Fig.10].

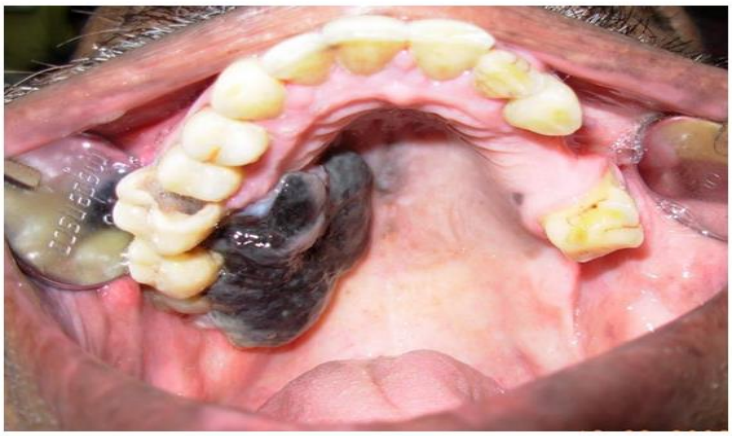

Figure 10. Oral melanoma

The oral melanoma is not subdivided into the classical cutaneous melanoma categories, which include superficial spreading melanoma, nodular melanoma and acral lentiginous melanoma [37]. Treatment involves radial surgical excision with clear margins. This may be difficult to accomplish because of anatomic constrains and proximity to vital structures. Radiation and chemotherapy are ineffective, which adds to the difficulties associated with management on this malignancy. Distant metastases often affect the lungs, brain, liver or bones. The prognosis for patients with oral melanoma is much worse than for those with cutaneous lesions and the overall 5-year survival rate is 16% [38].

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