

Drug Induced Oral Pigmentation : A Review.

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Review Article

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Abstract

Pigmented lesions of the oral mucosa are encountered on a routine basis in clinical practice. Oral health-care providers must assess several parameters associated with pigmented lesions. Oral mucosal color changes can be significant and gives diagnostic value of local or systemic disease though it requires clinical experience and thorough evaluation. Color changes in the oral mucosa can be attributed to the deposition of either endogenous or exogenous pigments as a result of various mucosal diseases. The various pigmentations can be in the form of blue/purple vascular lesions, brown melanotic lesions, brown heme-associated lesions, gray/black pigmentations. Therefore, watchful examination of all the oral mucosa is frequently required. There are variable manifestation of oral pigmentation. The specific shade, extent, site, spreading of lesion gives diagnostic importance. Interactions between the dentist and the patient's medical specialist are very important to provide a definitive diagnosis as it increase the possibility to recognize these forms of lesions. Further and more work will be done to clarify the pathogenesis and to improve the diagnosis of the disease. The historical and current scientific history and the comprehensive research on the use of patients' medications have played a vital role. Such pigmentations can be caused by both systemic and topical drugs. Interactions between the dentist and the patient's medical specialist are very important to provide a definitive diagnosis as it increase the possibility to recognize these forms of lesions.

Key words- Oral pigmentation, ACTH, Antimalarial Drugs, Anticonvulsant drugs, Antiviral drugs, Antimicrobial

Introduction

Oral mucosa is not homogeneously colored. Oral soft tissues those are healthy exist a typical pink to red hue with slight geographical variations of color. Oral mucosal epithelial lining compose of many tissue. Interactions in this tissue provide chromatic range of oral mucosa. These tissues are composed of keratin, lobules of adipocytes, and melanin pigmentation. [1, 2] Oral mucosal color changes can be significant and gives diagnostic value of local or systemic disease though it requires clinical experience and thorough evaluation. Therefore, watchful examination of all the oral mucosa is frequently required.[3,4,5]

There are variable manifestation of oral pigmentation [6]. The specific shade, extent, site, spreading of lesion gives diagnostic importance. In differential diagnosis of patients with oral pigmentation, adverse drug reaction would also take into consideration. [7] Color of the mucosa due to melanin is related to the intrinsic level of enzyme and protein action. [8,9] Thus an understanding of different medications that may lead to oral mucosal pigmentation is important for proper patient assessment, diagnosis and treatment.. This review will highlight the drugs responsible for oral pigmentation with pathophysiology.

Pathophysiology

The oral mucosa is pigmented primarily due to the Melanin, Carotenoids, Reduced HB and Oxygenated HB. [10].

Possible causes for abnormal pigmentation include [11-16]:

1. Melanin accumulation.
2. Increased melanin production
3. Increased melanocyte count (melanocytosis)
4. Deposition of exogenous elements, which were mistakenly added.
5. Localized substance accumulation beneath skin coat.
6. Drug-induced inflammatory changes in the iron accumulation throughout the dermis.

Reddish-black, or gray discoloration is commonly caused by an aggregation of melanin, haemosiderin, or foreign body.¹⁷

DRUGS ASSOCIATED WITH ORAL PIGMENTATION

Various drugs may often give rise to multiple oral manifestations, chiefly oral mucosal pigmentation.

ACTH [18, 19]

Adrenal deficiency results in a decline of main adrenal hormones leading to the rise in the production of adrenocorticotropin (ACTH) by the pituitary gland. Melanocytes promote the development of ACTH-derived peptides that induce skin and oral mucosa hyperpigmentation. Some of the utmost important symptoms for Addison's disease are skin pigmentation, mucosal pigmentation due to ACTH melanogenesis. It affect skin, genitalia eyes and oral cavity. Exposure to sun increases its intensity. It is characterized by dark brown maculae occurs on mucosal surface involving alveolus, diffuse pigmentation on lips and multifocal pigmentations on buccal and edentulous mucosa .

Antimalarial Drugs

Quinacrine, chloroquine, hydroxychloroquine, the antimalarial drugs known to play an important role in oral pigmentation[20,21,22]. Most commonly blue–grey or blue–black pigmentation occur on hard palate due to direct stimulatory influence on the melanocytes. [21,23,24,25] These changes are reversible and resolve after the discontinuation of drug. Other oral sites are also affected but hard palate has the highest prevalence. [26]

Anticonvulsant drugs

Phenytoin and oxcarbazepine are medications used in the treatment of people with intermittent epilepsy and it is very important for doctors to re-evaluate the duration of medication in order to avoid adverse effects. [27] Alternatively, antiepileptic medications can induce numerous variations in the oral cavity, for example gingival overgrowth, periodontal insufficiency and caries. [28]. Some of these antiepileptic agents are Valproic acid, Carbamazepine, Lamotrigine, Phenytoin Ethosuximide, Topiramate Oxcarbazepine, Topiramate, Zonisamide, Lamotrigine.

Antiviral drugs

It is likely to said that the up regulation of HIV-associated IL-1, IL-6, and TNF-5-007 activates keratinocytes and melanocytes for the development of alpha melanocyte stimulating hormone which has the potential to induce melanogenesis, subsequently increased melanin production, which is clinically expressed as HIV associated hyperpigmentation. [29]

Antimicrobial

Chlorhexidine

It is the most commonly used to inhibit the metabolism of microorganisms but when it is used in higher concentration cause pigmentation. [30,31]] some studies have shown that tea and coffee associated with the use of chlorhexidine in the mouth make a significant contribution to teeth and tongue staining. [32,33]

Minocycline

Minocycline hyperpigmentation affect all parts of oral cavity via the following mechanisms:

- (a) Enamel get demineralized by minocycline through saliva, causing extrinsic staining;
- (b) Breakdown product in dentin causes intrinsic stains via pulp circulation

In addition, several reported cases shows discoloration of the alveolar and palatal bone without the intervention of the overlying mucosa. [33,34] Blue, gray, green, or blue-black discoloration seen below the semitranslucent alveolar mucosa in . Most commonly seen on gingival region sometimes black-purple macules can be seen on tongue.[35-37] Minocycline causes grayish-blue discoloration of fully formed teeth. [38-41]

Chemotherapeutic agents

Chemotherapeutic agents that induce significant skin pigmentation, oral capecitabine is widely approved Chemotherapeutic agents in clinical practice because it allows for easy administration. Hyperpigmentation is due to an increase in the accumulation and secretion of the substance by sweat glands, which are heavily concentrated on the palms and soles.

Chemotherapy may let the deregulation of the MGSA gene in melanocytes, which stimulate the variation, growth, and expansion of melanocytes into normal or atypical nevi [42].

Other chemotherapeutics are doxorubicin, busulfan, and cyclophosphamide also causes oral pigmentation [43].

Miscellaneous

Methyldopa induced oral pigmentation has been identified in many cases and are resolved after termination of the drug. The mechanism behind is that the melanin developed secondary to dihydroxyphenylalanine (DOPA) metabolism.[44]

Ketoconazole can also contribute to oral pigmentation via the same ACTH-pathway.[45] Clofazimine is used mainly for the treatment of leprosy also has strong anti-inflammatory properties is also identified as a cause of oral pigmentation. The metabolized substance is red in color so the pigmentation process can be related. [46,47] Laxatives such as phenolphthalein can also induce oral pigmentation.[43,48]

Conclusion

A wide variety of medications can give rise to various adverse orofacial manifestations. Pigmentation must be assessed irrespective of its causes and occurrence. Further and more work will be done to clarify the pathogenesis and to improve the diagnosis of the disease. The historical and current scientific history and the comprehensive research on the use of patients' medications have played a vital role. Such pigmentations can be caused by both systemic and topical drugs. Interactions between the dentist and the patient's medical specialist are very important to provide a definitive diagnosis as it increases the possibility to recognize these forms of lesions.

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