A Review of the Presentations and Treatment of Oral Pigmentation

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ABSTRACT

Background
Oral pigmentation can be either normal or abnormal discolouration of the oral mucosa.

Objective: To help clinicians establish a better approach towards the care of patients with pigmented oral lesions and to establish early diagnosis and treatment of such conditions.

Data source: Works of literature concerning oral pigmentations, clinical features and treatment were reviewed thoroughly from renowned electronic databases such as PubMed, Medline, Google Scholar, and Cochrane Library and personal clinical experience in managing such conditions. The following words were used for the search: oral pigmentation, aetiology, and clinical presentations.

Findings: Oral pigmentation presents in various clinical patterns that can range from just physiologic changes to oral manifestations of systemic diseases and malignancies. Oral pigmentation may be physiological or pathological. Knowledge of the different presentations of oral pigmented lesions is quite crucial to improve and mastering the skill of differential diagnosis, definitive diagnosis and prompt treatment. The deposition of pigments in oral tissues may be due to various etiological factors. It can arise from intrinsic and extrinsic factors and can be physiological or pathological.

Conclusion: A good understanding of the various presentations of oral pigmented lesions would aid in the proper diagnosis and treatment of the condition.

KEYWORDS: Pigmentation, oral mucosa, endogenous, exogenous, presentations.

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Received: 9-Nov, 2022
Revision: 4 Jan, 2023
Accepted: 20 Jan, 2023

Citation: Okoh M, Okoh DS. A review of the presentations and treatment of oral pigmentation. Nig J Dent Res 2023; 8(1):7-13. https://dx.doi.org/10.4314/njdr.v8i1.3

INTRODUCTION

Oral mucosal pigmentation, which ranges from brown to black, may be of superficial (extrinsic) or deep (intrinsic) causes. It is a relatively common condition that may involve any portion of the oral cavity. Multiple causes are known, and may range from simple iatrogenic mechanisms, such as implantation of dental amalgam, to complex medical disorders, such as Peutz-Jeghers syndrome. [1] The vascularity, the blood haemoglobin concentration, the degree of keratinization of the epithelium, and the type and amount of melanin pigment present are variable determinants of the colour of the oral mucosa.

The degree of melanin pigmentation *per se* is determined by the number and distribution of melanocytes in the basal cell layer of the oral epithelium of each anatomical region, by their melanogenic activity, by the degree of arborisation of the dendritic processes of the melanocytes, and by the number, size, and distribution of melanosomes in the melanocyte-keratinocyte unit. [2, 3] Normal intrinsic pigmentation is due to melanin, produced by melanocytes which are dendritic cells prominent in the basal layer. This originates from amino acid tyrosine, which is converted to dihydroxyphenylalanine (DOPA) and then to melanin.

The different types of melanin are: Eumelanin, pheomelanin, mixed type melanin, neuromelanin and oxymelanin. The colour change of the oral mucosa could be due to accumulation of one or more pigments in tissues. Pigmentation is defined as the process of deposition of pigments in tissues. Various diseases can lead to varied colorations in the mucosa. The various pigmentations can be in the form of blue/purple vascular lesions, brown melanotic lesions, brown heme-associated lesions and gray/black pigmentations. [4] Pigmented lesions of oral cavity are due to augmentation of melanin production, increased number of melanocytes and deposition of accidentally introduced exogenous materials. Oral pigmentation can be either normal or abnormal discoloration of the oral mucosa. This review mainly focuses on the various presentations of oral pigmented lesions in order to help clinicians establish a better approach towards the care of patients with pigmented oral lesions and to establish early diagnosis and treatment of such condition.

METHODOLOGY

Literatures concerning oral pigmentations, clinical features and treatment were reviewed thoroughly from renowned electronic databases such as PubMed, Medline, Google Scholar, Cochrane Library and personal clinical experience in managing such conditions. The following words were used for the search; oral pigmentation, aetiology, and clinical presentations. A total of twenty-three eligible studies comprising original studies, case studies and literature reviews were included

DISCUSSION

Classification of Oral Pigmentation

Oral pigmentation may be physiologic or pathologic. Pathologic pigmentation can be either exogenous or endogenous based the cause (Box 1). [4] Exogenous pigmentation could be induced by drugs, tobacco/smoking, amalgam tattoo or heavy metals induced. Also, endogenous pigmentation can be associated with endocrine disorders, syndromes, infections, chronic irritation, reactive or neoplastic lesions. [4, 5]

Box 1: Classification of Oral Pigmentation [4]

Physiologic:
- Racial

Pathologic:
- Endogenous
- Exogenous

Exogenous:
- Drug induced
- Tobacco-chewing/smoking
- Heavy metals induced
- Amalgam tattoo

Endogenous:

Endocrine disorders
- Addison's disease
- Diabetes
- Pregnancy
- Hyperthyroidism

Syndrome associated
- Peutz-Jegher syndrome
- Macune Albright syndrome
- Neurofibromatosis

Hemochromatosis
Leopard syndrome
Infections
Human immunodeficiency virus (HIV)
Tuberculosis
Candidiasis
Chronic irritation
Post traumatic
Post inflammatory (Lichen planus, pemphigus)
Reactive
Oral melanocytic macule
Oral melanoacanthoma
Neoplastic
Benign (Nevus)
Malignant (melanoma)

Physiologic Pigmentation (Racial).

Racial pigmentation of oral mucosa is the most common cause of oral pigmentation. However, it is not directly related to the color of the skin. It is more common in African, Asian and Mediterranean populations. This increase in pigmentation is due to increase in melanocyte activity and not due to greater number of melanocytes. The degree of gingival pigmentation is directly related to skin pigmentation. In light skinned individuals gingiva is mostly non-pigmented but in dark skinned people the chance of having pigmented gingiva is extremely high. [6]

It is seen in all ages and is equally distributed among the sexes especially of African or Asian heritage. The pigmentation is symmetrically distributed, especially on the gingival and buccal mucosa, on the hard palate, lips and tongue (figure 1). It may also be seen as brown patches with well-defined borders. There is no treatment for this form of pigmentation except counselling.

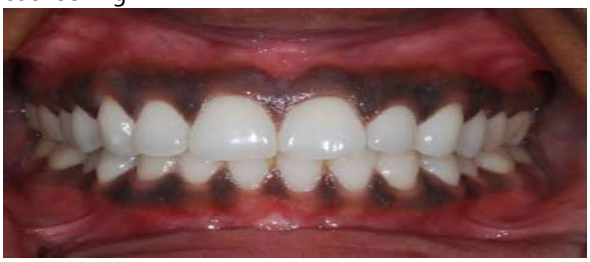

Fig 1: Physiologic pigmentation: Generalized hyperpigmentation affecting the marginal gingivae

Pathologic Pigmentation

A variety of pathological processes can cause oral pigmentation, which can be exogenous or endogenous in origin. Example of exogenous pigmentation is drug induced macular mucosal discolouration, and oral pigmentation of endogenous cause is Addison's disease.

Exogenous Pigmentation:

Drug Induced Pigmentation

Pigmentation can be produced by various drugs like, hormones, oral contraceptives, chemotherapeutic agents like cyclophosphamide, busulfan, bleomycin and fluorouracil, transquilizers, antimalarials like clofazamine, chloroquine, amodiaquine, anti-microbial agents like minocycline, anti-retroviral agents like zidovudine and antifungals like ketoconazole.[4] The pathogenesis underlying drug-related pigmentation can be categorized as that due to drug or drug metabolite deposition in dermis and epidermis, enhanced melanin deposition with or without increase in melanocytes, drug-induced post-inflammatory changes to the mucosa especially if the drugs induce an oral lichenoid reaction and bacterial metabolism. [7]

These lesions may appear as macular mucosal discolouration (brown, black, grey). The palate and gingiva are the most common sites affected. In addition to mucosal changes, teeth may be bluish grey owing to minocycline/tetracycline use. Treatment involves drug withdrawal.

Smoker's Melanosis

Smoker's melanosis is due to long-term tobacco smoking. The pigmentation is usually distributed along the gingival layer in the upper and lower anterior teeth. It may also be seen in the soft palate, buccal mucosa, and floor of the mouth. Pigmentation is diffused and uniformly distributed, and the intensity of pigment is dose and time related. Smoking cessation is the treatment of choice. The hyperpigmentation then disappears in a few months.

Heavy Metals

Increased levels of heavy metals for example lead, bismuth, mercury, silver, arsenic and gold) in the blood are commonly known to cause oral mucosal discoloration. Various metals cause various types of pigmentation. For example, pigmentation due to lead poisoning also called as plumbism appears as a blue-black line along the marginal gingiva known as Burtonian line. Occupational exposure to heavy metal vapors is the common cause of pigmentation

in adults. The most common cause in the past was, treatment of syphilis with drugs containing heavy metals, such as arsenicals for syphilis. [8] The lesion appears as grey to black colouration along the gingival margin. It has a kind of linear distribution. The bismuth and lead staining are known as bismuth and lead line respectively. The deposits can be detrimental to health. To treat the lesion, the cause needs to be eliminated.

Amalgam Tattoo and other Foreign-body Pigmentation

Amalgam tattoo is one of the most common causes of intraoral pigmentation. The aetiology is due to implantation or passive/frictional transfer of dental silver amalgam into mucosa. Diascopy is a test whether lesion is vascular or nonvascular or hemorrhagic by applying pressure with a finger glass slide and observing colour changes. A negative response is seen with diascopy if discoloration is due to amalgam tattoo. In some cases, especially when the amalgam particles are large enough, they can be seen in intraoral radiographs as fine radiopaque granules. In these circumstances, the diagnosis of amalgam tattoo can be made on the basis of the clinical and radiographic findings. [9, 10]

Pencil points are occasionally broken off in gingival tissue and if not completely removed, may cause permanent discoloration as graphite tattoo. Graphite particles resemble those of amalgam particles. [11] They present clinically as a localized flat, blue-gray lesion of variable dimensions. The gingiva and alveolar mucosa are the most common sites, but these lesions may also involve the floor of the mouth and the buccal mucosa. No signs of inflammation are present at the periphery of the lesion. It may be visible radiographically as radiopaque. Treatment involves observation, or biopsy of the amalgam and graphite particles.

Endogenous Pigmentation:

Melanotic Macules

An oral melanotic macule, by conventional definition, is a focal, well-defined, uniformly coloured oral mucosal hyperpigmentation, less than 1 cm in diameter, of unknown aetiology. The colour of the macule may range from light to dark brown. Microscopically, this melanin deposit is mainly in the basal cell layers. Melanin may also be seen in the connective tissue near the basal cell layer. The lesion appears flat and asymptomatic. Melanotic macules may be solitary or multiple, and can involve the gingiva, lip, palate, buccal mucosa, and alveolar ridge.

Oral melanotic maculae that are irregularly pigmented or have recently increased in size should be viewed with suspicion and microscopically examined to exclude melanoma; and melanotic maculae of the maxillary gingiva or the palatal mucosa which are the most common sites of melanoma should be viewed with even greater suspicion. [4]

Actinic Lentigo

Actinic lentigo is also referred to as a solar lentigo. Lentigo presents as light-tan macules on the face, but it also may involve the upper and (especially) the lower lip as a result of sun exposure. It is common in elderly white persons. Microscopically, marked melanin pigments are present within the basal keratinocytes. Treatment may not be necessary except for aesthetic reasons. Retinoid and laser therapy are useful in treating this condition.

Oral Mucosal Melanotic Naevus

Nevis is also called birthmarks. Broadly, the term oral naevus refers to a congenital or acquired melanotic pigmentation of the oral mucosa brought about by abnormal excessive accumulation of melanocytes/naevomelanocytes at the junction of the epithelium and the lamina propria or in the lamina propria. [2, 4] The sequence of biological events leading to the development of oral naevomelanocytic naevi is largely unknown. Microscopically based on the location of the nexus cells, they are classified as junctional, intradermal or intramucosal and compound nevi. It forms circumscribed, elevated brown to black papule about 5 or 6mm across (Figure 2), also common on skin. Intraorally, palate and gingiva most often involved. Treatment entails observation for changes in the pigmentation since malignant transformation of oral naevi probably does not occur except in the rare junctional naevi.

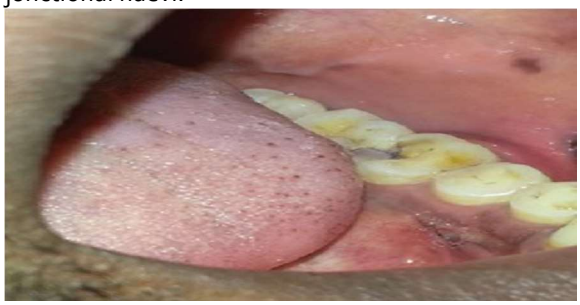

Fig 2: Oral Naevus: An elevated small black papule on the buccal mucosa

Oral Mucosal Melanin Hyperpigmentation associated with Syndromes and systemic diseases:
Oral mucosal melanin hyperpigmentation is often observed in the systemic conditions such as Peutz-Jegher syndrome, McCune-Albright syndrome, Laugier-Hunziker syndrome, Addison disease, and neurofibromatosis. The clinical appearance is one of the brown to black spots or macules, with a histopathological increase in melanin in the basal cell layer of the oral epithelium and melanin incontinence in the upper portion of the lamina propria, but without an increase in the number of melanocytes.[2]

Peutz-Jeghers Syndrome
This is an autosomal dominant disorder. It is associated with germline mutations in the LKB1/STK11 gene, located on the short arm of the chromosome. [11] Characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules. It appears as pigmented macules, often confluent and varying in size and shades of brown, appear in almost all cases periorally and on the lips and buccal mucosae. Any oral site may be involved. Pigmented macules on the cutaneous surfaces covering the extremities and face are less frequently observed. The relative risk of developing cancer in this syndrome is increased 15-fold compared with that of the general population. The cancer primarily involves the gastrointestinal tract (including the pancreas and the luminal organs), the female and male reproductive tracts, and the lungs. [12]

Addison's disease
The aetiology is due to adrenal cortical atrophy (idiopathic or autoimmune). Primary adrenal cortical insufficiency is due to infections such as tuberculosis of adrenal gland and HIV/AIDS. Pigmentation of the oral mucosa is considered pathognomonic for Addison disease. Oral manifestation is due to secondary melanocytes stimulation by increased levels of adrenocorticotropic hormone (ACTH). The oral hyper-pigmented macules of Addison's disease can be found diffusely on the tongue, gingiva, buccal mucosa, and hard palate. The macules tend to be blue-black or brown and can be spotty or streaked in the configuration. Pigmentation seen is associated with weakness, weight loss, salt craving, nausea, vomiting and hypotension.[4] Treatment involves management of underlying adrenal insufficiency by corticosteroid replacement therapy

Hemochromatosis:
Hemochromatosis is a chronic, progressive disease that is characterized by excessive iron deposition in the liver and other organs and tissue, leading to organ toxicity. It is also called bronze diabetes. The cause for hemochromatosis is a genetic defect, which leads to excessive iron absorption. The palate and gingiva are most commonly affected in the oral cavity. The oral pigmentation is often diffuse and brown to gray in appearance. It is treated by phlebotomy. [13, 14]

Post-inflammatory Pigmentation
Mucosal diseases in particular lichen planus can cause mucosal pigmentation. These pigmented areas are clinically presented as multiple brown-black pigmented areas adjacent to reticular or erosive lesions of lichen planus. These areas microscopically show increased production of melanin by the melanocytes and accumulation of melanin-laden macrophages in the superficial connective tissue. [9]

Human Immunodeficiency Virus (HIV) Hyperpigmentation
Oral melanin hyperpigmentation is common in HIV-seropositive subjects. It may develop secondarily to HIV-induced cytokine dysregulation, to medications used in the treatment of HIV infection or HIV-associated diseases (zidovudine, clofazimine and ketoconazole), or to adrenocortical deficiency may be seen in HIV-seropositive subjects with a low CD4+ T cell counts. [2, 15] Oral melanotic hyperpigmentation could be used as markers of immunosuppression depicted by CD4+ counts < 200 cells/ml in HIV-positive patients. [16] It is unknown whether structural proteins of HIV can stimulate melanocyte activity directly to upregulate their melanin biosynthesis. It is possible that HIV-associated mucosal hyperpigmentation may fortuitously represent a local protective immune reaction against subclinical oral infections and concomitant inflammatory processes.

Melanoacanthoma
This is a reactive and reversible alteration of oral mucosal melanocytes and keratinocytes, usually associated with local trauma. Clinical presentation is that of a unilateral dark plaque; rarely multiple which occurs more often in women than men in a ratio of 3:1. There is a positive history of trauma and local irritation. It forms rapidly most often on buccal/labial mucosa measuring 5-20mm in diameter. More in blacks/ non-Caucasians. [17] Treatment is not necessary after establishing the diagnosis as it often resolves spontaneously.

Malignant Melanoma

Oral mucosal melanoma is rare. It accounts for less than 1% of all oral malignancies. It is characterized by proliferation of malignant melanocytes along the junction between the epithelium and connective tissue or may occur deep inside the connective tissue. [18] The palate is the most common site, which accounts for about 40% of cases, and gingival account for one third of case (Figure 3). [17] Other oral mucosal sites may also be affected. Oral melanoma is generally encountered between the fourth and seventh decades of life, with a greater incidence in men than women. Clinically, oral melanoma may present as an asymptomatic, slowly-growing brown or black patch with asymmetric and irregular borders or as a rapidly enlarging mass associated with ulceration, bleeding, pain and bone destruction. It is seen more on the palate and gingival. A few oral melanomas are non-pigmented (amelanotic). Treatment involves surgical excision, and neck dissection in case of deep invasion. Although oral mucosal melanomas are rare, they represent a serious and often fatal disease. [18, 19, 20] Metastatic melanoma is a malignancy with a poor prognosis. The introduction of immunotherapy, alone or in combination with chemotherapy, radiotherapy, or targeted molecular therapy, has significantly changed the approach to this tumor. [21,22] An article in the *New England Journal of Medicine* in late 2019, [23] showed that 52% of patients were alive after five years of treatment with immunotherapy drugs.

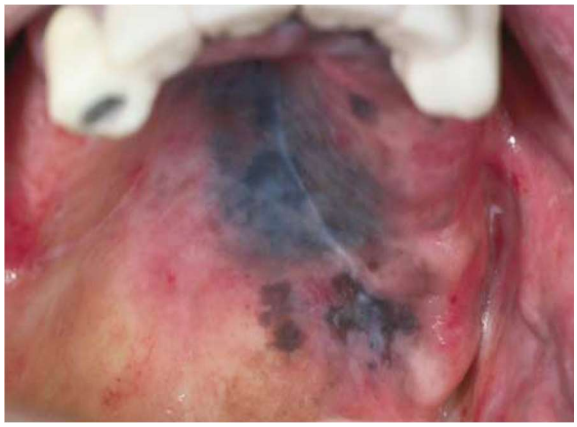

Fig 3: Malignant melanoma: Asymmetrical and diffused black patch on the palate

CONCLUSION

Deposition of pigments in oral tissues may be due to various aetiological factors. It can arise from intrinsic and extrinsic factors and can be physiological or pathological. A good understanding of the various presentations of oral pigmented lesions would aid in proper diagnosis and treatment of the condition.

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