Review Article

Overview on Disorders of oral pigmentation

Abstract: Oral pigmentation is a very frequent disorder that can affect any area of the mouth. Oral pigmentation can be a symptom of a physiologic or pathologic condition. There are a variety of reasons, ranging from basic iatrogenic processes like dental amalgam implantation to sophisticated medical illnesses like Peutz-Jeghers syndrome (PJS) and Addison disease. pathologic pigmentation can be classed as exogenous or endogenous. Drugs, tobacco/smoking, amalgam tattoos, or heavy metals can all cause exogenous pigmentation. Endogenous pigmentation is linked to endocrine abnormalities, syndromes, infections, chronic irritation, and reactive or neoplastic conditions. For any oral pigmented lesion that is not easily identified, clinicians must physically evaluate the oral cavity, gather clinical histories, and be willing to do a biopsy. Management depends on the causing factor of the oral pigmentation disorder and thus multiple approaches can be considered. The decisive therapy for early-stage melanoma is surgery, such as broad local excision with sentinel lymph node biopsies, elective node dissection, or both.

Introduction:

Oral pigmentation is a very frequent disorder that can affect any area of the mouth. There are a variety of reasons, ranging from basic iatrogenic processes like dental amalgam implantation to sophisticated medical illnesses like Peutz-Jeghers syndrome (PJS) and Addison disease. Local irritants, such as smoking, can also cause variable degrees of melanosis. Exogenous materials implantation or endogenous, excessive melanin deposition are the most prevalent causes of oral pigmented lesions. These lesions can, on occasion, be caused by an increase in the number of cells, which can range from benign nevi to deadly oral melanoma. [1-4]

Oral pigmentation can be a symptom of a physiologic or pathologic condition. Depending on the aetiology, pathologic pigmentation can be classed as exogenous or endogenous. Drugs, tobacco/smoking, amalgam tattoos, or heavy metals can all cause exogenous pigmentation. Endogenous pigmentation is linked

to endocrine abnormalities, syndromes, infections, chronic irritation, and reactive or neoplastic conditions. [5]

Increased melanin synthesis is prevalent in oral diseases, while those caused by an increase in the number of melanocytes are uncommon. For any oral pigmented lesion that is not easily identified, clinicians must physically evaluate the oral cavity, gather clinical histories, and be willing to do a biopsy. Early biopsy of unclear origin localised pigmentations is critical for detecting oral melanomas at an early stage. Patients with oral melanoma frequently recall past pigmentation in the same location months or years before the melanoma diagnosis, and the disease may have even provoked a prior notice from physicians or dentists. [1]

Patients with Laugier-Hunziker syndrome (idiopathic lenticular mucocutaneous pigmentations) and Carney complex have been documented to exhibit oral melanocytic pigmentations (spotty skin pigmentations, myxomas and endocrine overactivity). Multiple well-circumscribed melanotic macules on the buccal and palatal mucosa, gingiva, and lips. and also it have been linked to human immunodeficiency virus infection. However, the link might be just accidental. Classic melanotic macules have a similar histopatho-logic look. It's yet unknown if the virus, medication, or other factors are to blame for these pigmentations. [6]

Physiological Vs Pathological Pigmentation:

Physiological pigmentation is a typical occurrence that occurs when the melanocytes produce more melanin pigment. People with darker complexion are more likely to be impacted. Physiological pigmentation can be pale brown to virtually black in hue. Smoking, hormones, and systemic drugs can all affect the severity of physical pigmentation, which rises with age. The connected gingiva is the most common site, although physiological pigmentation can occur elsewhere in the oral cavity, including the ends of the fungiform papillae on the dorsal tongue. Physiological pigmentation is often diagnosed clinically and does not require treatment. [6] Oral pigmentation was seen in 93.2 percent of black Brazilian students, 12.5 percent of white Brazilian schoolchildren, and 70 percent of intermediately pigmented native youngsters. Physiologic pigmentation was discovered in 13.5 percent of 1,300 Israeli Jewish kids in a later investigation. Children of Middle Eastern ancestry had the greatest rate of infection. [1]

Factors that can cause/change oral Pigmentation:

Drugs: Hormones, oral contraceptives, chemotherapeutic agents such as cyclophosphamide, busulfan, bleomycin, and fluorouracil, transquilizers, antimalarials such as clofazamine, chloroquine, and amodiaquine, antimicrobials such as minocycline, anti-retroviral agents such as zidovudine, and antifungals such as ketaconazole can all cause oral pigmentation. The palate and gingiva are the most commonly afflicted areas. Minocycline/tetracycline usage can cause teeth to become blue grey in adults and children, in addition to mucosal abnormalities. Drug-related pigmentation can be classified as that which occurs as a result of drug or drug metabolite deposition in the dermis and epidermis, enhanced melanin deposition with or without an increase in melanocytes, drug-induced post-inflammatory changes to the mucosa, particularly if the drugs cause an oral lichenoid reaction, and bacterial metabolism, either alone or in combination. [5,7]

Smoker's melanosis: Cigarette smoking can cause oral mucosal pigmentation, in addition to cancer and a variety of other systemic problems. Smoker's melanosis is not seen as a precursor to cancer. Although the specific aetiology is unknown, melanin activation might be a defensive mucosal reaction to the smoke's heat or an irritant within the cigarette. Females are the ones that are most impacted. Smoker's melanosis is characterised by widespread, patchy, and uneven pigmentation of the maxillary and mandibular gingivae in the front face. Other mucosal locations are impacted less frequently. The results histologically are non-specific, with considerable melanin inside the basal cell layer and melanin incontinence. Melanocytic macule, as well as a variety of other disorders that appear as diffuse pigmentation, have similar histologic results. To achieve an accurate diagnosis of smoker's melanosis, a clinicopathologic correlation is necessary. Melanoma can show as diffuse patchy pigmentation, which is important to note. Melanoma should be included in the differential diagnosis if just one mucosal location is affected. A patient with multifocal pigmentation affecting non-contiguous mucosal locations is unlikely to have melanoma. [8,9]

Human Immunodeficiency Virus: The immune system is dysregulated in human immunodeficiency virus (HIV), resulting in an increase in inflammatory mediators such as interleukin (IL)-1, (IL)-6, and tumour necrotic factor (TNF), which cause a

febrile response and the release of melanocytes stimulating hormone (MSH) from the anterior pituitary. This counteracts the fever caused by IL-1, 6, TNF. MSH is a powerful melanocyte activator, and IL-1 increases MSH receptor expression in melanocytes. As a result of the body's natural system for regulating fever and inflammation, MSH is released, contributing to pigmented lesions in HIV patients. In HIV, the patient is infected with Mycobacterium avium, which then infects and destroys the adrenal cortex. As a result of the adrenal hypofunction, the levels of adrenocorticotropin hormone (ACTH) and MSH rise, causing hyperpigmentation in these people. Oral pigmentation is also caused by medicines used to treat these individuals, such as ketaconazole and zidovudine. [5,10,11]

Melanocytic nevus: Melanocytic nevi are a type of benign tumours that develop as a result of melanocytic proliferation and development. The mucosa is seldom impacted by these lesions; the skin is far more usually affected. The number of morphologically diverse nevi is growing. The intramucosal nevus is the most prevalent within the oral cavity, while the blue nevus is the second most common. Compound nevi and junctional nevi, on the other hand, are less common. There have also been a few instances of oral melanocytic nevi with unusual histologic characteristics. Regardless of the specific nevus subtype, they virtually always have comparable clinical characteristics. Patients beyond the age of thirty are more likely to have oral nevi. The lesion is usually asymptomatic and appears as a tiny, single brown or blue nodule or macule with a well-circumscribed border. Clinical pigmentation may or may not be present in some nevi. The hard palate, buccal and labial mucosae, and gingival mucosae are the most common mucosal sites affected. The melanotic macule is second only to amalgam tattoo as one of the most prevalent pigmented lesions of the oral mucosa. Oral and labial melanotic macules were the most prevalent in a study of 773 instances of solitary pigmented melanocytic lesions of the oral mucosa, accounting for 86 percent of all cases. Melanocytic nevi in the mouth are infrequent. Over a 19-year span, OMN constituted barely 0.1 percent of all accessioned samples at an oral pathology laboratory in Northern California. [1,8,12-16]

Foreign bodies: Many metals have been linked to the development of pigmentation in the mouth. Lead causes a broad cutaneous 'lead hue' and 'lead lines' on the gingiva (grey patches of discolouration below the gingival borders),

mercury causes slategrey gingival hyperpigmentation, gold, bismuth, and amalgam are among them. The presence of metallic substance in the oral tissues causes amalgam tattoo. This most usually occurs when dental filling material is accidentally implanted into the gingival or buccal mucosa. Amalgam tattoos are non-painful gray-blue macules that range in size from a few millimetres to over one centimetre. A single tattoo or a collection of tattoos are possible. The gingiva and edentulous mucosa are the most common sites for amalgam tattoos, although they can also be seen on the hard palate, buccal mucosa, and mouth floor. A favourable radiographic assessment is possible. A biopsy may not be indicated when mucosal pigment has a blue-gray tint and the patient has a history of dental amalgam restorations in either the primary deciduous or permanent dentition. A biopsy is recommended if one of these criteria is not satisfied. Fine black granular or fibrillar material lodged in connective tissue or in a perivascular position with little or no inflammatory response is found on histological examination. Giant cell responses to foreign bodies are unusual. In general, amalgam tattoo is one of the most prevalent oral pigmentations, affecting 3.3 percent of the adult population in the United States. [6,17]

Addison disease: Addison disease can strike anybody at any age, although it is most common in the second or third decades of life. Fatigue, generalised weakness, weight loss, nausea, vomiting, stomach discomfort, dizziness, tachycardia, and/or postural hypotension are some of the first symptoms. Hyperpigmentation is a common symptom that affects virtually all individuals. It's normally widespread, although it's more noticeable in sun-exposed and high-pressure places. The causes are elevated ACTH and melanocyte-stimulating hormone. ACTH is thought to bind to the melanocyte receptors, which are involved in pigmentation. Palmar creases, gingival mucosa, lips, elbows, knuckles, posterior neck, breast areola, nipples, and nail beds show greater hyperpigmentation. Because ACTH and MSH levels are low in secondary insufficiency, hyperpigmentation does not occur. It's possible that many new nevi will appear. In female patients, axillary and pubic hair may be sparse or absent. Approximately 92 percent of Addison disease patients have diffuse cutaneous and oral pigmentations. [18]

Candidiasis: The earliest report of a link between hypoparathyroidism and candidiasis appeared in 1929, and the first report of a link between these two

disorders and idiopathic adrenal insufficiency was in 1946. Mucocutaneous candidiasis, adrenocortical failure, and hypoparathyroidism are all symptoms of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, a rare inherited condition. The diagnosis can be made with any two of these triads. In the majority of instances, candidasis appears first, generally before the age of five years, followed by hypoparathyroidism (usually before the age of ten years), and then Addison's disease (usually before 15 years of age). As a result, the coloration here is most likely due to the Addissonian effect. Antifungals, such as ketoconazole, can also produce oral pigmentation, potentially through the ACTH route. [5,19]

Malignant melanoma: Melanoma is a cancer that develops from malignant melanocytes. Melanoma is the deadliest type of skin cancer. When these tumours originate in mucosal areas, such as the oral cavity, the prognosis is significantly worse. All focally pigmented lesions and most diffusely pigmented lesions require a biopsy for diagnosis due to the possibility of oral mucosal melanoma. Primary oral mucosal melanomas account for fewer than 1% of all incidences of melanoma. These malignancies usually strike people over the age of 50, and men are more likely to be impacted. Oral melanoma can affect people of any race or ethnicity, however Japanese individuals tend to have the highest prevalence. The hard palate and maxillary gingiva are the most typically impacted areas. OMMs account for fewer than 1% of all melanomas and 0.26 percent of all malignancies of the oral cavity. [1,8,20-22]

Peutz-Jeghers syndrome: The Peutz-Jeghers syndrome (PJS) is defined by the coexistence of GI polyposis, mucocutaneous pigmentation, and cancer propensity. The jejunum, ileum, and duodenum are the most prevalent locations for PJS-type hamartomatous polyps, although they can also arise in the stomach, large intestines, and extraintestinal sites such as the renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, and ureters. Chronic bleeding, anaemia, and recurring blockage and intussusception caused by GI polyps might necessitate repeated laparotomies and intestinal resections. Dark blue to dark brown macules appear around the lips, eyes, and nose, in the perianal region, and on the buccal mucosa in children with mucocutaneous hyperpigmentation. On the fingertips, hyperpigmented macules are prevalent. During puberty and maturity, the macules may diminish. It's crucial to recognise the different skin manifestations,

especially in those who have PJS as a result of a de novo pathogenic variation, because these skin findings typically come before GI signs and symptoms. PJS patients are more likely to develop a range of epithelial malignancies (colorectal, gastric, pancreatic, breast, and ovarian cancers). Sex cord tumours with annular tubules (SCTAT), a benign neoplasm of the ovaries, and adenoma malignum of the cervix, a rare aggressive malignancy, are both risk factors for females. If left untreated, massive calcifying Sertoli cell tumours of the testes can produce oestrogen and cause gynecomastia, advanced skeletal age, and eventually low height in men. The frequency of PJS is estimated to be 1 case in every 8,300 to 200,000 births. [23]

Laugier–Hunziker Syndrome: Multiple acquired, idiopathic pigmented macules on the oral mucosa and lips define LHS. The disorder is generally discovered in maturity, around the age of 48 on average. Females are twice as likely as guys to be afflicted. Cases appearing in dark-skinned persons may be confused as physiologic pigmentation, despite the fact that it is more frequent in Caucasians. Buccal mucosa, lips, gingiva, palate, and tongue are the most common sites for lesions. Other anatomic mucosae may be impacted as well. In 60–65 percent of individuals, the fingernails and/or toenails have longitudinal pigmented streaks (melanonychia). Patients with this clinical presentation should be sent to a gastroenterologist to rule for PJS because LHS is an exclusion diagnosis. [24-28]

Treatment:

Management depends on the causing factor of the oral pigmentation disorder and thus multiple approaches can be considered.

The decisive therapy for early-stage melanoma is surgery, such as broad local excision with sentinel lymph node biopsies, elective node dissection, or both. Consider surgical margins first before doing a large local excision. Skin grafts or tissue transfers may be required if the main closure isn't possible. Patients with advanced melanoma get medical care as adjuvant therapy. [29-33]

Peutz-Jeghers Syndrome management: Medications are targeted at the gastrointestinal (GI) elements of the condition. There are no drugs particularly designed to treat oral lesions.

Endoscopic monitoring with polypectomy on a regular basis reduces the need for emergency laparotomies and bowel loss due to intussusception. Video capsule endoscopy (VCE), CT enterography, and/or magnetic resonance enterography are all examples of small-bowel imaging (MRE). Deep small-bowel polyps can be removed by balloon-assisted enteroscopy. Large distal small-bowel polyps may require intraoperative enteroscopy and enterotomy to be removed. Treatment for intussusception and malignancies should be routine. [23]

In the treatment of cutaneous melanoma, drug therapy (dacarbazine), therapeutic radiation, and immunotherapy are employed, although they are of dubious usefulness to individuals with oral melanoma. Dacarbazine is ineffective in the treatment of oral melanoma; however, dacarbazine in combination with interleukin 2 might be beneficial. The majority of knowledge on oral malignant melanoma (OMM) comes from single instances. Success with interferon alfa or hyperfractionated radiation treatment has been reported in anecdotal reports. To prevent or restrict recurrence, several cancer centres combine surgical excision with a course of interleukin 2 as an adjuvant treatment. [1]

Conclusion:

Oral pigmentation is a common condition that affects any part of the mouth. Exogenous and endogenous pigmentation are two types of pathologic pigmentation. Exogenous pigmentation can be caused by drugs, tobacco/smoking, amalgam tattoos, or heavy metals. Endocrine disorders, syndromes, infections, chronic irritation, and reactive or neoplastic diseases have all been associated to endogenous pigmentation. Multiple therapies might be suggested depending on the underlying cause of the oral pigmentation problem.

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