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Case Report

Vitamin B12 deficiency masquerading Addison's disease: a case report of an adolescent male

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ABSTRACT

Intraoral pigmentations range from innocuous physiologic pigments to life-threatening malignant conditions. It is at the discretion of the observing clinician to identify the abnormal clinical manifestations and provide necessary intervention. There are controversies about delineating the definite etiology of the pigmentation such as race, exposure to ultra-violet radiation, drug-induced pigmentation post-inflammatory pigments of the oral cavity.

Keywords: Adolescent, Oral diseases, Oral pigmentation, Treatment of vitamin B-12 deficiency, Vitamin B-12 deficiency

INTRODUCTION

Oral hyper-pigmentation may be focal or diffuse, acquired or familial, and due to exogenous or endogenous in nature of origin.[1] Exogenous pigmentation is commonly due to foreign-body implantation in the oral mucosa. Endogenous pigments include melanin, melanoid, oxyhemoglobin, reduced hemoglobin, and carotene; others caused due to bilirubin and iron.[2] Localized areas of excessive melanin in the oral mucosa that are not associated with any systemic diseases, syndromes or conditions are entitled as ephelis, lentigo, melanoplakia, melanotic macule and focal physiologic melanosis (Figure 1).[3]

Mechanisms involving pigmentation include an increase in melanin production. E.g., Melanotic macule, Abnormal distribution of melanin. E.g., pigmented basal cell carcinoma, Hyperplasia or neoplasia of melanocytes. E.g., Melanotic nevi.[4]

In countries like India, Africa, and the Mediterranean, there is an apparent endogenous melanin production; and this racial predilection is noticed within the second decade of life. Attached gingiva represents the most common site followed by hard palate, labial mucosa, and tongue.[5] However, this type of racial pigmentation is symmetrical and is prevalent throughout life. Hence smoker's melanosis, Addison's disease, Peutz-Jegher's syndrome, and melanoma are to be differentiated.[6] Biopsy serves as a gold standard in clinicopathological correlation. To rule out hormone-related causes, changes in cortisol and thyroid profile necessitates further diagnosis.

It is crucial to have a thorough examination of all the functional systems of the body and to study the previous medical and surgical history to determine the presence of any atypical, unstable or malignant skin lesions (Figure 2).[7] Consequently, a positive family history of oral pigmentation or hereditary systemic diseases is crucial in the overall evaluation of the patient.

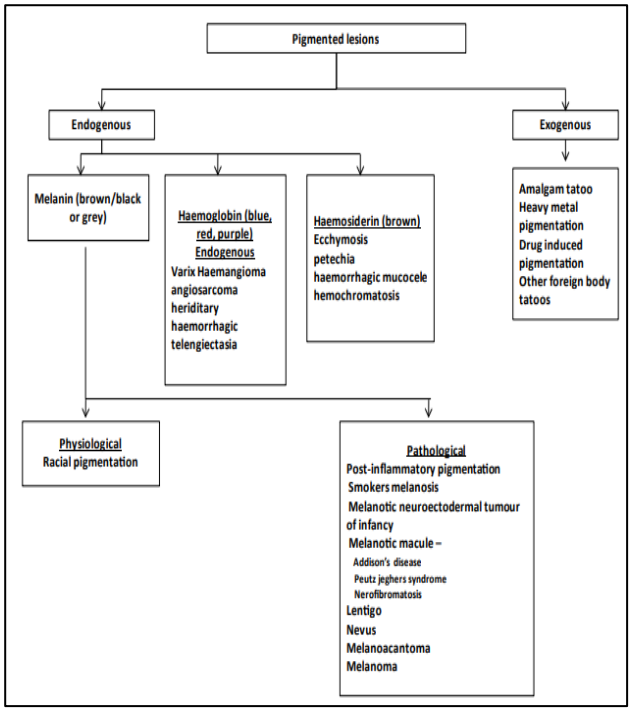


Figure 1: Working classification of oral pigmented lesions.[8-12]

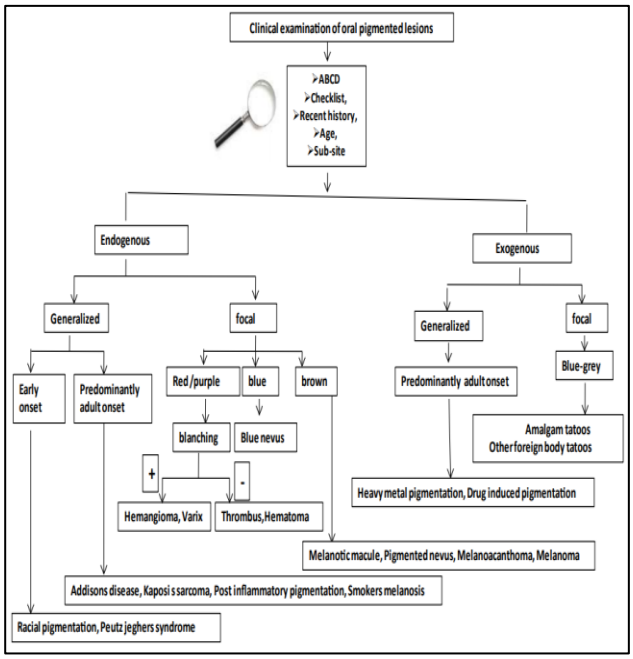


Figure 2: Clinical diagnostic algorithm for oral pigmented lesions.[8-12]

CASE REPORT

Patient a 15-year old male reported along with his mother to the department of oral medicine and radiology with a chief complaint of blackish patch seen concerning right inner cheek for five months. On eliciting history, the patient initially observed small diffuse blackish patch seen in right lower teeth region and inner cheek region five months ago, since two weeks before reporting the complaint the diffuse patch appeared to be progressing in size, extent and is currently seen in its present dimension. The patient gives no history of habits about tobacco and alcohol, no history of previous medical, surgical conditions, or drug allergy. The patient appeared well built, well-nourished, conscious, and co-operative to time and place. On General examination BMI was 23.74 kg /m2, Blood pressure 128/88 mm/hg, 72 beats per minute, IPA chart revealed growth spurt above 97th percentile. Examination of skin revealed uniform colour on the face of the skin (Figure 3) and the rest of the body. No scars, eruptions, lesions were present. The texture of skin and hair was healthy.



Figure 3: Profile of the patient.

Clinical examination revealed diffuse blackish-brown pigmented macular lesions concerning the mandibular anterior gingival region and right buccal mucosa (Figure 4), and diffuse pigmentation was seen extending anteriorly from commissure of right buccal mucosa and posteriorly 4 cm from pterygomandibular region within confines of the buccal mucosa. Supero-inferior extensions are vestibular fornix with 16 regions extending obliquely towards the vestibular fornix of 31 regions lateral to the midline. A less defined blackish-brown diffuse macular patch was present within the confines of the left buccal mucosa. A well-defined ovoid patch was seen in the junction of the hard and soft palate in the midline region (Figure 5); it was approximately of size 2x1 cm. The surface over the pigmented regions appeared smooth and regular. The macular lesions were non-tender, firm in consistency, and no evidence of subsequent changes was present on palpation.

The patient was advised for levels of serum cortisol and thyroid profile, and results were 5.29 mugm/dl (6.00am) of free cortisol by electrochemiluminescent immunoassay (ECLIA), 3.67 pg/dl of free T3, 1.26 ng/dl of free T4,

4.25 uIU/ml. Since the reference range for total serum cortisol in the AM was 6.2 to 19.4 patient was referred to a pediatric endocrinologist for an opinion regarding the same. Biochemical assessment of serum vitamin B12 revealed 87 pg/Ml (reference range- 180-914) by electrochemiluminescent immunoassay (ECLIA).

The patient was advised Synactin stimulation test, and basal levels of cortisol and the results were at 0 minutes 249.50 nmol/L, at 30 minutes 462.50 nmol/L, and at 60 minutes 499 nmol/L suggestive of borderline cortisol insufficiency. Following which the patient was diagnosed with vitamin B12 deficiency-induced pigmentation and advised Injection methylcobalamin 1cc Intramuscular administration one a month for three months.



Figure 4: Diffuse pigmented macular patch in right buccal mucosa.



Figure 5: Pigmentation is seen concerning palatal region.

DISCUSSION

Cook in 1944 first described Vitamin B12 deficiency and later by Baker et al, in the year 1963. Currently, vitamin B12 deficiency is defined as a concentration in plasma concentration of <148 pmol/L (200 pg/ml) and marginal status defined as a concentration of 148-221 pmol/L. The value averages in children between the ages of 15½ and 19 years around 369 pmol/L. These values are considerably higher than the adult value. The folic acid level drops slowly until the age of 15, and from then corresponds with adult levels.[13]

An investigation of the B12 values was done in 3766 children from the age of 4 days to 19 years, and the results revealed that three children had values lower than 74 pmol/L, and a frequency of 1 in 1255 and 18 children had values below 148pmol/L. The highest group of children with values below the 148 pmol/L occurred in the age group of 12-19 years, with a frequency of 1 to 112. The least values were found in white children between 9-12 years.[14] The values of biochemical assessment of serum vitamin B12 revealed 87 pg/Ml in the present case.

Consumption of meat, poultry, and dairy products is the primary source of vitamin B12 (cobalamin) in humans. The Recommended Dietary Allowances (RDA) varies with different age groups. B12 deficiency prevalently varies from 3% to 5% in the general population and 5% to 20% among people older than 65 years.[15] Inadequate intake and low consumption of animal-derived foods with pernicious anaemia (low intrinsic factor) in younger adults are observed. In older persons, food-bound cobalamin malabsorption in part due to gastric atrophy is the predominant cause of lowered serum vitamin B12 and likely the leading cause in poor populations worldwide. In this present case, the cause of vitamin B12 deficiency was decreased intake with low intrinsic factor.[16]

The significant causes of hypocobalaminemia are insufficient dietary intake (e.g., in vegans and vegetarians) and malabsorption of the vitamin.[17] The nearly concomitant use of drugs can interrupt the cobalamin absorption. This includes intake of gastric acid-blocking agents and metformin, which may also contribute to a growing prevalence of cobalamin deficiency.[18] In a retrospective study conducted by Sami El Toum on Prevalence and Distribution of Oral Mucosal Lesions by Sex and Age Categories of Patients Attending Lebanese School of Dentistry found that the second most common lesions were melanotic macule (11.2%).[19]

Vitamin B12 is known to play a critical role in cell metabolism. It is a co-factor of two enzymes: Methionine synthase, which enables catalyzes methylation of homocysteine into methionine with the reconstitution of simultaneous tetrahydrofolate and methylmalonyl-CoA mutase. This, in turn, catalyzes the conversion of methylmalonyl-CoA into the succinyl-CoA compound. At the cellular level, Deficiency of cobalamin results in the purine synthesis inhibition and the accumulation of methylmalonic acid and homocysteine (Hcy).[20] Hcy has been demonstrated to act as a pro-oxidant in various types of cells.[21,22]

Melanin serves as a dominant pigment in determining the hair and skin color. Melanin is a naturally occurring

pigment, and it determines the color of skin and hair. The melanin biosynthesis takes place in melanocytes-dendritic cells located mainly in the basal layer of the epidermis and hair follicles.[23,24] Physiological, pathological functions of skin and skin's responsiveness to ultraviolet radiation depend on the ability of melanocytes to synthesize melanin. Melanogenesis is a complex process. Management of various processes such as the receptor-mediated pathways activated by hormones; cytokines, neurotransmitters, and eicosanoids, as well as receptor-independent mechanisms are modulated by nutrients, microelements, pH, ions, and redox homeostasis.[25,26]

Cobalamin deficiency causes significant symptoms that are of hematological, psychiatric, and neurological nature.[27] Less frequently occurring presentations include irresolute cutaneous hyperpigmentation, mostly localized in the dorsum of limbs, lateral surfaces of the legs, skin folds, and oral mucosa.[28,29] Strikingly, several clinical cases of vitiligo and depigmentation of scalp hair due to cobalamin depletion have been reporte.[30] Thus, the impact of cobalamin deficiency on melanogenesis and melanocytes homeostasis is not apparent. Hence the patient was advised to be treated with intramuscular administration of 1cc methylcobalamin to overcome any further cobalamin depletion.

The cutaneous manifestation of vitamin B12 Deficiency is skin hyperpigmentation, vitiligo, changes in the texture of hair, and recurrent angular stomatitis. Notable hyperpigmentation of extremities over the dorsum of the hands and feet are seen. Accentuated pigmentations over the inter-phalangeal joints and terminal phalanges associated with pigmentation of the oral mucosa are cutaneous characteristics of vitamin B12 Deficiency. Aaron *et al*., had reported that 12 out of 63 (19%) patients had glossitis (31%), which was the most common mucocutaneous manifestation, followed by skin hyperpigmentation (19%), hair changes (9%), angular stomatitis (8%), and vitiligo (3%).[30]

As evidenced by Gilliam et al, histology from the hyperpigmented area showed irregular epidermal atrophy, absence of basal orientation of epidermal cells, patchy pigmentation of the lower epidermis, and numerous pigment-laden macrophages in the upper dermis and increase of melanin in the basal layer.[31] It is suggested that Deficiency of vitamin B12 causes a decrease in intracellular reduction potential that leads to oxidation of the reduced glutathione and decrease in GSH/GSSG ratio. The epidermal melanocytes are then revived to produce melanin as the tyrosinase inhibiting effect of GSH has been diminished. So, the predominant mechanism of hyperpigmentation in vitamin B12 is hypothesized as 1) Deficiency of vitmin B12 decreases the level of reduced glutathione, which activates tyrosinase and thus leads to transfer to melanosomes. 2) Defect in the melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence.[32] Authors consider that in the present case, the dominant mechanism of hyperpigmentation is not a defect in melanin transport but is instead an increase in melanin synthesis. Therefore, the excess melanin synthesis has cascaded to the remarkably compelling oral manifestations of vitamin B12 deficiency.

The individual in the present case had no significant variation in general findings associated with anemic conditions. Examinatory findings revealed absence of altered skin, nail, hair texture, fissured tongue, angular chelitis and palor which remarkably signify deficient vitamin complexes. This study intends to highlight the distinguished role of oral physician in identifying systemic vitamin B12 deficiency exclusively based on oral pigmentation.

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