International Journal of Research in Medical Sciences
Sudhaa MM et al. Int J Res Med Sci. 2020 May;8(5):1932-1936
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20201955

Case Report

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

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Received: 24 February 2020
Accepted: 27 March 2020

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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.

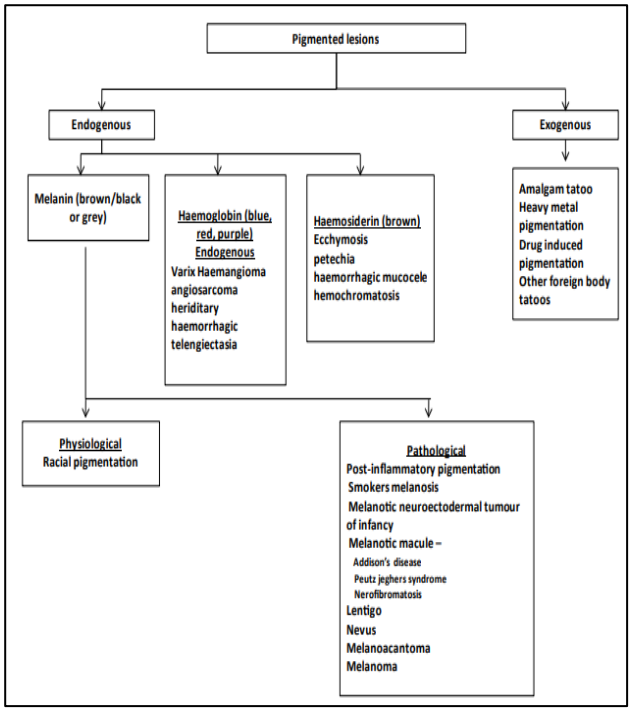

Figure 1: Working classification of oral pigmented lesions.[8-15]

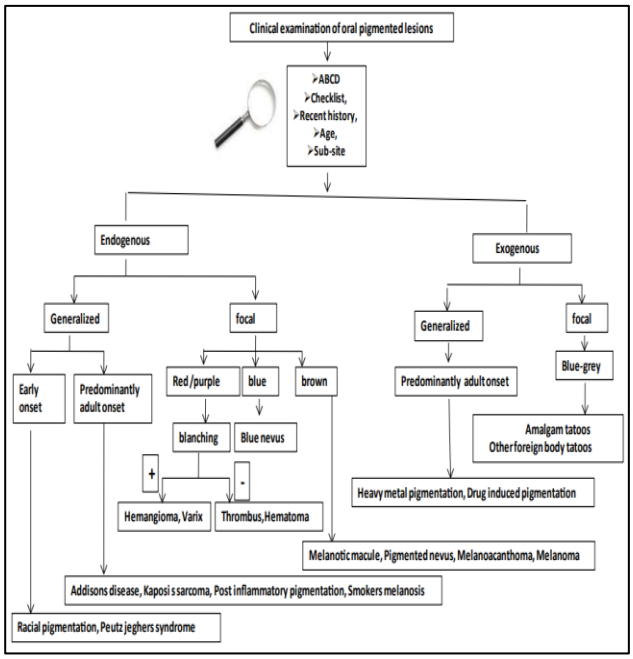

Figure 2: Clinical diagnostic algorithm for oral pigmented lesions.[8-15]

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.

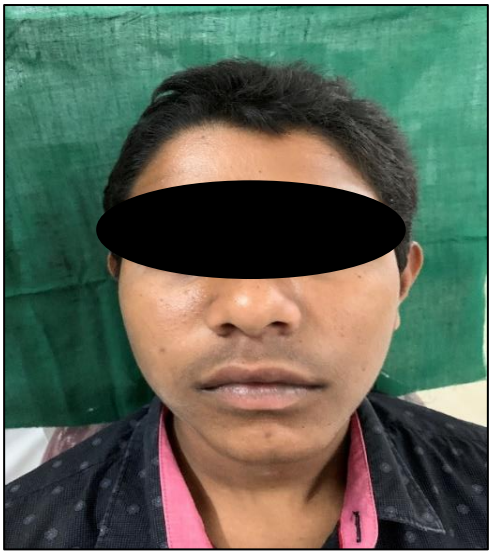

Figure 3: Profile of the patient.

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.

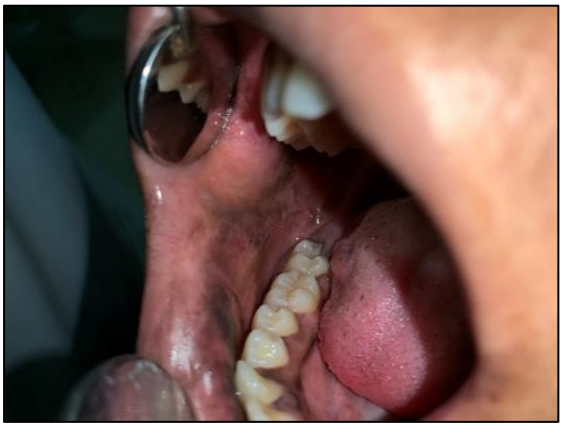

Figure 4: Diffuse pigmented macular patch in right buccal mucosa.

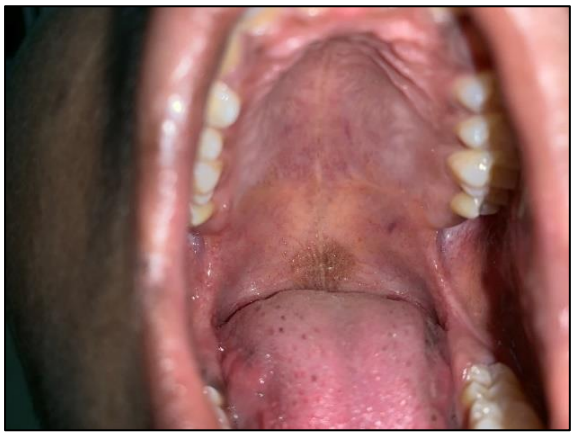

Figure 5: Pigmentation is seen concerning palatal region.

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.[10]

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.[11] 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.[12] 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.[13]

The significant causes of hypocobalaminemia are insufficient dietary intake (e.g., in vegans and vegetarians) and malabsorption of the vitamin.[14] 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.[15] 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%).[16]

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).[17] Hcy has been demonstrated to act as a pro-oxidant in various types of cells.[18,19]

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.[20,21] 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.[22,23]

Cobalamin deficiency causes significant symptoms that are of hematological, psychiatric, and neurological nature.[24] 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.[25,26] Strikingly, several clinical cases of vitiligo and depigmentation of scalp hair due to cobalamin depletion have been reporte.[27] 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%).[27]

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.[28] 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.[29] 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.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Eisen D. Disorders of pigmentation in the oral cavity. Clini Dermatol. 2000 Sep 1;18(5):579-87.
2. Lenane P, Powell FC. Oral pigmentation. J Eur Acad Dermatol Venereol. 2000 Nov;14(6):448-65.
3. Lewis MA. Book Review: Burket's Oral Medicine. In: Martin S, Greenberg, Michael Glick, Eds. Diagnosis and Treatment. 10th ed. BC Decker Inc. Hamilton, 2003: 658.
4. Adel Kauzman BD, Pavone M, Blanas N, Bradley G. Pigmented lesions of the oral cavity: review, differential diagnosis, and case presentations. J Can Dent Assoc. 2004;70(10):682-3.
5. Marx RE, Stern D. Oral and maxillofacial pathology: a rationale for diagnosis and treatment. Hanover Park, IL: Quintess Pub. Co.,; 2012.
6. Cawson RA, Odell EW. Cawson's Essentials of Oral Pathology and Oral Medicine. 7th edn, Churchil Livingstone, London. 2002:472.
7. Rajendran R Sivapathasundaram B. Textbook of Oral Pathology. 7th ed, Elseviers, India. 2012:1000.
8. Neville BW, Damm DD, Allen CM, Chi AC. Oral and maxillofacial pathology. 3rd ed. Elsevier Health Sciences; 2015 May 13:928.
9. Amir E, Gorsky M, Buchner A, Sarnat H, Gat H. Physiologic pigmentation of the oral mucosa in Israeli children. Oral Surg, Oral Medi, Oral Pathol. 1991 Mar 1;71(3):396-8.
10. Rasmussen SA, Fernhoff PM, Scanlon KS. Vitamin B12 deficiency in children and adolescents. J Pediatr. 2001 Jan 1;138(1):10-7.
11. Van Beynum IM, Den Heijer M, Thomas CM, Afman L, Oppenraay-van Emmerzaal D, Blom HJ. Total homocysteine and its predictors in Dutch children. Am J Clini Nutr. 2005 May 1;81(5):1110-6.
12. Monsen AL, Refsum H, Markestad T, Ueland PM. Cobalamin status and its biochemical markers

methylmalonic acid and homocysteine in different age groups from 4 days to 19 years. Clini Chem. 2003 Dec 1;49(12):2067-75.
13. Briani C, Dalla Torre C, Citton V, Manara R, Pompanin S, Binotto G, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 2013 Nov;5(11):4521-39.
14. Zdilla MJ. Metformin with either histamine H2-receptor antagonists or proton pump inhibitors: A polypharmacy recipe for neuropathy via vitamin B12 depletion. Clini Diabet. 2015 Apr 1;33(2):90-5.
15. El Toum S, Cassia A, Bouchi N, Kassab I. Prevalence and distribution of oral mucosal lesions by sex and age categories: A retrospective study of patients attending Lebanese school of dentistry. Int J Dentist. 2018;2018.
16. Wang D, Chen YM, Ruan MH, Zhou AH, Qian Y, Chen C. Homocysteine inhibits neural stem cells survival by inducing DNA interstrand cross-links via oxidative stress. Neurosci Letter. 2016 Dec 2;635:24-32.
17. Tyagi N, Sedoris KC, Steed M, Ovechkin AV, Moshal KS, Tyagi SC. Mechanisms of homocysteine-induced oxidative stress. American J Physiol Heart Circulat Physiol. 2005 Dec;289(6):H2649-56.
18. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiolog Rev. 2004 Oct;84(4):1155-228.
19. Slominski A, Wortsman J, Plonka PM, Schallreuter KU, Paus R, Tobin DJ. Hair follicle pigmentation. J Investigat Dermatol. 2005 Jan 1;124(1):13-21.
20. Slominski A, Zmijewski MA, Pawelek J. L-tyrosine and L-dihydroxyphenylalanine as hormone-like regulators of melanocyte functions. Pigment Cell Melan Res. 2012 Jan;25(1):14-27.
21. Rusher DR, Pawlak R. A review of 89 published case studies of vitamin B12 deficiency. J Hum Nutr Food Sci. 2013 Jan 1;1(2):1008.
22. Hoffman CF, Palmer DM, Papadopoulos D. Vitamin B~ 1~ 2 Deficiency: A Case Report of Ongoing Cutaneous Hyperpigmentation. Cutis New York. 2003 Feb 1;71(2):127-30.
23. Agrawala RK, Sahoo SK, Choudhury AK, Mohanty BK, Baliarsinha AK. Pigmentation in vitamin B12 deficiency masquerading Addison's pigmentation: A rare presentation. Ind J Endocrinol Metab. 2013 Oct;17(Suppl1):S254.
24. Chiang TT, Hung CT, Wang WM, Lee JT, Yang FC. Recreational nitrous oxide abuse-induced vitamin B12 deficiency in a patient presenting with hyperpigmentation of the skin. Case Rep Dermatol. 2013;5(2):186-91.
25. Demir N, Doğan M, Koç A, Kaba S, Bulan K, Ozkol HU, et al. Dermatological findings of vitamin B12 deficiency and resolving time of these symptoms. Cutan Ocular Toxicol. 2014 Mar 1;33(1):70-3.
26. Mori K, Ando I, Kukita A. Generalized hyperpigmentation of the skin due to vitamin B12 deficiency. J Dermatol. 2001 May;28(5):282-5.
27. Niiyama S, Mukai H. Reversible cutaneous hyperpigmentation and nails with white hair due to vitamin B 12 deficiency. Eur J Dermatol. 2007 Oct 19;17(6):551-2.
28. Aaron S, Kumar S, Vijayan J, Jacob J, Alexander M, Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. Neurol Ind. 2005 Jan 1;53(1):55.
29. Gilliam JN, Cox AJ. Epidermal changes in vitamin B12 deficiency. Arch Dermatology. 1973 Feb 1;107(2):231-6.

Cite this article as: Sudhaa MM, Yasmeen AS, Nanitha LKG, Jesudasan A. Vitamin B12 deficiency masquerading Addison's disease: a case report of an adolescent male. Int J Res Med Sci 2020;8:1932-6.