ORIGINAL RESEARCH PAPER

Dermatology

KEY WORDS: knuckle hyperpigmentation, cutaneous sign, vegetarian population, megaloblastic anemia.

KNUCKLE HYPERPIGMENTATION AS A PRELIMINARY MARKER OF VITAMIN B 12 DEFICIENCY: A CASE SERIES

Dr. Manali Patil* Junior Resident, Department of dermatology, Dr Panjabrao Deshmukh memorial medical college, Amravati, Maharashtra. *Corresponding Author

Dr. S. N. Agrawal MBBS, DNB, DVD (Skin), Professor and Head of department, Department of dermatology, Dr Panjabrao Deshmukh memorial medical college, Amravati, Maharashtra.

Dr. V. V. Saoji MBBS, MD (Skin), Associate professor, Department of dermatology, Dr Panjabrao Deshmukh memorial medical college, Amravati, Maharashtra.

ABSTRACT

Vitamin B12 deficiency is common in vegetarian population in India and can present with variable Hematological (megaloblastic anemia), Neuropsychiatric, Mucocutaneous (glossitis, angular stomatitis), Skin (pallor, hyperpigmentation) and Hair changes (dry, brittle, thin, lustreless, prematurely grey). Knuckle hyperpigmentation has been described in vitamin B12 deficiency but usually these patients are dermatologically asymptomatic but they have systemic manifestations like megaloblastic anemia, pancytopenia or neurological deficits. The foreground of this study is highlighting the importance of knuckle hyperpigmentation as an early cutaneous sign of vitamin B12 deficiency which points an important clue towards the aetiology of Megaloblastic anemia.

INTRODUCTION

Vitamin B12 deficiency is not uncommon in vegetarian population. Knuckle hyperpigmentation is an early marker of this deficiency and needs to be investigated further to know the entire picture better. Knuckle pad hyperpigmentation specifically is much more oftenly seen in contrast to diffuse pigmentation of the palms and/or soles in these patients. This study emphasizes that knuckle pad hyperpigmentation is a well-founded marker of megaloblastic anemia and is a clue for early diagnosis and prompt management, thereby decreasing the preventable morbidity. Herein we report 3 cases of knuckle hyperpigmentation associated with Vitamin B12 deficiency.

Case 1

A 33-year-old female presented to the dermatology clinic with chief complaints of hyperpigmentation of dorsal aspect of both hands since past 3 months. There was no history of application of any topical steroid, drug intake, excessive sun exposure. She had been a vegetarian since birth. On examination, well demarcated areas of hyperpigmentation localized specifically to the knuckle pad of both hands was noticed. The overlying skin over the knuckles was normal and there were no associated complaints.

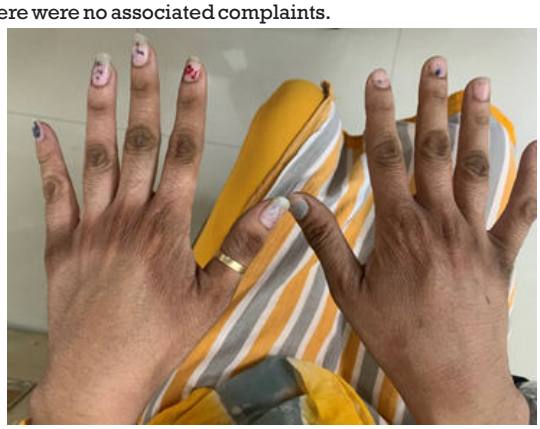

Figure 1- *Marked hyperpigmentation over knuckles and dorsa of hands*

On lab investigations,
Hemoglobin- 10.3 g/dl, Total leucocyte count- 7,600 , Platelets- 2,83,000
On peripheral smear- Normocytic normochromic anemia
MCV- 73.1 fL; MCH- 25.0 pg, MCHC- 34.2g/dl
Serum B12 level was 86.1 pg/ml (reference range: 239-931),
On taking thorough history, clinical and lab findings, the diagnosis of vitamin B12 deficiency was established. Patient was treated with Tab. Folic acid 5 mg OD per orally daily and Cap. Autrin OD per orally along with Inj. Eldervit intramuscularly once every month for 6 months.

Case 2

38-year-old male presented with chief complaints of hyperpigmentation over knuckles since 1 month. He also had complaints of easy fatiguability, loss of appetite and bleeding while defecation in the last 15 days. He had been a vegetarian since birth. On examination, well demarcated areas of hyperpigmentation localized specifically to the knuckle pad of both hands was noticed. The overlying skin over the knuckles was normal. Diffuse hyperpigmentation with well-defined multiple hyperpigmented macules were seen on palmar aspect of both hands.

Figure 2- *diffuse hyperpigmentation with knuckle pad hyperpigmentation*

Figure 3- *hyperpigmented macules over fingers and palmar aspect*

Lab findings-
Hemoglobin- 5.2 g/dl, Total leucocyte count- 3100, Platelets- 47,000
MCV- 106.7 Fl, MCH- 38.4 pg, MCHC 36 g/dl
On peripheral smear- red blood cells- Macrocytic hypochromic anemia with reduced platelets on peripheral smear
Vitamin B12 levels- 77 pg/ml (reference range: 239-931),
Retic count- 0.5%

Treatment-
Patient was started with Tab. Folic acid 5mg OD per orally along with Cap. Autrin OD per orally. Patient was given Inj. Eldervit intramuscularly once a week for 6 weeks followed by once a month for 12 months. Patient was also transfused with III ® PCV on alternate days.

Case 3
31-year-old male presented to the dermatology clinic with chief complaints of easy fatiguability, dyspnoea on exertion and diffuse hyperpigmentation over dorsa of both hands. On examination, hyperpigmentation localized over the knuckle pads with normal overlying skin. Diffuse hyperpigmentation with dusky-hyperpigmented macules over noted on palmar surfaces of both hands.

Figure 4- *knuckle pad hyperpigmentation with diffuse hyperpigmentation over both dorsal and palmar aspect of hands*

Figure 5- *knuckle pad hyperpigmentation*

On lab investigations-
Lab findings-
Hemoglobin- 2.9 g/dl, Total leucocyte count- 2000, Platelets- 23,000
MCV- 124.7 fL, MCH- 43.1 pg, MCHC 34.6 g/dl
On peripheral smear- red cells- Macrocytic hypochromic anemia with markedly reduced platelets on peripheral smear
Serum Vit. B12 levels- 69 pg/ml (reference range: 239-931)

DISCUSSION-
The deficiency of vitamin B12 often manifests as hematological, mucocutaneous and neurological findings. Pigmentary changes in the form of pigmentation of knuckles, oral mucosa, and Addisonian pigmentation have also been described [1]. Vitamin B12 deficiency commonly occurs in vegetarians as the important sources of vitamin B12 are animal products [2]. Vegetarian diets can be classified as lacto- vegetarian, ovo-vegetarian, lacto-ovo-vegetarian or vegan. Vegan diets have very low cobalamin content [3]. The recommended dietary allowance for a standard adult is 2.4µg/day. In our study, we observed a strong association of cutaneous hyperpigmentation particularly the knuckle pad pigmentation as an early and consistent feature of vitamin B12 deficiency associated with megaloblastic anemia.

Vitamin B12 deficiency can commonly present with megaloblastic anemia, anorexia, weight loss, fatigue, orthostatic hypotension, paraesthesias and subacute combined degeneration of spinal cord [4], [5].

The pathophysiologic mechanism associated with hyperpigmentation in B12 deficiency seems to be complex and is poorly understood [6]. Three hypotheses proposed regarding pathophysiology of B12 deficiency- induced hyperpigmentation are first, decrease in reduced form of glutathione increasing the activity of tyrosinase; second, defective melanin transfer between melanocytes and keratinocytes; and finally, disturbed melanin distribution due to megaloblastic changes in the keratinocytes [7].

For these patients we chose both oral and parenteral therapy simultaneously along with blood transfusions. It has been demonstrated in several studies that oral supplementation is as effective as intramuscular injections, and oral therapy can be utilized even in cases of pernicious anemia [8]. However, it must be noted that patients with severe neurological deficits or critically low levels of vitamin B12 should be treated with parenteral therapy, to ensure rapid replenishment of body stores to prevent irreversible consequences. Such patients can later be shifted to oral therapy [8]. The usual improvement of mucocutaneous findings within weeks with complete resolution in a few months following correction of this deficiency motivates patient's compliance to maintain adequate dietary/pharmacologic intake [9].

As this hyperpigmentation often resembles that seen in Addison disease, hypocortisolemia should be ruled out [1]. Knuckle pigmentation may occur even before the development of hematological and neurological complications. Therefore, clinicians especially dermatologists must be aware of this sign so that such cases may be diagnosed and treated early.

CONCLUSION
This study emphasizes the fact that Vitamin B12 deficiency is very common in vegetarian people but there is lack of awareness in the society for the same. Knuckle pad hyperpigmentation can be an early yet reliable marker for detection of Vitamin B12 deficiency for dermatologists. This may lead to early diagnosis and prompt management of such cases thereby decreasing the preventable morbidity.

Declaration of patient consent
The author certifies that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for the images and other clinical information to be reported in journal. The patient understands that the name and initials will not be published and due efforts will be made to conseal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Agrawala RK, Sahoo SK, Choudhury AK, Mohanty BK, Baliarsinha AK. Pigmentation in vitamin B12 deficiency masquerading Addison's pigmentation: A rare presentation. *Indian J Endocrinol Metab.* 2013;17(Suppl

1):S254–256. doi: 10.4103/2230-8210.119591. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Herrmann W, Obeid R. Causes and early diagnosis of vitamin B12 deficiency. Dtsch Arztebl Int 2008;105(40):680-685.
3. Herrmann W, Schorr H, Obeid R, et al. Vitamin B12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr 2003;78(1):131-136.
4. Cherqaoui R, Husain M, Madduri S, Okolie P, Bland G, Williams J. A reversible cause of skin hyperpigmentation and postural hypotension. Case Rep Hematol 2013;2013:680459.
5. Aaron S, Kumar S, Vijayan J, Jacob J, Alexzander M, Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. Neurol India 2005;53:55-8.
6. Brescoll J, Daveluy S. A review of vitamin B12 in dermatology. Am J Clin Dermatol 2015;16(1):27-33.
7. Jen M, Yan AC. Cutaneous changes in nutritional disease. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw Hill 2012. p. 1499-1525.
8. Chan CQ, Low LL, Lee KH. Oral Vitamin B12 Replacement for the Treatment of Pernicious Anemia. *Front Med (Lausanne)* 2016;3:38. doi: 10.3389/fmed.2016.00038. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
9. Jithendriya M, Kumaran S, Bhat I. Addisonian pigmentation and vitamin B12 deficiency: A case series and review of the literature. Cutis 2013;92:94-9.