

## Case Report

# A case report on hyperpigmentation in vitamin B12 deficiency

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**Received:** 19 February 2019

**Accepted:** 28 March 2019

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## ABSTRACT

Cobalamin (Vitamin B12) is a water-soluble vitamin. Cobalamin is synthesized only by microorganisms. The only source of vitamin B12 for humans is food of animal origin. Hyperpigmentation of skin has been reported only rarely as the presenting manifestation of vitamin B12 deficiency. We report a patient who had hyperpigmentation as her presenting medical complaint and in whom Vitamin B12 deficiency was the cause. A 36-year-old female presented with generalised weakness and progressive and asymptomatic hyperpigmentation of hand and feet for 5 months. She is vegetarian by diet. On examination, hyperpigmentation was present over dorsal aspect of metacarpophalangeal, proximal and distal interphalangeal joints. Hyperpigmentation were present over dorsum of the foot and over the joints. The tongue was depaillated, and hyperpigmentation was present. Her serum level of vitamin B12 was diminished (83pg/ml). Megaloblastic anemia presents with protean manifestations. The association between vitamin B12 deficiency and hyperpigmentation, although unusual, has been described. Cutaneous manifestations associated with B12 deficiency include characteristic mucocutaneous hyperpigmentation (most common), vitiligo, angular cheilitis, and hair-nail changes. It mainly affects knuckle pads and oral mucosa. It is an under-recognized sign of megaloblastic anemia and should always be looked for in the setting of pallor. Hyperpigmentation could be the earliest manifestation of vitamin B12 deficiency before anemia sets in. It is worthwhile to consider the possibility of vitamin B12 or folate deficiency in a patient with unexplained pigmentary changes. Early detection and adequate treatment will prevent anemia and various neurological manifestations.

**Keywords:** Cobalamin, Megaloblastic anemia, Nutritional deficiency

## INTRODUCTION

Vitamin B12 is a water-soluble vitamin. It exists in various forms like cyanocobalamin, hydroxocobalamin and methylcobalamin.<sup>1</sup> Cobalamin (vitamin B12) exists in a number of different forms with a cobalt atom at the center of a corrin ring. Cobalamin is synthesized only by microorganisms. The only source of vitamin B12 for humans is food of animal origin, for example, meat, fish, and dairy products. Vegetables, fruits, and other foods of non-animal origin are free from cobalamin. Vitamin B12 deficiency presents with different combinations of neurological manifestations, hematological changes,

discoloration of skin, hair and nails and weakness. Common cause of vitamin B 12 deficiency is malabsorption, due to pernicious anemia or gastric resection and rarely inadequate intake.<sup>2</sup>

Vegetarians are more prone for vitamin B12 deficiency due to inadequate intake. Hyperpigmentation of skin has been reported only rarely as the presenting manifestation of vitamin B 12 deficiency. Folate and B12 act as coenzymes in one carbon metabolism in which a carbon unit from serine or glycine is transferred to tetrahydrofolate (THF) to form methylene-THF; DNA and RNA synthesis require these reactions.<sup>3</sup> The

spectrum of disease associated with vitamin B12 deficiency is wide, from asymptomatic to life-threatening pancytopenia or myelopathy. The folate and B12 deficiency may be due to the prior gastrointestinal surgery and vegetarian food habits.<sup>4</sup>

Vegetarians have increased predisposition to B12 deficiency as it is obtained only from animal sources.<sup>5</sup> Cutaneous hyperpigmentation is the characteristic dermatological sign seen in vitamin B12 deficiency, which can be reversed by administration of vitamin B12.<sup>6</sup> Hyperpigmentation is seen in palmar creases, on the dorsum of the hand and feet, in intertriginous areas, on oral mucosa and in recent scars. A few patients have generalized hyperpigmentation.<sup>7</sup>

### ***Pathophysiology of hyperpigmentation***

The pathophysiologic mechanism associated with hyperpigmentation in B12 deficiency is poorly understood.<sup>8,9</sup> However, the most accepted hypotheses are:

- Increased melanin synthesis, and
- Defective melanin transfer from melanocytes to adjacent keratinocytes.

Reduced cobalamin causes a reduction in intracellular reduced glutathione (GSSH) which in turn, activates tyrosinase enzyme. Tyrosinase act in the L-phenylalanine-L-tyrosine-melanin pathway. Also, there is defective DNA synthesis which leads to activation of micro-opthalmia associated transcription factor (MITF), which upregulates both tyrosinase and tyrosinase related proteins (TRP 1 and 2).<sup>8</sup> Studies in skin biopsies have suggested that hyperpigmentation is due to an increase in melanin synthesis not due to defect in transport.<sup>10</sup> Moreover, increased angiogenesis secondary to upregulation of vascular endothelial growth factor (VEGF) has also been postulated to be responsible for the reddish brown discoloration seen in some cases.<sup>9</sup> However, the reason for the localized regional hyperpigmentation over the knuckle regions and greater prevalence among dark skinned individuals remains unknown.

Hyperpigmentation also has been attributed to a defect in the melanin transfer between melanocytes and keratinocytes, resulting in pigmentary incontinence. There are an increased number of melanocytes in the basal layer with numerous melanophores in the papillary dermis and increased melanin in the dermis and epidermis.<sup>11</sup> Reversible premature greying of hairs is usually associated with cutaneous hyperpigmentation.<sup>12</sup>

Generalized acquired cutaneous hyperpigmentation is a challenging problem. Although not frequently cited, hyperpigmentation can occur in patients with megaloblastic anemia from folate or vitamin B12 deficiency.<sup>13</sup> Authors report a patient who had

hyperpigmentation as her presenting medical complaint and in whom vitamin B12 deficiency was the cause.

### **CASE REPORT**

A 36-year-old female presented with generalized weakness and progressive and asymptomatic hyperpigmentation of hand and feet for 5 months. She also had easy fatigability with loss of weight and appetite. She had noted progressively increasing darkening of skin and discoloration nails. The lesions had appeared initially on her knuckle and extended gradually over 5 months to involve the dorsum of the fingers and feet. The palms and soles were also involved. She is a vegetarian. There was no significant past history or family history.

On examination, hyperpigmentation was observed on skin of the dorsal aspect of the hands (Figure 1) and the feet.



**Figure 1: Hyperpigmentation of the knuckles.**

The tongue was depapillated and hyperpigmentation was present (Figure 2).



**Figure 2: Loss of papilla and hyperpigmentation of tongue.**

Hyperpigmentation were present over dorsal aspect of metacarpophalangeal, proximal and distal interphalangeal joints. Hyperpigmentation were present over dorsum of the foot and over the joints. Abdominal examination revealed mild hepatosplenomegaly with no ascites. Other systemic examination was non-contributory.

Biochemical tests including complete hemogram (Table 1), renal function tests and liver function tests and serum electrolytes were done.

**Table 1: Biochemical and hematological reports.**

Blood parameters	Value
Total WBC count	7.9*10 <sup>3</sup> /μL
RBC count	4.18* 10 <sup>6</sup> /μL
Haemoglobin	16.2 g/dL
Platelet count	275*10 <sup>3</sup> /μL
MCV	99.5 fL
MCH	38.8 g/dL
MCHC	38.9 g/dL
Serum VIT B12	83 pg/dL

Abdominal ultrasonography revealed mild hepatosplenomegaly without ascites. Serum level of vitamin B12 was diminished (83pg/ ml; reference range:187-883 pg/ml).

## DISCUSSION

Megaloblastic anemia presents with protean manifestations. In our case report authors have described a case of vitamin B12 deficiency presenting with hyperpigmentation of skin. The association between vitamin B12 deficiency and hyperpigmentation, although unusual, has been described. In most of the reported cases, the hyperpigmentation was confined to the dorsum of the hands and feet, particularly over the interphalangeal joints.<sup>10,14,15</sup> Cutaneous manifestations associated with B12 deficiency include characteristic mucocutaneous hyperpigmentation (most common), vitiligo, angular cheilitis, and hair-nail changes, which are often missed or overlooked in early, asymptomatic phases of the disease.<sup>16</sup>

The prevalence of hyperpigmentation is not known. Few studies have stated that about 10% of vitamin B12 deficient patients show reversible melanin skin pigmentation. It mainly affects knuckle pads and oral mucosa.<sup>17</sup> In our case patient had both skin as well as oral mucosa hyperpigmentation. It is an under-recognized sign of megaloblastic anemia and should always be looked for in the setting of pallor.

Hyperpigmentation could be the earliest manifestation of vitamin B12 deficiency before anemia sets in. In our patient the hemoglobin level was within normal range for the age and sex. Anemia occurs in patient with severe vitamin B12 deficiency for a longer duration. Many

patients with vitamin B12 deficiency present with asymptomatic elevation of MCV or nonspecific complaints. Nutritional deficiency had been the main culprit for widespread disease manifestations in a large population, especially among low income groups. Strict vegetarians are more prone for deficiency due to lack of cobalamin in vegetables and fruits.<sup>18</sup>

It is worthwhile to consider the possibility of vitamin B12 or folate deficiency in a patient with unexplained pigmentary changes. Early detection and adequate treatment will prevent anemia and various neurological manifestations.

## CONCLUSION

Cutaneous hyperpigmentation is an early manifestation of vitamin B12 deficiency. Presenting complaint in megaloblastic anemia due to vitamin B12 deficiency is anorexia, generalized weakness, irritability manifesting clinically as pallor, hyperpigmentation and hematologically as macrocytic anemia or pancytopenia. Megaloblastic anemia is a preventable and treatable cause of progressive neurologic disease. This study describes hyperpigmentation in vitamin B12 deficiency without anemia. Further study into this relation is required.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Verma VK, Vijayavarman V. A case report on hyperpigmentation in vitamin B12 deficiency. *Int J Res Med Sci* 2019;7:1944-7.