

Vitamin B₁₂ Deficiency: A Case Report of Ongoing Cutaneous Hyperpigmentation

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GOAL

To recognize and be able to treat vitamin B₁₂ deficiency

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the clinical manifestations of vitamin B₁₂ deficiency.
2. Discuss the differential diagnoses of vitamin B₁₂ deficiency.
3. Explain the treatment for vitamin B₁₂ deficiency.

CME Test on page 138.

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We describe an interesting case of a man with recurrent cutaneous and hematologic manifestations of vitamin B₁₂ deficiency. In this deficiency, the skin, central nervous system, blood, and blood-forming tissues are commonly involved. We describe an overview of vitamin B₁₂ deficiency and the successful treatment of a patient's ongoing cutaneous hyperpigmentation.

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A 54-year-old Haitian man with a medical history significant for type 2 diabetes mellitus, alcohol abuse, liver disease, and vitamin B₁₂ deficiency presented to the dermatology clinic. For the past several years, he has experienced increasing darkening of the hands, feet, and tongue. The patient's only medication was glyburide.

The patient had 3 similar episodes of hyperpigmentation, shortness of breath, and weakness during the past 9 years. According to the patient's history, each episode cleared following treatment. During the first episode, laboratory test results revealed the patient had a hemoglobin level of 8.4 g/dL (reference range, 14–18 g/dL), a hematocrit level of 26.6% (reference range, 42%–52%), and a

vitamin B₁₂ level of 35 pg/mL (reference range, 200–800 pg/mL). Folic acid and ferritin levels were within reference range. The patient underwent a Schilling test, which revealed results within reference range. The patient was treated with a 1-mg dose of vitamin B₁₂ injected intramuscularly every week for 2 months, followed by a 1-mg dose injected intramuscularly every month for 3 months. After the third month, the patient's cutaneous hyperpigmentation cleared, and he was lost to follow-up until 5 years later. At that time, results of the Schilling test revealed no malabsorption, and the patient was subsequently treated with a 1-mg dose of vitamin B₁₂ injected intramuscularly every month for 5 months. Again, the patient was lost to follow-up until the third episode, which occurred one year later. At that point, the patient was treated with a 1-mg dose of vitamin B₁₂ injected intramuscularly every month for 8 months.

Two years later, the patient presented to our dermatology clinic with his fourth episode of hyperpigmentation. Due to the patient's intermittent symptoms, he underwent further testing. Part of his workup included a Schilling test, which again revealed results within normal limits.

On physical examination, the patient's vital signs were within reference range. He presented with a few discrete hyperpigmented macules measuring 1 cm along the lateral sides of the tongue, along with well-defined hyperpigmented patches measuring 10 cm on the dorsolateral portion of both feet, and a diffuse hyperpigmentation of both palms (Figure). The patient had pallor of all of his nail beds. There was no involvement of the conjunctiva, buccal mucosa, lips, genitals, or hair. There were no signs of neurological involvement.

Testing determined the probable cause of the patient's vitamin B₁₂ deficiency was malnutrition. The patient was aware of the cause of his ongoing cutaneous hyperpigmentation and was interested in further treatment. The treatment regimen consisted of a 1-mg dose of vitamin B₁₂ injected intramuscularly every week for 1 month, then a 1-mg dose every 2 weeks for 1 month, followed by a 1-mg dose every month for 10 months. There was resolution of the patient's cutaneous hyperpigmentation and all symptoms after 2 months of therapy. It was recommended that the patient continue with a 1-mg dose of vitamin B₁₂ injected intramuscularly every month for life. To date, the patient is experiencing complete resolution of his cutaneous hyperpigmentation.

Comment

Vitamin B₁₂ deficiency was first described by Cook¹ in 1944 and later by Baker et al² in 1963.

Figure not available online

Diffuse palmar hyperpigmentation prior to treatment.

Vitamin B₁₂ is essential for the normal functioning of cells and the synthesis of nucleic acids.^{3,4} A deficiency can be caused by a congenital lack of transcobalamin II, a lack of intrinsic factor, achlorhydria, ileal disease, malnutrition, and malabsorption syndromes.⁵ Vitamin B₁₂ deficiency usually occurs 3 to 6 years after the onset of gastrointestinal abnormalities because of the large body stores found in adults.⁵ There is multisystem involvement in this deficiency, with the skin, central nervous system, and bone marrow being affected.⁵

The skin manifestations include hyperpigmentation, glossitis, and canities.⁵ The hyperpigmentation is usually generalized and symmetrical, involving the hands, nails, and face.⁵ The areas most commonly affected include the palmar creases and the flexural regions of the body.⁵ Linear longitudinal hyperpigmented nail plate streaks and pale nail beds are the nail findings associated with this deficiency.^{6,7} There is a broad differential diagnosis to consider with cutaneous hyperpigmentation (Table). Glossitis manifests as an atrophic, bright red, sore tongue.⁵ A paradoxical finding is premature graying.⁵ The exact mechanism of hyperpigmentation is unknown, but there are many hypotheses.⁶⁻⁸ It has been suggested that a deficiency of vitamin B₁₂ causes a decrease in the amount of intracellular-reduced glutathione.⁶⁻⁸ This inhibits tyrosinase and permits an increase in

Differential Diagnosis of Hyperpigmentation

Acquired immunodeficiency syndrome
Addison disease
Alkaptonuria
Amyloidosis
Cushing syndrome
Diffuse melanosis cutis
Heavy metal deposition
Hemochromatosis
Hyperthyroidism
Malignancies
Medications including: minocycline, amiodarone, antimalarials
Pheochromocytoma
Porphyria cutanea tarda
Postinflammatory hyperpigmentation
Syphilis
Type 2 diabetes mellitus
<u>Vitamin B₁₂ deficiency</u>

melanogenesis, resulting in clinical hyperpigmentation.⁶⁻⁸ Another possible site of interaction in melanin synthesis is bipterin, a substance necessary for the hydroxylation of phenylalanine.^{6,7} Hydroxylated phenylalanine is needed for melanin synthesis and elevated levels are found in folate deficiency.^{6,7} This could explain the hyperpigmentation also found in vitamin B₁₂ deficiency.^{6,7} Another possibility could be a defect in melanin transport and its incorporation into megaloblastic keratinocytes.⁷ Lastly, there is evidence indicating that there may be a disorder in purine or pyrimidine metabolism leading to a decrease in the ability to synthesize DNA.⁷ This may lead to the keratinocyte and epidermal changes found with this deficiency.⁷

Most patients with vitamin B₁₂ deficiency experience neurological symptoms, which may occur in

the absence of anemia.⁹ Collectively, the neurological symptoms are referred to as subacute combined degeneration of the spinal cord. The initial symptoms include generalized weakness and paresthesia, followed by ataxia and loss of vibration that is more pronounced in the lower extremities. Optic neuropathy and central scotomas also may occur with this deficiency. These manifestations may or may not improve with vitamin B₁₂ replacement therapy. Patients also experience various mental symptoms, including irritability, apathy, somnolence, psychosis, and intellectual deterioration. The pathogenesis of the neurological manifestations is not well understood. It is known that vitamin B₁₂ deficiency impairs the function of methionine synthetase and methylmalonyl CoA mutase. This impairment causes an accumulation of fatty acids that alters the production of myelin and results in swelling of the myelin sheaths. There is resultant demyelination of the posterior columns of spinal cord, lateral columns of spinal cord, and optic nerves, causing the symptoms described above.⁹

In patients experiencing the hematologic manifestations of vitamin B₁₂ deficiency, the blood and bone marrow show megaloblastic changes.¹⁰ The anemia can be severe, with a hematocrit level as low as 15%. A common cause of vitamin B₁₂ deficiency is a lack of intrinsic factor due to gastric mucosal atrophy.¹¹ This condition is referred to as pernicious anemia. With continuous vitamin B₁₂ replacement therapy, patients experience lifelong resolution of all hematologic abnormalities. The symptoms associated with anemia include weakness, vertigo, palpitations, and angina.¹⁰

The diagnosis of vitamin B₁₂ deficiency can be confirmed by a positive Schilling test result, a low vitamin B₁₂ serum level, an elevated methylmalonic acid serum level, and an elevated total homocysteine serum level. The Schilling test is performed by simultaneous administration of an oral dose of radiolabeled vitamin B₁₂ and an intramuscular dose of nonradiolabeled vitamin B₁₂.¹² If the urinary excretion of radioactivity in the 24 hours following administration is less than 8%, then vitamin B₁₂ deficiency is confirmed.¹² The test is then repeated with intrinsic factor, then with pancreatic enzymes, and finally with antibiotic administration.¹² With ileal disease or resection, results of the Schilling test will remain persistently abnormal.¹² Of the tests available, the tests to evaluate the elevation of serum methylmalonic acid and total homocysteine are the most sensitive and specific in diagnosing vitamin B₁₂ deficiency and can be used to help differentiate vitamin B₁₂ deficiency from folate deficiency.⁴

If lesional skin is biopsied for histological examination, it may reveal epidermal thinning, vacuolar change of keratinocytes, enlargement of the nuclei of many of the keratinocytes, increased number of melanocytes in the basal layer, and numerous melanophages in the papillary dermis.^{6,8} Electron microscopy of a biopsied specimen may reveal many intracytoplasmic desmosomes, numerous aggregated bundles of tonofilaments within the cytoplasm of the keratinocyte, and highly condensed keratohyalin granules.⁷

Treatment consists of a 1-mg dose of vitamin B₁₂ injected intramuscularly every day for 5 to 10 days, then a 1-mg dose every week for 1 month, followed by a 1-mg dose every month for life.^{5,13} Treating the underlying cause of this deficiency must be carried out prior to the initiation of vitamin B₁₂ replacement therapy. A decrease in hyperpigmentation usually occurs within 2 weeks of starting the vitamin B₁₂ treatment.⁷ On occasion, it has taken 6 to 12 weeks for skin color to return to normal.⁷ The most important factor influencing response to treatment is the duration of symptoms.⁵ Following successful treatment of this deficiency, there is a reversal of the nuclear enlargement of the keratinocytes found histologically, along with a resolution of skin, hair, and nail changes found clinically.⁶⁻⁸

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