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Case Report

A hidden deficiency unveiled by hyperpigmentation: a case report of vitamin B12 deficiency

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ABSTRACT

Vitamin B12 deficiency is a common nutritional disorder that frequently manifests with hematologic and neurologic symptoms. Dermatologic signs, such as hyperpigmentation, can occur as an early sign of deficiency but are less commonly recognized, potentially leading to delayed diagnosis. This is particularly relevant in regions with a high prevalence of nutritional deficiencies, like Nigeria. A 35-year-old Nigerian woman presented with a one-year history of progressive, non-scaly hyperpigmentation on her hands and feet, primarily affecting the palms, soles and knuckles. She had no underlying medical condition typically associated with vitamin B12 deficiency and her symptoms persisted due to misdiagnosis for presumed skin allergies by several doctors. Upon proper diagnosis, the patient received standard vitamin B12 supplementation, resulting in marked improvement in her condition. Importantly, pernicious anaemia was demonstrated as the cause of vitamin B12 deficiency, necessitating long-term treatment. This case underscores the importance of recognizing early dermatologic signs like hyperpigmentation as potential indicators of vitamin B12 deficiency. Increased awareness among healthcare providers can facilitate early diagnosis, allowing timely intervention to prevent irreversible neurological damage and ensuring potential for full recovery.

Keywords: Vitamin B12 deficiency, Hyperpigmentation, Pernicious anaemia, Case report

INTRODUCTION

Pernicious anaemia, is an autoimmune disorder often caused by the destruction of gastric parietal cells, and thus, loss of intrinsic factor necessary for vitamin B12 (cobalamin) absorption.[1] Vitamin B12 is essential for DNA synthesis, red blood cell production and neurologic functions. The absence of intrinsic factor, causes insufficient vitamin B12 absorption in the terminal ileum resulting in the development of megaloblastic anaemia, intramedullary haemolysis and cytopaenias.[1] Asides these notable haematological effects, megaloblastic anaemia often has a clinical manifestation of neurological, gastrointestinal and dermatological symptoms.[2] However, the dermatological manifestations, particularly cutaneous hyperpigmentation are infrequently addressed in literature texts and only occasionally documented. Hyperpigmentation is a nonspecific symptom, and clinicians may not immediately link it to vitamin B12 deficiency unless other widely recognized symptoms, such as megaloblastic anaemia or neurological deficits, are present. In addition, hyperpigmentation as a primary symptom found on sun exposed skin areas can indicate the search for other pathologies, such as Addison's disease where increased melanin production is the hallmark.[3] Delayed recognition of vitamin B12 deficiency can lead to serious complications, including irreversible neurological damage.[2] This emphasizes the need for clinicians to take a detailed clinical history and conduct a thorough physical examination to guide the selection of appropriate diagnostic tests, allowing for proper diagnosis, timely treatment and prevention of long-term sequelae. This case report describes a young African female with vitamin B12 deficiency due to pernicious

anaemia, presenting primarily with diffuse skin hyperpigmentation on the hands and feet. Patient was initially worked up for other causes of skin hyperpigmentation, stressing the importance of recognizing the dermatological signs associated with vitamin B12 deficiency.

CASE REPORT

A 35-year-old female Nigerian trader, presented with a 1-year history of progressive skin hyperpigmentation of both hands and feet. Skin hyperpigmentation initially started on the dorsum of the hands and progressed to the palms, dorsum of the feet and the soles. At this time patient did not have signs and symptoms of anaemia or neurological manifestations.

She had no significant medical history, surgeries, chronic conditions or allergies and no history of use of creams that could cause skin changes. There was no history of gastrointestinal surgery or malabsorption disorders. She did not have a history of chronic drug use and no evidence of weight loss. There was no history of smoking or taking alcohol and no history of following a vegan or vegetarian diet. She gave a history of visiting some doctors who prescribed some skin medications for possible skin allergies but there was no resolution. As a trader, she did not feel confident to go to work as her customers were too superstitious to handover money to her black-coloured palms. She decided to seek spiritual care as she assumed it was a spiritual attack but that also failed to cure her skin lesions.

Physical examination revealed mild palor, no jaundice, no lymphadenopathy and no pedal oedema. She exhibited diffuse, non-scaly hyperpigmentation on both hands, predominantly on the palmar surfaces of the fingers and knuckles, as well as on both feet, affecting the knuckles and soles (Figure 1). No hyperpigmentation in the oral cavity was observed. Her vital signs were stable. She had no neurological signs and hepatosplenomegaly was not detected. She was counselled on the need to carryout investigations, including screening for Addison's disease to determine the possible cause of hyperpigmentation. Next day follow up presentation, patient complained of tingling sensation on both feet. She was also discovered to have positive findings on neurological examination showing mildly decreased sensation to light touch and joint position sense in the lower limbs. Full blood count showed haemoglobin (Hb) of 8.0 g/dl, macrocytic anaemia with a mean cell volume (MCV) of 107fl and low reticulocyte count of 0.2%. The white blood cell count and platelet count were within reference limits at 4.2×109/l and 200×109/l respectively. A peripheral blood film showed anisocytosis, oval macrocytes and presence of hyper segmented neutrophils. Other investigations done-liver function test, electrolytes, urea and creatinine, serum folate and serum iron and thyroid function test were within normal limits. Stool for ova of parasite was negative.

The ACTH stimulation/ Synacthen test showed a baseline cortisol level of 10 µg/dl (reference <20 µg/dl), 30-minute post-Synacthen cortisol of 25 µg/dl (reference >20 µg/dl) and a 60-minute post-Synacthen cortisol 28 µg/dl (reference> 20 µg/dl). These were within reference limits which ruled out adrenal insufficiency. However, serum vitamin B12 was lower than reference limits-139 pg/ml (reference range: 200–900 pg/ml), while serum homocysteine level was higher than reference limits -25 µmol/l (reference range: 5-15 µmol/l) suggesting a vitamin B12 deficiency.

She received intramuscular (IM) cyanocobalamin injections 1,000 µg daily for 7 days, thereafter 1,000 µg once weekly for 3 weeks, then 1,000 µg once monthly for 6 months at the hospital's injection room with nurses documenting good drug compliance and no side effects. Oral folic acid tabs 5 mg daily was also introduced as a preventive measure, despite the patient's normal folate levels. Nutritional counselling was provided, by the hospital's nutritionist and the patient was encouraged to incorporate dietary sources of vitamin B12.

Table 1: Post treatment Hb, MCV, reticulocyte and vitamin B12 changes.

Parameter	Baseline	Week 2 post treatment	Week 4 post treatment	Week 8 post treatment	Week 16 post treatment
Hb (g/dl) (ref: 12- 16g/dl)	8	9.5	11.2	13.5	13.7
Mcv (fl) (ref: 80-100fl)	107	102	98	92	90
Corrected reticulocyte count (%) (ref: 0.5-2.5 %)	0.2	2.5	5.5	2	2.1
Vitamin b12 assay (pg/ml) (ref:200–900 pg/ml)	139	Not done	Not done	Not done	390

ref: reference limit

By the 2nd-4th week after commencement of treatment, reticulocyte count and Hb had a steady rise while MCV declined (Table 1), patient felt better and had resolution of tingling sensation on both feet and there was clearing of the hyperpigmented skin lesions. Upon further investigation, antibodies to serum antibodies to parietal cells and intrinsic factor were found to be positive suggesting a diagnosis of pernicious anaemia as the cause of vitamin B12 deficiency. She was thereafter counselled

on the need for proper follow up and 3 monthly lifelong vitamin B12 replacement. At 8 weeks of commencement of treatment, reticulocyte count, MCV and Hb had returned to normal levels (Table 1). At 16 weeks of commencement of treatment, vitamin B12 levels had normalized at 390 pg/ml (reference range: 200–900 pg/ml), skin lesions had resolved (Figure 2), neurological signs had disappeared and patient was now able to go to work. She was also more confident to handover cash to her customers. We scheduled her for long term monitoring including regular assessment for hematological and neurological status. Additionally, we requested continuous incorporation of dietary sources of vitamin B12, although absorption was limited due to the underlying autoimmune disorder. She was further counselled to schedule a possible endoscopy which she declined**.**

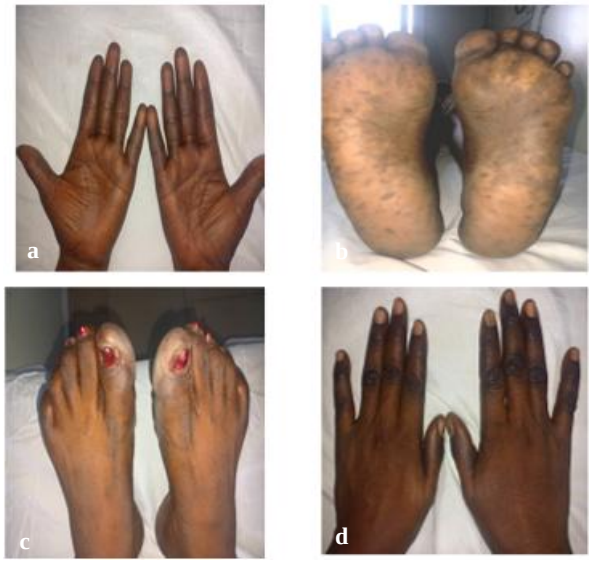

Figure 1 (a-d): Hyperpigmentation on the palms, knuckles and soles.

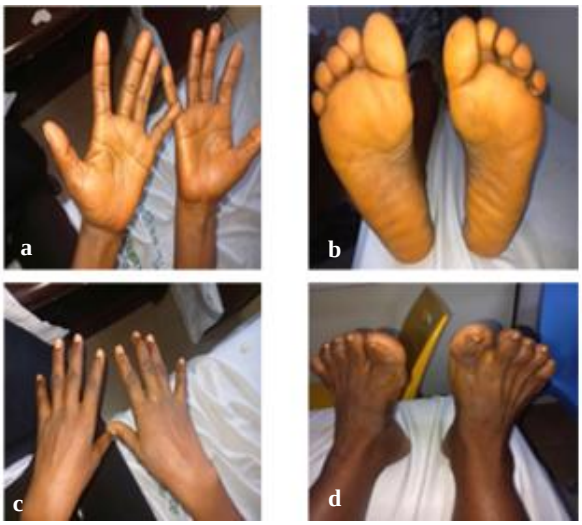

Figure 2 (a-d): Resolution of hyperpigmentation on the palms, knuckles and soles.

DISCUSSION

Pernicious anaemia is a common cause of clinically evident vitamin B12 deficiency, which typically presents with heamatological and neurological abnormalities.[4] Documentation exists of various dermatological manifestations of vitamin B12 deficiency, including early greying of hair, hair loss, brittle nails, angular cheilitis, vitiligo and skin hyperpigmentation with hyperpigmentation being the most commonly observed symptom.[5,6] However, these skin lesions are underappreciated because most patients with vitamin B12 deficiency present to the hospital with symptoms of anaemia as the first sign of the disease. Only a few case reports in literature search document dermatological manifestations as the sole presentation of megaloblastic anaemia making diagnosis a challenging one.[7-9]

Furthermore, the diagnosis of vitamin B12 can be passed over because the skin manifestations resemble those occurring in other diseases. For instance, Addison's disease has similar pattern of presentation of hyperpigmentation in sun-exposed areas and pressure points, potentially leading to confusion between the two conditions. Other notable conditions with hyperpigmentation are hyperthyroidism, hypothyroidism and drug induced hyperpigmentation.[3] The index patient had skin hyperpigmentation as the primary symptom for a year, however, she was misdiagnosed by several clinicians as having skin allergies. The delay in reaching an accurate diagnosis could have been overcome with a thorough medical history and a heightened index of suspicion, especially in cases of non-responsive skin lesions. This would guide the clinician to perform the appropriate investigations sooner.

Research indicates that up to 20% of patients with vitamin B12 deficiency may exhibit cutaneous hyperpigmentation as part of their clinical presentation highlighting the importance of recognizing this non-heamatological sign.[10] The characteristic skin hyperpigmentation seen in vitamin B12 deficiency is a blackish brown discolouration over the dorsum of the hands and feet with accentuation over the knuckles, distal phalanges and oral mucosa.[5] The index patient exhibited diffuse hyperpigmentation, notably involving the knuckles of the hands and feet, as well as similar pigmentation changes on the palms and soles. This reversible and often overlooked sign of vitamin B12 must be promptly recognized and corrected to ensure a full recovery and prevent further complications. At the time this patient presented to our facility, we recognized hyperpigmentation as a clue to vitamin B12 deficiency.

However, there was a 2 weeks delay in retrieving our patient's vitamin B12 and ACTH stimulation / Synacthen test results as these tests were outsourced. Despite this limitation, we initiated parenteral vitamin B12 treatment based on the findings from the full blood count and peripheral blood film, which indicated a high MCV and

the presence of oval macrocytes, along with the emergence of neurological symptoms. These clinical indicators justified the commencement of therapy, reflecting the urgency of addressing potential vitamin B12 deficiency and preventing further neurological decline. Our patient demonstrated a complete resolution of all skin and neurologic symptoms by the 16th week following treatment. A similar pattern of dramatic recovery of mucocutaneous symptoms have been documented in literature.[9,11,12]

Such improvements emphasize the positive impact of timely intervention with vitamin B12 supplementation in reversing the clinical manifestations of deficiency. And, by addressing the cause of vitamin B12 deficiency, disease recurrence was prevented. Our patient had vitamin B12 deficiency due to pernicious anaemia-an autoimmune malabsorption disease and she was placed on lifelong maintenance therapy. Women are generally at higher risk for autoimmune diseases than men. This difference may be due to hormonal influences which contribute to the immune dysregulation.

Other known causes of vitamin B12 deficiency such as gastric and ileal resection, Crohn's disease, long-term use of proton pump inhibitors or metformin and vegan diet were excluded in the patient. However, we added folate supplements to her initial treatment as this approach ensures the avoidance of potential folate deficiency, which could complicate the clinical picture and hinder the optimal treatment of vitamin B12 deficiency, particularly in patients with absorption issues.

The prevalence of vitamin B12 deficiency in Nigeria is not known, because a comprehensive National data is lacking. However, some research across different regions of Nigeria indicates a significant occurrence ranging from 8% - 41% among various populations including pregnant women, adolescent girls and individuals with type 2 diabetes.[13-17] This shows a potentially high prevalence among the general population signifying the need for increased awareness of the disease.

Furthermore, the prevalence of vitamin B12 deficiency tends to be higher among women compared to men, globally.[18] The disparity may be attributed to several factors, including hormonal influences that can affect metabolism and nutrient absorption. Additionally, hormonal fluctuations may play a role in the immune dysregulation observed in various autoimmune diseases, which can further contribute to vitamin B12 deficiency.

Vitamin B12 is required as an essential cofactor in the conversion of homocysteine to methionine. This reaction is needed to produce tetrahydrofolate (THF), a co-factor which is crucial for purine and thymidine synthesis and ultimately deoxyribonucleic acid (DNA) synthesis. Disruption of this pathway by vitamin B12 deficiency, leads to inhibition of DNA replication in maturing red blood cells and formation of megaloblasts.[1,2] The index patient had oval macrocytes seen on a peripheral blood film with an MCV of 107 fl, indicative of macrocytic anaemia. However, unlike the typical primary presentation of symptoms of anaemia in vitamin B12 deficiency, her initial clinical manifestation was skin hyperpigmentation, an uncommon early indicator of the condition. The mechanism behind hyperpigmentation in vitamin B12 deficiency is not fully understood but histopathological studies suggest that hyperpigmentation is caused by increased melanin production in the basal layer of the epidermis, rather than a defect in its transport.[19,20] This is possibly due to a defect in DNA synthesis upregulating tyrosinase-related proteins and reduced intracellular glutathione (GSSH) which further activates tyrosinase in the melanin synthesis pathway.[21,22] In addition, raised cysteine levels seen with the presence of hyperhomocysteinaemia in vitamin B12 deficiency can contribute to increased melanin production.[23] This symptom of hyperpigmentation is more frequently reported in individuals with darker skin, as seen in this case. This may be due to higher baseline melanin levels and racial variations.[3]

Neurological symptoms, such as paraesthesia and sensory loss, are common in vitamin B12 deficiency. Other neurological manifestations include cognitive and psychiatric symptoms. Neurological damage is caused majorly by the demyelination of nerves in the central and peripheral nervous systems as well as disruption of DNA synthesis.[1,2] Vitamin B12 is crucial for converting homocysteine to methionine, a process that leads to the production of S-adenosylmethionine (SAM), necessary for myelin sheath lipid methylation. It also serves as a cofactor for methylmalonyl-CoA mutase, aiding in the conversion of methylmalonyl-CoA to succinyl-CoA, essential for fatty acid synthesis.[1,2] Without this, methylmalonyl-CoA accumulates, forming methylmalonic acid (MMA), which is toxic to neurons. These processes disrupt nerve function and signal transmission and if untreated, the neurological deficits can become irreversible. Thus, early recognition and treatment of vitamin B12 deficiency is essential. Our patient was scheduled for long term follow up to include assessment for potential neurological complications at each visit, which will ensure timely intervention and prevent irreversible damage.

CONCLUSION

This case highlights the importance of recognizing vitamin B12 deficiency as a potential cause of diffuse hyperpigmentation, particularly in a region like Nigeria, where nutritional deficiencies are prevalent. Clinicians should maintain a high index of suspicion for vitamin B12 deficiency when encountering unexplained hyperpigmentation as the sole complaint to avoid delayed diagnosis and treatment. The patient responded well to standard vitamin B12 supplementation, with both dermatologic and neurologic symptoms resolved. Early

diagnosis and timely intervention can therefore prevent irreversible complications of vitamin B12 deficiency.

Patient perspective

From our patient's perspective, the treatment given for vitamin B12 deficiency induced hyperpigmentation was reassuring, as she could see visible improvement in her skin tone. She expressed relief from the distress caused by her by dark hands and feet. By the time she had full restoration of her natural skin tone, she felt a sense of normalcy and she was no longer self-conscious. Treatment improved her confidence especially in social gatherings and at work, enhancing her overall spiritual, emotional and mental well-being. She was happy and relieved that a doctor was finally able to diagnose her condition and provide a simple treatment to her disturbing skin lesions. Initially, she feared the worst, assuming her symptoms were indicative of a serious, perhaps incurable condition.

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