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Case Report

Cutaneous hyperpigmentation as a diagnostic marker of vitamin B12 deficiency: a case report

Eshan B. Henshaw[1,2]*, Love E. Okafor[2], Henry J. Ekpenyong[2]

[1]Department of Internal Medicine, University of Calabar, Calabar, Nigeria
[2]Department of Internal Medicine, University of Calabar Teaching Hospital, Calabar, Nigeria

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***Correspondence:**
Dr. Eshan B. Henshaw,
E-mail: eshenshaw@unical.edu.ng

ABSTRACT

Cutaneous hyperpigmentation and glossitis are recognized but often overlooked early signs of vitamin B12 deficiency (VB12D). Pernicious anaemia is the most common cause of VB12D. Many clinicians miss the diagnosis of this potentially fatal but treatable condition in the absence of the more often reported life-threatening neuropsychiatric and haematologic features, notwithstanding the concomitant presence of characteristic cutaneous signs. These apperceptions of conspicuous and early dermatologic signs lead to diagnostic delay, which can result in dire consequences for the patient. We report the case of a 24-year-old young woman who for two years had repeated blood transfusions, iron supplementation and haematinics on account of anaemia of undetermined aetiology of a yet to be determined aetiology, despite the simultaneous presence of a constellation of glaring dermatologic clues to VB12D. Following diagnosis and the institution of the appropriate therapy, the patient made remarkable improvement with a reversal of pigmentation and correction of the anaemia within a month. She continues to see the haematologists for follow-up.

Keywords: Cutaneous, Hyperpigmentation, Vitamin B12, Pernicious anaemia, Skin, Megaloblastic

INTRODUCTION

In a review by Castle, vitamin B12 deficiency (VB12D) was considered a syndrome consisting of the classical triad of jaundice, glossitis and myeloneuropathy.[1] Some other investigators thought the classic triad comprised megaloblastic anaemia, gastrointestinal symptoms or glossitis and neuropsychiatric symptoms.[2] While these are all definite features of VB12D, the categorization of just a handful of signs, from an array of potential signs, into specific diagnostic criteria, may largely be responsible for the observed inattention to the often preceding or co-existing innocuous cutaneous features.

As far back as 60 years ago, Baker et al described the characteristic pattern of pigmentation in VB12D to be more pronounced in the hands and feet; maximal over the dorsa of the fingers and toes; with accentuation at the interphalangeal and terminal phalangeal joints.[3] He considered this pattern as practically diagnostic of VB12D. Unfortunately, although these characteristic cutaneous features have been reported by several authors, they continue to be overlooked, precluding their being used as clues to the diagnosis of this condition.[4,5] This has resulted in late diagnosis and the attendant pernicious outcome.

Pernicious anaemia (PA) is the most common cause of VB12D, and results from insufficient intrinsic factor (IF) - a protein secreted by the parietal cells of the gastric mucosa - which enables the absorption of VB12. It has been linked to gastric neoplasia like adenocarcinomas, lymphomas and carcinoid syndromes.[6,7]

In the past, PA was considered rare in blacks, but with increasing reports, it is obvious that the perceived rarity was due to missed-diagnosis of early disease, occasioned by the absence of dreaded neuropsychiatric and haematologic features.[4,8,9]

The anaemia of VB12 and folate deficiency is megaloblastic. However, dermatological manifestations are more common in the former, include skin hyperpigmentation, stomatitis, brittle hair, premature depigmentation and nail changes. Although hyperpigmentation has been reported in folate deficiency, it is more common in VB12D, where it is sometimes the initiating feature.[3,5,10,11]

Thus, the presence of characteristic cutaneous hyperpigmentation with or without megaloblastic anemia and/or neuropsychiatric symptoms should heighten the index of suspicion of clinicians to the diagnosis of VB12D. An increased awareness is requisite to prompt diagnosis, avoidance of frequent, unnecessary and potentially deleterious blood transfusions, and prevention of the irreversible and sometimes deadly sequelae. It is against this backdrop that we report this case.

CASE REPORT

We herein present the case of a 24-year-old female oil palm plantation worker, admitted through the accident and emergency (A and E) with a two-year history of generalized body weakness, increased skin pigmentation especially of the hands and feet. There were associated episodes of easy fatigability, headache, dizziness, dyspnea on mild exertion and jaundice. She also described sore tongue, paraesthesia and weight loss.

Although not certain about the exact sequence of occurrence of all symptoms, she recalls the initiating symptoms to be generalized body weakness and increased skin pigmentation. The episodic symptoms often transiently abated following admission and blood transfusion.

She developed abdominal pain and jaundice in addition to other aforementioned symptoms a week to her presentation at our facility. She is not a vegetarian, on any fad diet nor is she on medications other than the haematinics and multivitamins she was placed on since the onset of her health challenge. She has no personal or family history of autoimmune disease or diabetes mellitus, and denied similar symptoms in any family member or colleague at work.

She volunteered a history of repeated blood transfusions at several medical facilities; with extensive investigations to ascertain the cause of hepatomegaly. However, a definitive cause of the anaemia remained elusive. Endoscopy was not done due to financial constraints.

Table 1: The results of investigations carried out.

Investigations	Result (normal values)
Haematocrit (pre-diagnosis)	10%- pre-transfusion (35-45%)
Full blood count (post transfusion)	White blood cell: 1.0×10^3/µl (4.0-12.0); lymphocytes: 89%, and neutrophils: 11%
	Haemoglobin: 5.1 g/dl (11.0-17.0)
	Haematocrit: 16.8% (35.0-55.0)
	Platelets: 78×10^3/µl (150-400)
Peripheral blood film	Red cells: sparsely distributed; anisopoikilocytosis; microcytic hypochromic cells; normocytic normochromic cells; microspherocytes; numerous nucleated cells; target cells and few tear-drop cells
	White cells: reduced with hypersegmented neutrophils; normal lymphocytes
ESR	6 mm/hour (0-30) Westergren's method
Bone marrow aspirate	Cellularity: hypercellular
	Myeloid-erythroid ratio: reversed (1:2)
	Erythropoiesis: erythroid hyperplasia with megaloblastic maturation; florid megaloblasts and dying cells
	Granulopoiesis: giant metamyelocytes; scanty but normal lymphocytes; scanty plasma cells
	Megakaryopoiesis: megakaryocytes with open nuclear chromatin and multilobulation
Viral serologies	HIV-negative
	HBsAg-negative
	AntiHCV-negative
Serum vitamin B12	39 pmol/l (133-675)
Serum folate	>20 ng/ml (3.1-20.5)
Intrinsic factor antibody	91.1 U/ml (0-6.0)
Haematocrit (post-diagnosis)	32% (one month after therapy with cobalamin)

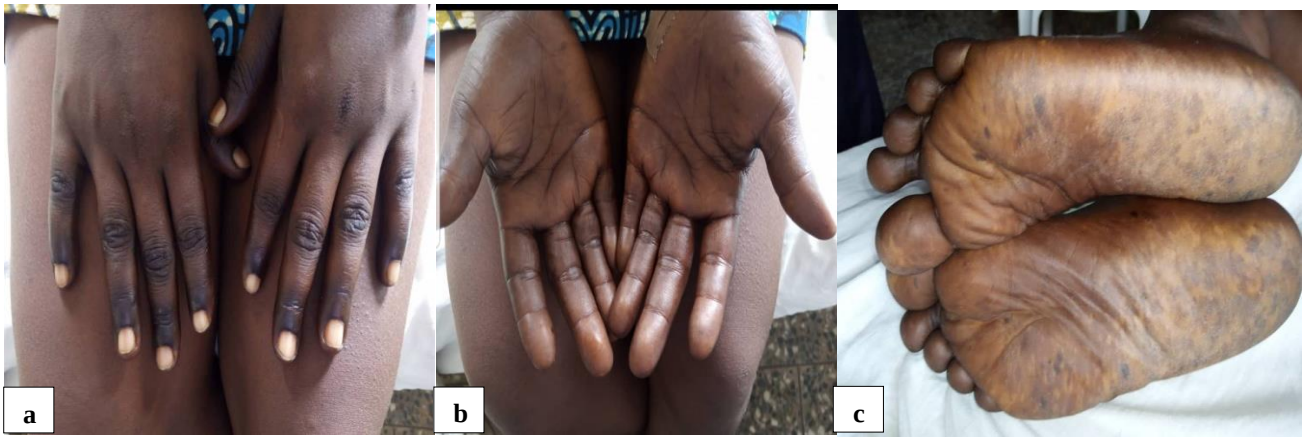

Figure 1: (a) Characteristic hyperpigmentation of vitamin B12 deficiency with accentuation of the interphalangeal joints and distal phalanges in the patient; (b) palmar hyperpigmentation due to vitamin B12 deficiency; and (c) mottled hyperpigmentation of the soles of the feet in pernicious anaemia.

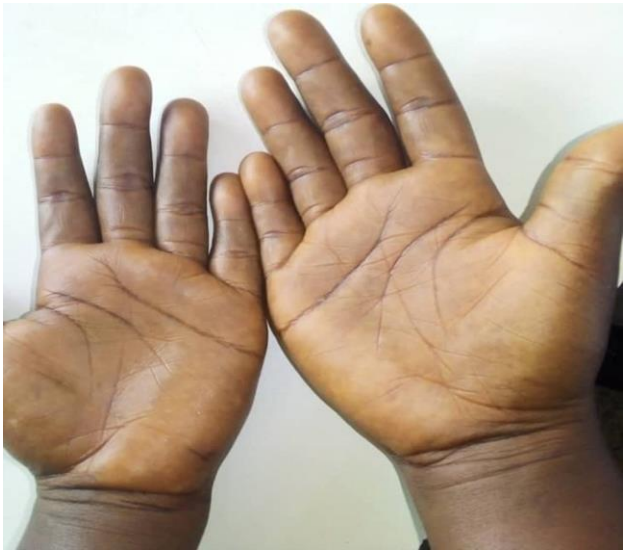

Figure 2: Palms after one month of therapy with hydroxocobalamin.

Our initial request for a thorough investigation of the anaemia was rebuffed with the following words 'I have done many tests already; all I need is blood and I will be fine and ready for discharge'.

Examination revealed a young woman in respiratory distress, marked palor, fluffy hair and angular stomatitis. She was icteric and had a beefy-red smooth tongue with atrophied papillae. The pattern of acral hyperpigmentation was diffuse on the palms, but mottled on the soles; the pigmentation extended to the dorsa of the digits, with accentuation over the interphalangeal joints and terminal phalanges (Figure 1).

She had obvious signs of heart failure including tachycardia, a third heart sound, a haemic murmur and tender hepatomegaly. There was no paresis or loss of sensation in the limbs, neither was there ataxia.

Presumptive diagnoses were vitamin B12 deficiency, Addison's disease or haemochromatosis.

Her decompensated cardiovascular status with a haematocrit of 10% led to immediate transfusion with two units of packed cells.

Complete blood count revealed pancytopaenia; with a megaloblastic picture on bone marrow aspiration. Serum vitamin B12 was markedly low, with normal folate level. Intrinsic factor antibody titre was high. Endoscopy was not performed for financial reasons. Table 1 shows details of the results obtained.

Intramuscular hydroxocobalamin was commenced, and she made remarkable improvement with resolution of the hyperpigmentation within a month of therapy as shown in Figure 2. She continues to see the haematologists for follow-up.

DISCUSSION

Cutaneous hyperpigmentation is an incontrovertible sign of VB12D irrespective of the cause- particularly the prototypical pattern showing hyperpigmentation over the dorsa of the fingers and toes; with accentuation at the interphalangeal and terminal phalangeal joints. This has been documented both in adults and children. It may be the first, and sometimes the only sign of VB12D.[5,11-15]

The index patient had pernicious anaemia and the well-documented pattern of acral hyperpigmentation was evident right from the onset of the disease, nonetheless, even in the presence of anaemia and myriad mucocutaneous pointers, VB12D was not considered. This may be due to the absence of the overt neurological features of sub-acute combined degeneration of the spinal cord, a late manifestation of VB12D often erroneously considered to be requisite to its diagnosis.

Pernicious anemia was initially believed to be restricted to Caucasians, especially among elderly Europeans of Scandinavian and Celtic origin, but it is now known to occur in all races. However, as observed in our patient, the age of onset is younger among blacks compared to Caucasians.

Mild deficiency of vitamin B12 may be asymptomatic but as it progresses, it presents with haematologic features such as anaemia, dermatologic, gastrointestinal, and neurologic features which may include paraesthesia, difficulty walking, mood changes, depression, memory loss, disorientation, dementia may develop. There is no definite sequence of occurrence of symptoms. Our patient had megaloblastic anaemia based on assay of the bone marrow aspirate. It is important to note that folate deficiency also causes megaloblastic anemia. However, compared to VB12D, neuropathy and skin pigmentation are rarely observed in folate deficiency; besides, the folate level in our patient was normal. The recurrent blood transfusion put her at risk of blood transfusion disorders; not to mention infection with blood-borne pathogens such as HIV and hepatitis B virus.

The most common cause of VB12D is pernicious anemia which our index patient has. She presented with the classic triad of- weakness, sore tongue and paresthesia. About 50% patients with pernicious anemia have smooth tongue with loss of papillae, sometimes the tongue may be painful and beefy red; this may also be found in Fe deficiency anaemia, however, in our patient, the megaloblastic picture ruled out the latter. Aaron et al studied of 63 patients, and found glossitis to be the most common mucocutaneous sign, followed by skin hyperpigmentation (19%), hair changes (9%), angular stomatitis (8%), and vitiligo (3%).[16] Gastric cancer is a sequelae of atrophic gastritis which is seen in pernicious anaemia; a patient with the latter requires long term endoscopic follow up, reinforcing the need for early diagnosis of PA.[6]

CONCLUSION

Knowledge of the mucocutaneous signs of VB12D and excellent observational skills may sometimes be all an astute clinician requires to suspect a diagnosis of PA. Identifying characteristic cutaneous signs is a rapid inexpensive way of diagnosing a potentially deleterious disease condition; circumventing the risk of acquiring chronic blood-borne infections like HIV/AIDS, hepatitis B and C; and initiating the requisite therapy, and regular follow-up to prevent complications.

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REFERENCES

1. Wintrobe MM. Blood, Pure and Eloquent: A Story of Discovery, of People and of Ideas. 2nd edition. New York: McGraw-Hill. 1980;771.
2. Babior B, Bunn H. Megaloblastic anemias. In: Wilson J, Braunwald E, Isselbacher K, Petersdorf R, Martin J, Fauci A, editors. Harrison's Principles of internal medicine. 12th edition. New York: McGraw-Hill. 1991;1523-9.
3. Baker S, Ignatius M, Johnson S, Vaish S. Hyperpigmentation of skin. A sign of vitamin-B12 deficiency. Br Med J. 1963;1(5347):1713-5.
4. Akinyanju OO, Okany CC. Pernicious anaemia in Africans. Clin Lab Haematol. 1992;14(1):33-40.
5. Agarwal A, Saini AG, Attri S. Reversible Hyperpigmentation and Paraparesis: A Simple Remedy! J Pediatr. 2018;201:294.
6. Murphy G, Dawsey S, Engels E, Ricker W, Parsons R, Etemadi A, et al. Cancer Risk After Pernicious Anemia in the US Elderly Population. Clin Gastroenterol Hepatol. 2015;13(13):2282-9.
7. Lahner E, Esposito G, Annibale B. Pernicious Anemia: Time to Justify Endoscopic Monitoring? Clin Gastroenterol Hepatol. 2016;14(2):322.
8. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr; 2004;24:299-326.
9. Carmel R, Johnson CS. Racial Patterns in Pernicious Anemia. N Engl J Med. 1978;298(12):647-50.
10. Downham TF, Rehbein HM, Taylor KE. Hyperpigmentation and Folate Deficiency. Arch Dermatol. 1976;112:562.
11. Srivastava N, Chand S, Bansal M, Srivastava K, Singh S. Reversible hyperpigmentation as the first manifestation of dietary vitamin B12 deficiency. Indian J Dermatol Venereol Leprol. 2006;72(5):389-90.
12. Padhi S, Sarangi RL, Ramdas A, Ravichandran K, Varghese RGB, Alexander T, et al. Cutaneous hyperpigmentation in megaloblastic anemia: A five year retrospective review. Mediterr J Hematol Infect Dis. 2016;8(1):1-11.
13. Demir N, Doğan M, Koç A, Kaba S, Bulan K, Ozko H, et al. Dermatological findings of vitamin B12 deficiency and resolving time of these symptoms. Cutan Ocul Toxicol. 2014;33(1):70-3.
14. Kannan R, Ng M. Cutaneous lesions and vitamin B12 deficiency An often-forgotten link. Can Fam Physician. 2008;54(10):529-32.
15. Kuenyefu Awindaogo RA, Ekem I, Awuku NA, Salia S, Agyei M, Nartey YA, et al. Reversible hyperpigmentation in Vitamin B12 deficiency: an

addisonian mimic in clinical practice. PAMJ Clin Med. 2020;4(109):1-8.
16. 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 India. 2005;53(1):55-8.

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