Case Series

Variable presentations of Vitamin B12 deficiency in Eastern India: A Case Series

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Received: 27-11-2021 / Revised: 22-12-2021 / Accepted: 09-01-2022

Abstract
Vitamin B12 deficiency causes anemia with other hematological, neurological and systemic manifestations. Skin manifestations may also occur due to dietary deficiency in vegeterians. Acral hyperpigmentation occurring in distal parts of upper and lower limbs must be differentiated from Addison's disease and vascular occlusion. The cases presented here showed acral hyperpigmentation(Case 1 and 3) which reversed following vitamin B12 therapy and the patient recovered. Case 2 showed anemia and symptoms reversing after vitamin B12 replacement. Leukopenia also reversed in case 3 following therapy.The importance of the case series lies in the fact that vitamin B12 deficiency may present not only with anemia and neurological manifestations, but also as acralhyperpigmentation which reverses following treatment.

Keywords: VitaminB12 deficiency, Acral hyperpigmentation, reversible

Introduction
Vitamin B12 deficiency presents with anemia and other clinical manifestations. It may occur among vegeterians due to dietary deficiency. Clinical features are non specific and a high index of suspicion is needed. Neurological manifestations may also occur in the absence of anemia. Vitamin B12 deficiency causes acral hyperpigmentation which is non pruiritic and reverses with vitamin B12 replacement therapy. It is atypical example of skin manifestation of internal disease which should be promptly identified and treated as in evident from the case series presented here.

Case 1
A 50 year old non diabetic, non hypertensive , vegetarian female residing at Kolkata presented with blackish pigmentation of the distal part of the upper and lower limbs for the last one month with exertional breathlessness for the last 2 months. The skin lesions were non-itchy. Breathlessness was insidious in onset without any chest pain, but orthopnoea was present without any history of PND. There was no history of fever, loose motions, pain abdomen, vomiting, skin rash, joint pain or joint swelling. No addiction history was present and she had attained menopause earlier. There was no history of blood transfusion, visualimpairment, gaitabnormality, tingling or numbness of the upper and lower limbs. Also there was no history of tuberculosis, abdominal surgery, loss of consciousness or any history of any medications.
On examination, the patient was alert, conscious and co operative with propped up decubitus and respiratory rate was 26 per minute. There was moderate pallor with blackish discolouration of the distal extremities with affection of both the palmar and dorsal surfaces. Hyperpigmentation was marked over the creases, knuckles and terminal phalanges. First and second heart sounds were normal with tachcardia and bilateral vesicular breath sounds were audible.
A differential diagnosis of megaloblastic anemia due gto vitamin B12 or folic acid deficiency was made.
On investigation, hemoglobin was 7 gm/dl with Mean Corpuscular Volume of 116.4 Fl.MCH was 42.6pg and MCH was 37.0 gm/dl.WBC and platelet counts were within normal limits. Fasting blood glucose was normal with normal HbA1c.Urea, creatinine, sodium, potassium, serum cortisol and thyroid profile were normal.Serum Vitamin B12 was 90 pg/ml(200-911) wit normal levels of RBC Folate. Chest X Ray, ECG, Echocardiography and USG whole abdomen were normal. Anti -intrinsic factor antibody and Anti-parietal cell antibody were negative and Upper GI endoscopy revealed antral gastritis. Patient did not give permission for bone marrow study.
Adiagnosis of megaloblastic anemia due to vitamin B12 deficiency was made.One unit PRBC transfusion was done and vitamin B12 injection was started at the dose of 1000 mcg intramuscularly once every 3 days for a total number of 6 doses. The patient started to improve, was no longer breathless and the skin lesions started to fade proving that the hyperpigmentation was due to deficiency of vitamin B12.Hemoglobin was 9.0 gm/dl and MCV also decreased.

Case 2
A 48 years non diabetic, non hypertensive vegetarian, non addict male, farmer by occupation, residing in South 24 parganas district of West Bengal presented with exertional breathlessness for the last 2 months with generalised weakness and palpitatins for similar duration. There was no history of fever, vomiting, pain abdomen,

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loose motions, joint pain, joint swelling, hematemesis, melena or bleeding from any site. There was history of orthopnoea without any history of PND or chest pain. There was no history of any rash, photosensitivity, loss of consciousness. There was no suggestive family history, treatment history. No history of gait abnormality, visual impairment, skin discolouration, tingling or numbness of the extremities were present.

On examination the patient was alert, conscious and co operative with propped up decubitus. Moderate pallor was present.

Pulse was 102 bpm, regular, high volume with no radio radial or radiofemoraldelay. Bp was 120/60 mm of Hg. There were no skin changes or lymphadenopathy. Heart sounds were normal with an ejection systolic murmur at the apex without any radiation. Bilateral vesicular breath sounds were audible. On examination of the Hematological system there were no lymphadenopathy, sternal tenderness or organomegaly. Examination of the neurological system was unremarkable.

A provisional diagnosis of megaloblastic anemia due to vitamin B12 or folate deficiency was made with the differential of myelodysplastic syndrome. Hemoglobin was 7.0 gm/dl with hypersegmented neutrophils on peripheral blood smear(Figure 1).

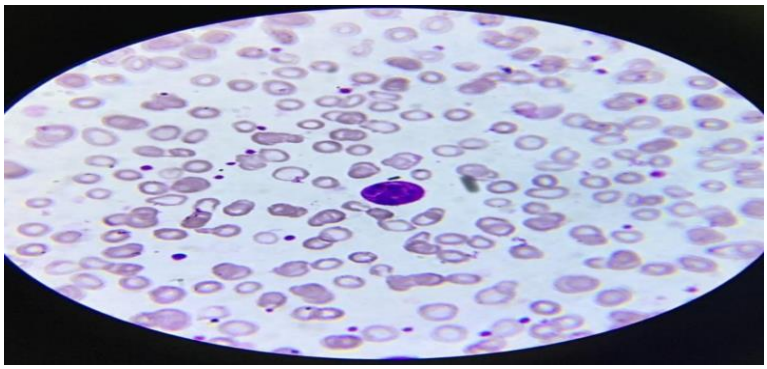

Figure 1 showing hypersegmentedneutrophils, macrocytes and ovalocytes

WBC and platelet counts were normal.MCV was 117.5 fl, MCH-43.7 Pg and MCH was 38 gm/dl. Fasting plasma glucose, urea, creatinine, sosium, potassium, thyroid profile were normal. Vitamin B12 was markedly reduced at 80 pg/ml with normal RBC folate levels. Chestx ray, USG whole abdomen, ECG, echocardiography were normal. Anti- parietal cell antibody and anti- intrinsic factor antibody were negative and patient did not give consent for bone marrow examination and Upper GI endoscopy.

A diagnosis of megaloblastic anemia due to vitamin B12 deficiency was made. The patient was treated with one unir PRBC transfusion and vitamin B12 injection was started after which the patient improved, no murmur was audible proving it to be a hemic murmur and the patient was discharged with rise of hemoglobin levels and decrease of MCV.

Case 3

A 51 years old non diabetic, non hypertensive, vegetarian, non addict female residing at Chitpur, Kolkata, house wife by occupation presented with loss of appetite for 3 months with blackening of terminal part of the digits of all the 4 limbs for the last 2 months. The patient was suffering from anorexia, easy fatiguability, loss of concentration, apathy to rotine work and breathlessness on exertion for the last 3 months. These symptoms were associated with pale skin and preceeded by a history of pain abdomen and diarrhoea 2 weeks before the onset.

For the last 2 months, there was blackening of the dorsum of the middle and terminal phalanges of both hands and feet. There was no history of raynaud's phenomenon, skin tightening, rash, oral ulcer, photosensitivity, dysphagia or dry cough. Past and family history were insignificant with no abnormality of bladder, bowel, sleep or appetite.

On examination patient was alert, conscious and co operative with glossitis, severe pallor. Cyanosis, edema, jaundice, clubbing were absent. Neck veins were engorged with no palpable neck glands. Pulse was 94 bpm, high volume, regular with all the peripheral pulses being palpable. BP was 130/70 mm of Hg with no postural drop. Respiration was thoraco abdominal with normal temperature.

Non itchy, hyperpigmented macular lesions were seen in the dorsum of middle phalanges of the toes of both feet with the presence of similar lesions in both hands(Figures 2 and 3).

Figure 2 showing hyperpigmentation of the hands

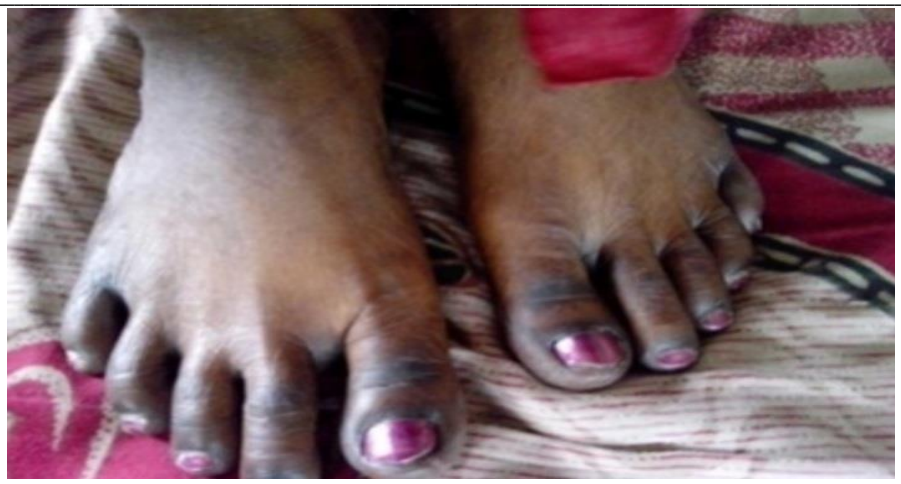

Figure 3 showing hyperpigmentation of the feet

Differential diagnosis of acral hyperpigmentation with anemia were Addison's disease,Vitamin B12 deficiency and acral lentiginous melanoma.

Examination of the GI system revealed no organomegaly, CVS examination and respiratory system examination were normal. Higher mental functions, cranium, neck and spine, cranial nerve and motor examination were normal. On examination of the sensory system, exteroceptive sensation was normal, but joint postion sense was absent. Cortical sensation was present and cerebellar examination was normal. Bilateral ankle jerks were lost.

Hemoglobin was 5 gm%, MCV-99 Fl, RDW 15, WBC - 3000/mm3(N57,L40 E1). PBS was predominantly microcytic hypochromic with mild anisocytosis.FBS, urea, creatinine, sodium, potassium, LFT were normal. Serum cortisol was normal and vitamin B12 was markedly reduced at 100 pg/ml with normal RBC folate levels. Stool examination and USG WA were normal. Upper GI endoscopy revealed antral gastritis and chest x ray and echocardiography were normal. Anti -parietal cell and anti-intrinsic factor antibodies were negative. The patient responded to 2 units of PRBC transfusion at the rate of one unit per day and injection vitamin B12 was started after which the patient started to improve, breathlessness reduced and acral hyperpigmentation started to fade proving vitamin B12 deficiency to be the cause of acral hyperpigmentation.TLC increased to 4500/ mm3 and hemoglobin increased to 8.6 gm% and MCV also reduced. Bone marrow was not done as the bicytopenia improved and the patient also refused to do the bone marrow examination. The patient was discharged after day 9 of admission.

Discussion

Megaloblasts are nucleated RBCs which are large in size.Common causes are vitamin B12 deficiency, folate deficiency and some drugs. It is a type of macrocytic anemia.Megaloblastsccur due to nuclear maturation arrest. The cause is mainly due to impaired synthesis of DNA.The cells which are dividing rapidly, exhibit the megaloblastic changes[1,2,3]. Hypersegmented neutrophils are also seen in the PBS. Vitamin B12 is stored in the liver which differentiates it from the other water soluble vitamins. Distal ileum is the site for absorption of vitamin B12.Dietary sources are meat, fish and dairy products. Demyelination and neurological features occur, but mechanisms are clear. Theories are[4] reduced SAM(S Adenosyl methionine) leading to defective myelination. Elevated MMA(methyl malonic acid) may produce abnormal odd chain and branch chain fatty acids with defect in myelination. Deficiency of cobalamin also leads to impact cytokines and growth factors which may be neurotoxic and lead to neuropathy[5].

Causes of cobalamin deficiency are

1. Gastric mucosal atrophy
2. Dietary insufficiency
3. Intestinal bacterial overgrowth
4. Fish tapeworm
5. Ileal mucosal disorders
6. Drugs etc

Deficiency in diet rarely causes megaloblastic anemia expect in persons who follow a strict vegetarian diet.

Symptoms are difficult to diagnose as anemia develops slowly. Intra medullary hemastopoesis may lead to a lemon coloured complexion. Psychosis, peripheral neuropathy may occur. Abnormality in proprioception, unsteadiness of gait may occur and patients may present without anemia only with neurological manifestations.

Skin manifestations include hyperpigmentation which is present in case 1 and 3 .Abnormality in pigmentation of the hair can occur. Vitamin B12 deficiency in infants present s with hyperpigmentation of the dorsum of the feet and hands and generalised hyperpigmentation may also occur. Hyperpigmentation may occur due to increase in synthesis of melanin due to enhanced tyrosinase activity. It leads to improper transfer of melanin to adjoining keratinocytes from melanocytes[6]. Skin manifestations are hyperpigmentation, scanty hypopigmented hairs, vitiligo and glossitis, but they are reversible with therapy[7,8]. Hypersegmented neutrophils contain 6 or more lobes[9]. They occur early but persists for a long period of time post treatment.[9].It is not a sensitive indicator in mild deficiency[10]. Leukopenia and thrombocytopenia rarely causes symptoms, but sometimes confusion with TTP may occur[11,12]. Non specific cytogenetic changes lead to broken and elongated chromosomes which resolves quickly within 2 days of treatment, but may persist[13,14]. For treatment apart from injections, oral doses may be given.Treatment by 6 intramuscular injections 1000 mcg at 3-7 days interval is needed Alternatively 1000-2000 mcg oral dose is needed with compliance monitoring[15]. Hyperpigmentation due to vitamin B12 deficiency was first reported by Cook in 1944, Baker et al in 1963[16].

Conclusion

The 3 cases presented here showed variable manifestations of vitamin B12 deficiency.The first and third case showed reversible hyperpigmentation with vitamin B12 deficiency.The second case was a case of anemia due to vitamin B12 deficiency.Leukopenia and neurological manifestations were present in the third case.Leukopenia resolved with successful therapy.The importance of these cases lie in the fact that acral hyperpigmentation may be an indicator of vitamin B12 deficiency which should be differentiated from Addison's disease to timely and appropiete management as delay in treatment can lead to severe complications.Morover, treatment fully reverses the pigmentations avoiding unnecessary investigations.

Conflicts of interest
None

Source of Funding
None

References

1. Antony AC. Megaloblastic Anemias. Hoffman R, Benz EJ Jr, Silberstein LE, Heslop HE, Weitz JI, Anastasi J. *Hematology: Basic Principles and Practice*. 6th ed. Philadelphia, PA: Elsevier; 2013. 473-504.
2. Wang YH, Yan F, Zhang WB, et al. An investigation of vitamin B12 deficiency in elderly inpatients in neurology department. *Neurosci Bull*. 2009 Aug. 25(4):209-15.
3. Hoffbrand AV. Megaloblastic Anemias. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill Education; 2015.
4. Singh NN. Vitamin B-12 Associated Neurological Diseases. Medscape Drugs & Diseases. Available at https://emedicine.medscape.com/article/1152670-overview. October 22, 2018; Accessed: April 29, 2021.
5. Leishear K, Ferrucci L, Lauretani F, et al. Vitamin B12 and homocysteine levels and 6-year change in peripheral nerve function and neurological signs. *J GerontolABiol Sci Med Sci*. 2012 May. 67(5):537-43. [QxMD MEDLINE Link].
6. Oh R and Brown D. Vitamin B12 deficiency. Am Fam Physician. 2003; 67:979-986.
7. Aaron S, Kumar S, Vijayan J, Jacob J, Alexander M and Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B 12 deficiency – related neurological syndromes. Neurol India. 2005; 53:55-58. https://doi.org/10.4103/0028-3886.15057
8. Santra G, Paul R, Ghosh SK, Chakraborty D, Das S, Pradhan S, et al. Generalised hyperpigmentation in vitamin B12 deficiency. J Assoc Physicians India. 2014; 62:714-716.
9. . Lindenbaum J, Nath BJ. Megaloblastic anaemia and neutrophil hypersegmentation. Br J Haematol. 1980;44(3):511-513.
10. . Carmel R, Green R, Jacobsen DW, Qian GD. Neutrophil nuclear segmentation in mild cobalamin deficiency: relation to metabolic tests of cobalamin status and observations on ethnic differences in neutrophil segmentation. Am J Clin Pathol. 1996;106(1):57-63.
11. Green R. Anemias beyond B12 and iron deficiency: the buzz about other B's, elementary, and nonelementary problems. Hematology Am Soc HematolEduc Program. 2012;2012: 492-498.
12. Dalsania CJ, Khemka V, Shum M, Devereux L, Lachant NA. A sheep in wolf's clothing. Am J Med. 2008;121(2):107-109.
13. . Das KC, Mohanty D, Garewal G. Cytogenetics in nutritional megaloblastic anaemia: prolonged persistence of chromosomal abnormalities in lymphocytes after remission. Acta Haematol. 1986;76(2-3):146-154.
14. Lawler SD, Roberts PD, Hoffbrand AV. Chromosome studies in megaloblastic anaemia before and after treatment. Scand J Haematol. 1971;8(4):309-320.
15. Jameson, Fauci, Kasper, Hauser, Longo, Loscalzo. Harrison's Principle of Internal Medicine, 20th Edition; Volume 1, page 707.
16. Baker SJ, Ignatius M, Johnson S, Vaish SK. Hyperpigmentation of skin. a sign of vitamin-B12 deficiency. Br Med J. 1963; 1:1713-1715. https://doi.org/10.1136/bmj.1.5347.1713.