

Case Report An Occasional Case of Met form in Induced Vitamin B₁₂ Deficiency

* Dr.K.M.Vignesh¹

¹Senior Resident, Department of General Medicine, Panimalar Medical College Hospital & Research Institute, Poonamallee, Chennai, Tamil Nadu, India. Email ID:

Corresponding Author: Dr. K.M. Vignesh

Email ID: kmvignesh3195@gmail.com

KEYWORDS

Metformin, Vitamin B₁₂ Deficiency, Hyperpigmentation.

ABSTRACT:

India is in the rising trend in incidence of diabetes mellitus, owing to its adherence to our lifestyle. As is all known India, the diabetes capital of the world got about 8 crores this year. Metformin is found in about 90% of all the diabetic prescriptions. Metformin is being the first choice for any diabetes mellitus patient. As like other drugs, this too has many safety concern. Hence, it is essential for a treating physician to know in and around about the drug. Some adverse effects have been evident for the past years. Here, is one such adverse effect which has occurred with a higher dosage and prolonged use of the drug. [4].

Introduction:

In haematology, the clinical spectrum pertains to both the circulating cells including T-cells, B-cells and the circulating volume. The clinical symptoms include fatigability, difficulty in breathing, swelling of both legs (including generalized anasarca), loss of weight and appetite. If any abnormality is to be screened, laboratory parameters are checked. A hematology analyser will measure directly haemoglobin concentration, red cell count, mean (Red) cell volume {MCV}, total white blood cell count (WBC) & platelet count. Other parameters that can be derived from the calculation are: Haematocrit (HCT) or packed cell volume (PCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC). Appearance of the red blood cells will tell us if any abnormality is found or not. Macrocytic i.e. larger cells occurs in the peripheral study due to a imbalance between nucleus & cellular cytoplasm. Megaloblastic anemia is one of the causes for macrocytic anemia. Macrocytic anaemia and Megaloblastic anaemia are not the same. Macrocytic anaemia with lack of nuclear maturation more than the cytoplasmic maturation is called as Megaloblastic anaemia. Megaloblastic anaemia is a spectrum of disorder with hemotological origin resulting from DNA synthetic failure. Hence, there will be reduced cell lines. There are many causes of macrocytic anaemia.

The two vitamins, cobalamin and folate has overlapping roles in the synthesis of thymidine and purine for synthesis of DNA. [1,2] This synthesis defect affects rapidly dividing cells in the bone marrow. In some instances, the entire scenario can also occur due to some drugs {Cell cycle synthesis inhibitors like antimetabolites (Hydroxyurea), antiviral drugs, etc.,}. These drugs causes anemia due to its ability to inhibit DNA replication. We found a diabetic drug, which is well known for years, causing this defect. [3,5]

Biguanide is a class of oral antidiabetic agent, which helps in glycemic control by inhibiting hepatic glucose production. It also reduces appetite, lowers triglycerides. It has added-benefits in insulin independent diabetes mellitus patients, like decreased hyperinsulinemia, weight reduction properties, fibrinolysis, augmented endothelial function. It has a weight neutral property more than a weight reduction. It is contraindicated in renal impairment, cardiac and respiratory insufficiency, liver disease, sepsis. [6] There occurs some side effects like lactic acidosis, nausea & diarrhoea (<5%). One of the side effect reported as illustrated by our case is vitamin B₁₂ deficiency. [7]

In India, dietary deficiency is the commonest cause for B₁₂ deficiency anaemia. Vitamin B₁₂ deficiency or malabsorption occurs in less than 0.2%. It is more seen in the elderly population (>10%). Other causes include autoimmune cause (Pernicious anaemia), gastrectomy, malabsorption

syndromes like tuberculosis, crohn's disease, tropical sprue & fish tapeworm. Recommended daily intake is 5-7 mcg/day. Total body content is 2-5 mg. It takes 3 to 4 years to deplete the stores.

Case Report:

A 72 years old male presented to our hospital with complaints of easy fatigability for 3 months. He had loss of appetite. He is a known case of type 2 diabetes mellitus for 20 years under treatment (Tab. Metformin 1000 mg twice daily). No other comorbidities was found. He is an alcoholic for 25 years (Abstinence for 3 years). He consumes mixed diet; Bowel & bladder habits were normal. His sensorium is normal, Temperature-98.2 F. Good built; Moderate nourishment. He is not dysneic; tachypneic.

Patient has increased areal pigmentation, noted mostly at palmar creases, knuckles & nose. (Fig 1) Glossitis was noted. He was found to be pallor. No other positive findings could be elicited.



Fig 1. Patient has increased areal pigmentation with accentuation at Palmar creases, Knuckles. We can also appreciate the Glossitis.

Routine blood investigations were done. Lab Investigations revealed severe anemia, with decreased thrombocytes too. MCV & MCH were found to be elevated. Reticulocyte count is normal. Other lab parameters like liver function tests, renal function tests, thyroid function tests were within normal limits. Speciality opinion was also obtained. Endoscopic study didn't reveal any other abnormality.

Peripheral smear report: Red cell mass- decreased. Predominantly, microcytic hypochromic RBC's with marked anisopoikilocytosis, macro-ovalocytes, elongated cells, tear drop cells & few schistocytes, hyperpigmented neutrophils seen; Platelets were decreased.

Further evaluation: Serum cortisol at 8:00 AM is 12.80 µg/dl (6.7 - 22.6), which ruled out Addison's disease. Vitamin B₁₂ was found to be 85.32 pg/mL (211-946). A provisional diagnosis of Vitamin B₁₂ deficiency anemia was made, probable due to metformin. Hence, metformin was

stopped. Inj. Methycobalamin 1000 mcg was started & given daily once for 1 week, weekly once for 1 month, monthly once for 6 months. Symptoms improved & skin hyperpigmentation was reversed following the treatment. Patient is in regular follow-up.

Discussion:

In the general population, prevalence of vitamin B₁₂ deficiency ranges from 1.2% to about 14% in older adults. Vitamin B₁₂ deficiency should be suspected in individuals with haematological abnormalities like decreased cell lines-Pancytopenia; Liver disease, chronic alcohol consumers or dietary practices like vegetarians are known to be associated with deficiency. In the longer run, metformin can lead to vitamin B₁₂ deficiency. Metformin interferes with the calcium dependent - membrane action, which is responsible for vitamin B₁₂ – intrinsic factor absorption in the terminal ileum.[8,9] Metformin increases accumulation of vitamin B₁₂ in the hepatocytes, due to its increased metabolism intracellularly. Many studies showed that vitamin B₁₂ levels are reduced with metformin & especially taken in a dose more than 2gms/day & for a period more than 4 years (In this case, patient was taking metformin 2 gms/day for more than 15 years; He is under abstinence of alcohol for about 3 years).[10] Risk is higher in patients receiving increased dose for a longer period. This made us to conclude that vitamin B₁₂ deficiency is most likely drug induced - Metformin.

Conclusion:

This case report elucidated the presentation of vitamin B₁₂ deficiency, which is most likely found to be drug induced - metformin. Vitamin B₁₂ deficiency not only causes hematological abnormality, but also affects other systems like neurological system (Peripheral neuropathy, subacute combined degeneration of spinal cord), cardiac manifestations (Thrombosis - Ischemic heart disease, pulmonary embolus occurring due to homocysteine defects).

Hence, vitamin B₁₂ level monitoring should be done on a serial basis in all geriatric patients and also in patients getting higher dose of metformin for a longer duration. Proper supplementation should be given to prevent the deficiency symptoms. [11,12]

References:

1. Metformin-Induced Vitamin B₁₂ Deficiency among Type 2 Diabetes Mellitus' Patients: A Systematic Review 2022 Apr 18 Rabie Khattab
2. Vitamin B₁₂ Deficiency in Patients with Diabetes on Metformin: Arab Countries. Alhaji JH. *Nutrients*. 2022 May 13
3. Vitamin B₁₂ deficiency in patients with type 2 diabetes mellitus using metformin and the associated factors in Saudi Arabia. Al Saeed RR, Baraja MA. *Saudi Med J*. 2021 Feb
4. Metformin revisited: A critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. 2013 Scheen AJ, Paquot N
5. Valdes-Ramos R, Guadarrama-Lopez AL, Martinez-Carrillo BE, et al. Vitamins and type 2 diabetes mellitus. *Endocr Metab Immune Disord Drug Targets* 2015
6. Obeid R, Jung J, Falk J, et al. Serum vitamin B₁₂ not reflecting vitamin B₁₂ status in patients with type 2 diabetes. *Biochimie* 2013
7. Greibe E, Miller JW, Foutouhi SH, et al. Metformin increases liver accumulation of vitamin B₁₂ – an experimental study in rats. *Biochimie* 2013
8. Leung S, Mattman A, Snyder F, et al. Metformin induces reductions in plasma cobalamin and haptocorrin bound cobalamin levels in elderly diabetic patients. *Clin Biochem* 2010
9. Greibe E, Trolle B, Bor MV, et al. Metformin lowers serum cobalamin without changing other markers of cobalamin status: a study on women with polycystic ovary syndrome. *Nutrients* 2013
10. de Groot-Kamphuis DM, van Dijk PR, Groenier KH, et al. Vitamin B₁₂ deficiency and the lack of its consequences in type 2 diabetes patients using metformin. *Neth J Med* 2013
11. Ahmed MA, Muntingh GL, Rheeder P. Perspectives on peripheral neuropathy as a consequence of metformin-induced vitamin B₁₂ deficiency in T2DM. *Int J Endocrinol* 2017
12. Zhang Q, Li S, Li L, et al. Metformin treatment and homocysteine: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 2016