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A Case of Metformin-Related Megaloblastic Anemia Presenting with Palpitation

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ABSTRACT

Introduction: Metformin is the cornerstone of medical treatment in most diabetic patients with many beneficial effects on cardio-metabolic parameters. However, long term metformin is a known pharmacological cause of vitamin B_{12} deficiency leading to neurological symptoms, megaloblastic anemia and increased levels of serum homocysteine. Moreover, it is well known that vitamin B_{12} deficiency-induced neurologic symptoms precede the appearance of megaloblastic anemia.

Case: We herein report the case of an old woman with a history of long term metformin consumption who visited the cardiology clinic with the chief complaint of palpitation due to megaloblastic anemia without any neuropsychiatric symptoms. She was successfully treated with a parenteral regimen of vitamin B_{12} within two months.

Conclusion: Although annual measurement of serum vitamin B_{12} levels could be considered in patients on long-term metformin therapy, yet it seems more reasonable and cost-effective to prevent vitamin B_{12} deficiency and its related adverse effects with annual prescription of parenteral vitamin B_{12} in all such patients.

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Introduction

Metformin is the only anti-diabetic agent associated with improvements in cardiovascular morbidity and mortality and is the cornerstone of medical treatment along with life style modification in most diabetic patients. Vitamin B_{12} deficiency has been recognized since many years ago as an important side effect in diabetic patients who take metformin for more than 5-10 years (1). Although it is well known that vitamin B_{12} deficiency-induced neurologic symptoms precede the appearance of megaloblastic anemia, we report a patient who came to us with the chief complaint of anemia-related palpitation without any neuropsychiatric deficits.

Case

A 68-year-old diabetic woman visited the cardiology clinic with the chief complaint of palpitation at rest and with minimal exertion. She had a history of type II diabetes mellitus for around 9 years treated with metformin 1500 mg/day, repaglinide 2 mg/day and pioglitazone 45 mg/day. Her other medications were as follows: aspirin 80 mg/day, atorvastatin 20 mg/day, losartan 25 mg/day and calcium + vitamin D (500 mg+ 200 IU)/day. She had morbid obesity (weight=95 kg, height=150 cm, body mass index=42.2) and very limited physical activity due to severe degenerative knee joint disease. She had no known history of ischemic heart disease while taking aspirin and atorvastatin as primary prevention and losartan due to micro albuminuria. She was a non-smoker and did not consume alcoholic beverages.

On physical examination, she was to some extent pale with sub icterus, otherwise unremarkable. 12-lead electrocardiography was normal while trans-thoracic echocardiography showed normal left and right ventricular size and global systolic function with mild to moderate mitral regurgitation and normal pulmonary arterial pressure. Laboratory examination revealed severe macrocytic anemia with hypochromia, anisocytosis and tear drop cells on peripheral blood smeartable 1. Thyroid and renal function tests were normal. She had neither neuropsychiatric nor gastro-entrologic symptoms. She was not taking proton-pump inhibitors or other antacid medications either.

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Therefore, megaloblastic anemia related to metformin-induced vitamin B_{12} deficiency was suspected. Treatment initiated with intra-muscular injections of 1000 µg vitamin B_{12} weekly for 8 doses followed by monthly injections for an additional 4 doses. The clinical improvement was remarkable and around two months later all the anemia-related laboratory indices normalized (Table 1). She was prescribed an annual injection of 1000µg vitamin B_{12} to prevent any recurrence.

Table1: Laboratory parameters at the time of presentation and 2 months after vitamin B_{12} supplementation

Serum parameter	At the time of presentation	2 months later	Reference ranges
Aspartate aminotransferase (AST)	16 IU/L	22 IU/L	< 40 IU/L
Alanine transaminase (ALT)	14 IU/L	29 IU/L	< 40 IU/L
Alkaline phosphatase (ALP)	173 IU/L	253 IU/L	70-300IU/L
Total bilirubin	2 mg/dl	0.8 mg/dl	0.51-1.2 mg/dl
Lactate dehydrogenase (LDH)	950 IU/L	337 IU/L	230-460 IU/L
Iron	116 µg/dl	63 µg/dl	40-160 µg/dl
Total iron binding capacity (TIBC)	378 µg/dl	315 µg/dl	230-440 µg/dl
Ferritin	34 ng/ml	37 ng/ml	7-172 ng/ml
Vitamin B_{12}	201 pg/ml	1166 pg/ml	243-894 pg/ml
Folic Acid	13 ng/ml	-	4.6-17.5ng/ml
Reticulocyte Count	3%	-	0.5-1.5 %
White blood cell (WBC) count	4.74×10^{9}/L	6.83×10^{9}/L	$4\text{-}11\times10^{9}$/L
Red blood cell (RBC) count	2.29×10^{12}/L	4.70×10^{12}/L	$3.5\text{-}5.5\times10^{12}$/L
Platelet count	294×10^{9}/L	197×10^{9}/L	$150\text{-}450\times10^{9}$/L
Hemoglobin	8.6 g/dl	14.3 g/dl	11-16g/dl
Hematocrit	27.3 %	41.5 %	35-50 %
Mean corpuscular volume (MCV)	119.2 fL	88.4 fL	78-100 fL
Mean corpuscular hemoglobin (MCH)	37.6 pg	30.4 pg	27-34 pg
Mean corpuscular hemoglobin concentration (MCHC)	31.5 g/dl	34.5 g/dl	32-36g/dl
Erythrocyte sedimentation rate (ESR)	84 mm	26 mm	Up to 12 mm

Discussion

Long-term metformin treatment is a known pharmacological cause of vitamin B_{12} deficiency leading to neurological symptoms, megaloblastic anemia and an increase in serum homocysteine concentration. Although decreased levels of serum vitamin B_{12} occur as early as 3–4 months following metformin use initiation, symptomatic deficiency happens 5–10 years later due to the huge body stores compared to very low daily requirements (1). The prevalence of vitamin B_{12} deficiency in patients with type 2 diabetes taking metformin is more than twice of those not using metformin (5.8 % vs. 2.4 % respectively), based on a data analysis performed by the National Health and Nutrition Examination Survey (NHANES; 1999-2006) on U.S. adults ≥ 50 years of age (2). However, in some studies the prevalence has been reported to be as high as (25.8%)(3).

The responsible mechanism for metformin-induced vitamin B_{12} malabsorption has been controversial and may be multifactorial including the competitive inhibition of calcium-dependent absorption in the ileum. Although calcium supplementation decreases the malabsorption, it does not increase serum vitamin B_{12} levels(1). Likewise in our patient, calcium supplement consumption along with metformin had not been capable of preventing vitamin B_{12} deficiency. The occurrence of vitamin B_{12} deficiency depends on the cumulative dose rather than the sole duration of metformin usage (3). Our patient was prescribed 1500 mg/day metformin for 9 years which results in a high cumulative dose. Metformin treatment could also induce decreased serum levels of folate contributing to the disease process and thus folate level should be measured along with vitamin B_{12} in the initial laboratory examination. Blood samples should be obtained on fasting and before any blood transfusions, because even a single meal or transfusion may normalize the serum concentrations of these two vitamins. In general, serum vitamin B_{12} concentration <200 pg/ml is diagnostic for vitamin B_{12} deficiency whereas if serum level is >300 pg/mL, deficiency is unlikely; although this could vary depending on the technique used for measurement (1). A serum concentration<2 ng/mL is diagnostic for folate deficiency and if the serum level is >4 ng/mL, folate deficiency is ruled out. In borderline results (B_{12}=200-300 pg/ml and folate=2-4 ng/ml) increased serum concentrations of their metabolic intermediates (homocysteine and methylmalonic acid) could be helpful in confirming the diagnosis. In vitamin B_{12} deficiency, the serum levels of both homocysteine and methylmalonic acid are elevated, while in folate deficiency only the serum homocysteine level is elevated (1). The serum vitamin B_{12} and folate levels in our patient were 201pg/ml and 13ng/ml respectively, so we were convinced that vitamin B_{12} is deficient and folate deficiency was excluded. Accordingly, we did not measure serum homocysteine and methylmalonic

acid concentrations forconfirmation of the diagnosis. If these measurements were performed, it could be helpful for better elucidation of the diagnosis; albeit the diagnosis was later confirmed based on the dramatic response to vitamin B_{12} supplementation. Worth noting that some other conditions (renal failure and hypothyroidism) and medications (e.g. fibrates and methotrexate) which can affect the serum homocysteine and/or methylmalonic acid levels, should be considered when interpreting the test results. It is also reasonable to exclude other etiologies of vitamin B_{12} deficiency especially pernicious anemia, food-cobalamin malabsorption syndrome and long-term use of proton pump inhibitors (1).

Our patient did not have any gastro-entrologic symptoms and did not take antacid medications. So, megaloblastic anemia related to metformin-induced vitamin B_{12} deficiency was considered as the most probable diagnosis. The prevalence of megaloblasticanaemia in diabetic patients taking long-term biguanides has been reported to be (9%)in a case series. After treatment initiation, the hemoglobin concentration begins to rise within 10 days and usually returns to normal within two months. A delayed response suggests the presence of a concurrent abnormality or an incorrect diagnosis (1). Nevertheless, at two months follow up, all anemia-related laboratory indices of our patient returned to normal (Table 1).

Although it is already known that vitamin B_{12} deficiency-induced neuropathy precedes the appearance of megaloblastic anemia, our patient did not have any apparent neurological deficits and she presented with the chief complaint of palpitation. The earliest neurological manifestations include newly diagnosed peripheral neuropathy or worsening of a known diabetic neuropathy. Therefore, one should be aware not to misinterpret these conditions with a sole diabetic neuropathy as the misdiagnosis and mismanagement will result in irreversible central and/or peripheral neuronal damage (1).

The other important issue is the additional effects of vitamin B_{12} deficiency induced hyperhomocysteinemia on peripheral neuropathy and/or cardiovascular risk. Numerous large-scale epidemiological studies have identified hyperhomocysteinemia as a moderate independent cardiovascular risk factor (4). Considering the fact that diabetes is a major risk factor for cardiovascular diseases, increased levels of serum homocysteine may augment the already high cardiovascular disease risk of diabetic patients.

Although annual measurement of serum vitamin B_{12} level could be considered in patients on long-term metformin therapy, a more practical and cost-effective approach to prevent vitamin B_{12} deficiency would be an annual injection of 1000 µg vitamin B_{12} in all such patients (1, 5). Worth noting that oral supplementation with current multivitamins is not effective in its prevention (2).Once the diagnosis of metformin-induced vitamin B_{12} deficiency is established, treatment should be initiated with parenteral vitamin B_{12}, effectively. Metformin deserves to be continued due to its invaluable effects. We did not withhold metformin in our patient either and anemia was treated successfully with a parenteral regimen of vitamin B_{12} within two months.

Another issue is the increasing rate of proton-pump inhibitors prescription by many physicians for gastro-esophageal reflux disorders or as primary prevention of gastro-intestinal bleeding for patients under dual antiplatelet therapy following acute coronary syndromes and/or percutaneous coronary interventions.

The combination of these two drugs significantly increases the incidence of vitamin B_{12} deficiency in diabetic patients (6). Therefore, these patients should be followed closely.

Conclusion

All physicians taking care of diabetic patients need to be more familiar with anti-diabetic medications specially metformin as the first line treatment and its potential adverse effect of vitamin B_{12} deficiency. One should bear in mind that vitamin B_{12} deficiency not only leads to megaloblastic anemia as well as neuropsychiatric disorders but also has deleterious effects on cardiovascular health due to iatrogenic hyperhomocysteinemia. Therefore, it is reasonable and cost-effective to prevent vitamin B_{12} deficiency with an annual injection of 1000 µg vitamin B_{12} in all diabetic patients taking long term metformin.

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