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Masked Iron Deficiency in Macrocytic presentation of Dimorphic Anemia with Diabetes: a case report.

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Abstract

Anemia is a health condition contributing significantly to morbidity and decreased productivity worldwide. Though iron deficiency in women is the leading cause, anemia in men is also an important health burden and is often underdiagnosed. Sometimes anemia can present in a dimorphic form with both macrocytic and hypochromic microcytic components due to multiple nutrient deficiencies or co-existing health conditions. It is important to therefore keep this in mind during clinical diagnosis and laboratory evaluation. Anemia is more common in diabetes and can also be associated with higher cardiovascular and renal risk. Treatment with both appropriate nutritional supplements and diet-lifestyle modification would be the right approach to manage anemia in such patients.

Keywords: Anemia, Lifestyle, Macrocytic, Nutrition

Introduction

Anemia affects 1.62 billion people globally, almost 1/4th of the population at some time or the other.[1] In India, the overall prevalence is almost 40%, being much higher in children and women. Therefore, anemia screening focuses on women and children, where it is seen more due to malnutrition and infections, while anemia in men may often be underdiagnosed. The global incidence of anemia in men is around 12.7%.[1] In men, a Hemoglobin below 13g/dL. (Mild 11-12.9g/dL; moderate 8-10.9g/dL and Severe <8g/dL)[2] Anemia among men in India is an important public health problem, with the prevalence being around 23·2% with an estimated 21·7% of anemic men having moderate or severe anemia.[3] Iron deficiency is the commonest cause of anemia in India but around 17.5% of anemia cases are of Dimorphic anemia which presents with either a microcytic hypochromic (initially normocytic normochromic), or a macrocytic clinical predominance in 37% and 63% respectively. Therefore, it is important to rule out masked iron deficiency and dimorphic anemia in patients who present a characteristic macrocytic blood picture on laboratory diagnosis as is also seen in the case study presented.[5]

Patient History

A 49-year-old male patient who was a corporate manager reported with symptoms of fatigue and weakness. On taking a detailed history, the patient elaborated that he feels tired frequently, is low on energy levels and feels week as compared to his usual working capacity and ability. He also revealed that he

experiences palpitation, and a feeling of slight breathlessness and early tiring on exercising. He often has headaches which are more towards the latter part of the day. He also expressed that he feels anxious and difficulty in sleeping on 2-3 nights every week. No history of cough, chest pain, breathlessness at rest, weight loss, dizziness or any other localized/generalized pain. Patient said he often experienced gas and constipation for which he would take herbal supplements.

The patient was diagnosed as hypertensive 6 months ago, and prescribed Olmesartan 20mg once daily. He is also a known Diabetic (diagnosed 5 years ago), controlled on Metformin-Vildagliptin combination 500mg/50mg once daily. He monitors his blood sugar weekly with SMBG (Self-Monitoring of Blood Glucose) by Glucometer. The patient has also been prescribed Rosuvastatin-Fenofibrate 10mg/160mg combination for lipid control since last 5 years. He has no history of any cardiac disease. He smokes 1-2 cigarettes/day for past 25 years, and takes alcohol occasionally socially. He is married with 2 children; and a vegetarian. On week days his diet was more packaged/processed food dominant and relatively low on vegetables, due to high travelling. In his family history, his father has hypertension and diabetes present, controlled on medication.

The patient had gone to a general physician a month back with the same complaints of weakness, fatigue, low energy, and reduced exercise tolerance and work capacity. He was evaluated with a Complete Blood Count (CBC) which showed a decreased Hemoglobin (Hb), Red Blood Cell (RBC) Count, and Hematocrit, with an increased Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin (MCHC), suggesting a diagnosis of Macrocytic Anemia. The Red cell Distribution Width (RDW) also showed an increase. (Table 1 – at baseline). The Total and Differential White Blood Cell (WBC) count and the Platelet count were normal.

The patient was prescribed Folic acid (1.5 mg/d) orally and given intramuscular Vitamin B12 injections 1500ug (as a combination injection with 100mg B6+100mg B3) on alternate days for 2 weeks. (total 7 injections).

The patient had also gone for an Eye test, which revealed 6/6 distance vision in both eyes, and no change in number of his +1.5 reading glasses for both eyes. Eye examination including fundus was normal.

Further Patient Evaluation

Patient's pulse rate initially was 88 beats/minute in the beginning and 80 beats/minute at the end of examination. Blood Pressure was 128/80 mm Hg and Respiratory Rate 12 breaths/minute. He was well oriented. Weight was 79kg. General examination showed pallor of the lower conjunctiva, while no icterus or pedal edema was seen. Heart sounds and lung auscultation were normal. Routine abdominal examination also appeared normal.

The patient was advised to repeat CBC, along with Iron Studies and Vitamin B12 levels. He was also advised to check blood sugar (fasting and post prandial), HbA1C, Vitamin D levels, Renal function test and lipid profile along with ECG and stool and urine test.

CBC revealed no change in Hemoglobin as compared to baseline after 1 month of taking Oral folate supplementation and 2 weeks of alternate day B12 injections. MCV had come down towards upper limit of normal and MCH had normalized, as compared to significantly high values of both these parameters one month back. (Table 1- at 1 month)

Iron studies revealed significantly decreased total blood iron as well as transferrin saturation, with the total Iron binding capacity in the upper range of normal (Table 2). Vitamin B12 (>2000pg) was much above the normal range.

Blood sugar, HbA1C, and Lipid profile was well controlled, Vitamin D was in normal range, Renal function tests as well as Urine examination was normal (no albuminuria or glycosuria). ECG showed a borderline Left Axis Deviation (LAD) and sinus rhythm. Stool test was normal with no presence of parasites, or occult blood.

Based on this, a diagnosis of Dimorphic anemia (masked Iron deficiency anemia) of moderate severity, was made.

The patient was started on Heme Iron Polypeptide 12mg, 2 tablets daily in the morning after breakfast with Vitamin C 500mg after breakfast and dinner. The patient was also given a multivitamin supplement which had Omega 3 Fatty acids 150 mg, Folic acid 5 mg, Vitamin B12 (as Methyl cobalamin) 500 mcg, Mixed carotene 10.33 mg, Copper 1 mg, Manganese 2 mg, Selenium 40 mcg, Chromium 65 mcg, and Zinc 22.5 mg. Appropriate dietary recommendation on nutritious food (with more vegetables, fruits, whole grains and proteins), increased water intake, and lifestyle modification (right exercise, smoking restriction, along with relaxation techniques for anxiety and better sleep) were also given.

Follow up

CBC was repeated after 1 month. Hemoglobin had improved significantly, with RBC count and MCV entering normal range. MCH and MCHC had reduced unmasking the Iron deficiency anemia. Hematocrit had also almost normalized. RDW was still high but decreased significantly over 1 month (Table 1 – at 2 months). Patient said that he felt more energy and less tiredness than before.

Patient was continued on the same treatment for a further 2 months after which his CBC and other blood tests were repeated. His Hb had further improved significantly and entered normal range with normalization of MCH and MCHC and reduction in RDW. (Table 1 – at 4 months). BP, Blood Sugar and HbA1C were normal. Patient said his symptoms had significantly improved and he felt his working capacity was optimum. He no longer experienced palpitation or breathlessness on exercising half hour daily, and also did not suffer from frequent headaches as before. He did not complain of any adverse effects after starting Heme Iron and other supplements. Patient was asked to continue same supplements for an additional 3 months, and incorporate dietary and lifestyle advise on a long-term basis.

Discussion

Dimorphic anemia can be caused by the simultaneous deficiency of iron, B12 and folate which can be seen due to diets low on green vegetables and animal products, as was seen in this case. Other causes include bone marrow suppression (will show pancytopenia on CBC) or parasitic infection and occult blood loss (will be seen in stool test), and malabsorption or inflammatory diseases of the bowel.[6,7] Since macrocytosis is the more common presentation of dimorphic anemia, seen by both peripheral blood and bone marrow examination, it is important to perform Iron studies to rule out masked iron deficiency.[4] Initially in this patient, decreased Hemoglobin, along with increased MCV, MCH, and RDW was suggestive of macrocytic anemia, while the underlying Iron deficiency was gradually revealed as B12 and folate were supplemented, and Iron studies performed. Such

patients often do not respond symptomatically or with satisfactory increments in Hemoglobin to folic acid and B12 supplements alone. While folate is usually supplemented orally, B12 injections are recommended in severe deficiency and malabsorption syndromes, while oral B12 replacement may be considered for patients in mild-moderate cases with no absorption or compliance concerns.[8]

Patients with type 2 diabetes mellitus are twice more likely to be prone to anemia than the patients without diabetes.[9] Anemia is often unrecognized in 25% of diabetic patients and is also an independent risk factor in diabetic patients for heart disease and renal failure. LAD especially in hypertensive relatively younger ambulatory adults without cardiac symptoms or disease can indicate association with glucose intolerance.[10] Therefore, screening for and treating Anemia is of multidimensional importance in Diabetic patients, and such patients should also be well monitored for Blood Sugar and Blood pressure control and presence or onset of cardiac/renal disease.

Intravenous Iron is recommended for patients with severe anemia, or those with inflammation (due to kidney disease, heart failure, or rheumatological diseases), patients who cannot tolerate oral iron, or are noncompliant with oral iron therapy. [11] Gastro-intestinal side effects like nausea, indigestion and constipation along with low and unpredictable absorption of iron salts limits the implementation and benefits of oral iron therapy. This patient had moderate anemia, no inflammatory disease and showed willingness to comply to oral therapy. Heme iron polypeptide was chosen as the suitable iron preparation due to its higher iron content, bioavailability, real world efficacy-consistency and tolerance.[12]

Iron absorption, utilization and RBC incorporation with Heme Iron has seen to be significantly higher than Ferrous Fumarate, and Ferrous Sulphate even with meals, and relatively unaffected by body Hepcidin levels.[13,14] A study comparing oral HIP and intravenous iron saccharate complex in iron deficiency anemia, showed no significant differences between groups for change in Hb (average 3g/dL change) and ferritin levels at 3 months.[15] The patient in this case responded well to treatment with Heme Iron with both satisfactory Hb incrementation and tolerance. Vitamin C in this case was given to enhance non-heme iron absorption from diet as vegetarian food does not contain heme iron and has very low levels of B12[16]. Folate and B12 supplements were also continued along with other B complex vitamins and minerals orally.

Conclusion

Anemia can present in a dimorphic form, with a predominant picture of macrocytosis, masking the underlying Iron deficiency. This needs to be considered and evaluated both clinically and by laboratory tests, and treatment given accordingly. Diet and Lifestyle assessment and modification form an important part of therapy along with appropriate dose and formulations of nutritional supplements. Iron formulations like Heme Iron can be suitable options to improve absorption, utilization and tolerance to oral iron. Anemia is more common in patients with Diabetes, and can increase cardiovascular and renal risk in such patients who should therefore be evaluated, monitored and treated for the same timely.

Table 1: RBC profile and parameters in CBC

	Baseline	1 month (1 month of B12-Folate)	2 months (1 month of Iron - HIP)	4 months (3 months of Iron - HIP)	Lab Reference Range	Unit
Hemoglobin	9.6	9.5	10.9	13.1	13-18	g/dL
RBC Count	2.38	2.92	4.49	4.74	4.7-6.0	Million/ µL
Hematocrit	29.5	32.4	41.1	41.6	42-52	%
MCV	123.9	111	91.5	87.8	78-100	fL
MCH	40.3	32.5	24.3	27.6	27-31	pg
MCHC	32.5	29.3	26.5	31.5	32-36	g/dL
RDW-CV	17.9	26.9	21.8	17.9	11.5-14.0	%

CBC: Complete Blood Count; RBC: Red Blood Cell, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW-CV: Red cell Distribution Width (Coefficient Variation), HIP: Heme Iron Polypeptide.

Table 2: Iron and B12 studies after 1 month of Folate-B12 treatment

	Value	Lab Reference range	Unit
Iron	26.4	Male: 65-175	mcg/mL
Total Iron Binding Capacity	496	Male: 225-535	mcg/mL
Transferrin Saturation	5.32	13-45	%
Vitamin B12	>2000	211-911	pg/ml

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