Case report

Triple Threat: Anemic Trio - Megaloblastic Anemia, Iron Deficiency Anemia And Hemolysis In A 64 Year Old Male

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Abstract:

A 64 year old male presented with complaints of generalised weakness and easy fatiguability for the past 1 year being treated for symptoms on & off. On examination, patient was pale& ictericwith no other abnormality noticed. Routine blood investigations done which showed Hb-4.5 g/dL, PCV-14.5, red cell distribution width-28.6%,MCV-125fL, MCH-38.8pg, MCHC-31g/dL, elevated total bilirubin-2.9mg/dL, Direct Bilirubin-1.1mg/dL, Indirect Bilirubin-1.8mg/dL. Serum Iron-31ug/dL, Serum Transferrin Saturation-10%, Serum LDH-1339U/L, Serum Haptoglobin-110mg/dL, Serum Vit B12-50pg/ml, Reticulocyte Count was 20%, ANA- weekly Positive, direct coombs test was negative. Peripheral blood smear showed,"Marked anisocytosis, poikilocytosis with predominantly macrocytic,normochromic with macroovalocytes,elliptocytes,tear drop cells and polychromatic macrocytes and occasional nRBC's, fragmented RBC's seen with mild thrombocytopenia". Bone marrow aspiration done which showed,"Erythroid series of cells with micronormoblastic and megaloblastic maturation with few scattered leucocytes". The patient was diagnosed with hemolytic anemia secondary to vitamin B12 deficiency with concomitant iron deficiency anemia.

Keywords: Vitamin B12, Iron Deficiency Anemia, Hemolysis, nRBC's, Macro-ovalocytes, Megaloblastic Maturation, Coomb's test, LDH

Introduction:

Anemia is functionally defined as an insufficient RBC mass to adequately deliver oxygen to peripheral tissues[1]. Megaloblastic anemia is a product of folate or cobalamin (vitamin B12) deficiency. Sometimes, they may coexist. The anemia is based on ineffective erythropoiesis. Dietary vitamin B12 deficiency is a severe problem in the indian subcontinent, especially among vegetarians. Hemolytic anemias are due to increased destruction of red cells. Iron deficiency anemia is associated with normocytic and normochromic red cells and an inappropriately low reticulocyte response[2].

Case presentation:

A 64 year old male from Pondicherry presented to our hospital with complaints of generalised weakness, easy fatiguability, dyspnoea on minimal activity for the past 1 year which was exaggerated for the past 6 months. He also complainedof decreased appetite with no marked weight loss. He denied any history of chronic diarrhoea, unusual food craving, bleeding manifestations or previous blood transfusions in the past.

The patient was diagnosed with anemia previously and received treatment with iron supplements. He denied any history of alcohol intake or use of any form of tobacco products. He used to have mixed

diet, predominantly vegetarian diet.He is married for 35years with 3 children, who are healthy with no congenital or any other abnormalities. There is no similar or significant family history.. The patient was admitted to our hospital for further workup.

On examination, the patient was conscious, alert, oriented, and in mild distress. Physically, he looked thin, pale and icteric. There was no lymphadenopathy. Oral cavity was normal with no angular chelitis or angular stomatitis. His vital signs were, pulse rate 86/min, regular, blood pressure 110/60 mmHg in right arm supine position, temperature 99 F, respiratory rate 24/min, abdomino thoracic, oxygen saturation was 92% on room air, with a height of 166 cm, and weight of 56 kg, BMI-20.3. His cardiopulmonary examination was normal. His abdomen was soft, not distended with no tenderness and no organomegaly. Patient had no other signs like rashes, skin lesions, or joint swelling. Rectal examination revealed normal prostate and no palpable mass or bleeding. Neurological examination was essentially normal.

On investigation, CBC revealed Hb-4.5g%, PCV-14.5, Red cell distribution width-28.6%, RBC-1,160,000/cu mm, MCV -125fL, MCH-38.8pg, MCHC-31g/dl, White blood cell and platelet count were mildly reduced. Reticulocyte count was 20% and corrected reticulocyte count was 3%. Peripheral blood smear showed "Marked anisopoikilocytosis with predominantly macrocytic, hypochromic with macroovalocytes, elliptocytes, tear drop cells and polychromatic macrocytes (figure-1) and occasional nRBC's (figure-2), fragmented RBC's seen with mild thrombocytopenia".

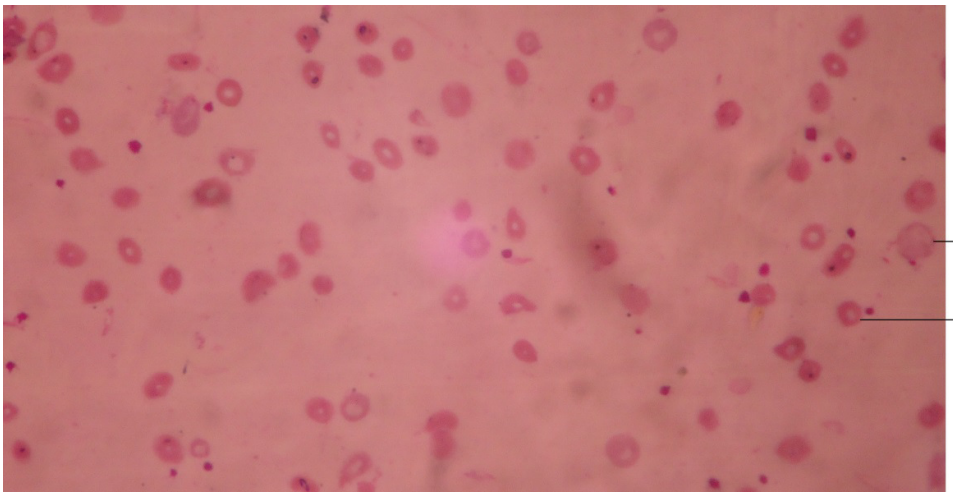

Figure 1

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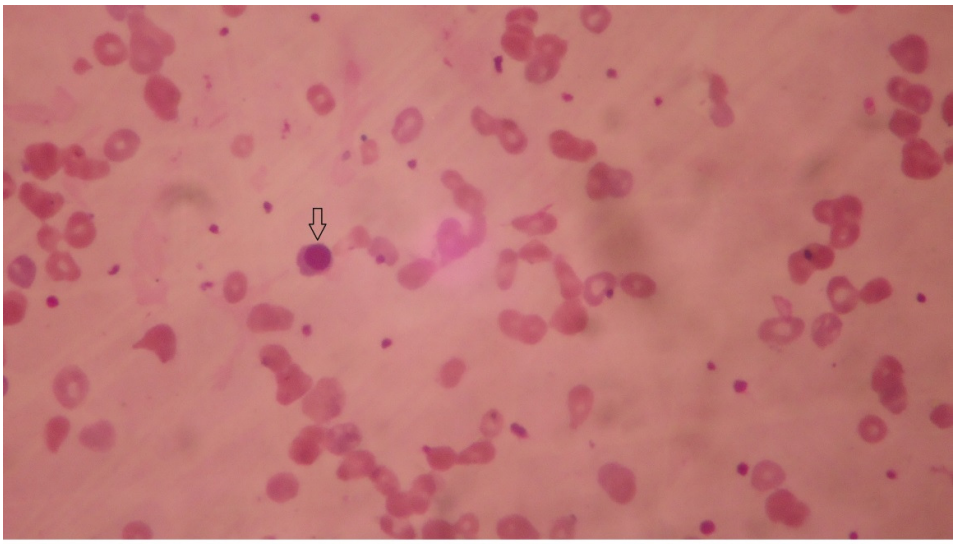

Figure 2 - nucleated RBC (nRBC) [Arrow marked]

Urine analysis done which showed normal study. Liver function test (LFT) showed elevated total bilirubin with predominant raise in indirect bilirubin level with normal liver enzymes. Other investigation reports are mentioned below on Table-1.

Based on initial investigations, further additional workup was sent including urine analysis, serum lactate dehydrogenase (LDH), serum haptoglobin, Coombs test, iron study, serum vitamin B12, serum folic acid, fibrinogen level, serum intrinsic factor antibody levels, homocysteine level, glucose-6-phosphate dehydrogenase level,Hb electrophoresis, thyroid profile, chest radiograph, 2D-echo, anti-nuclear antibody level, anti ds-DNA (by IFA), bone marrow aspiration and viral titres including HIV, viral markers for hepatitis to look for aetiology of anemia.Bone marrow aspiration showed, "Erythroid series of cells with micronormoblastic and megaloblastic maturation with few scattered leucocytes". Reports were summarised in Table-2.

TABLE – 1

INVESTIGATIONS	PATIENT'S VALUE ON ADMISSION	FOLLOW UP	NORMAL VALUE
WBC (/mm3)	3900/cu mm	6420 /cumm	4200–11000/cu mm
Hb (g/dL)	4.5 g/dl	12 g/dl	13.5-17 g/dl
Hct (%)	14.5 %	40.4 %	41.0–52.0%
Plt (/mm3)	135000/cu mm	219000 /cu mm	140000–400000 /cu mm
MCV (fL)	125fL	96.9fL	83-101 fL

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MCH (pg/red cell)	38.8pg	28.8 pg	27-32 pg
MCHC (g/dL)	31g/dl	29.7 g/dl	31-34 g/dl
RDW (%)	28.6%	16.2 %	11.6-14 %
Differential count (%) Neutrophil	58.5%	67 %	40.0–72.0%
Eosinophil	0.1 %	2.6 %	0.0–10.0%
Monocyte	1%	2.6 %	4.0–12.0%
Lymphocyte	40%	27.4 %	17.0–45.0%
Reticulocytes (%)	20 %	NA	0.5-2.8 %
Reticulocyte index	3 %	NA	1-2 %
Total bilirubin	2.9mg/dl	1 mg/dl	0-1 mg/dl
Direct bilirubin	1.1mg/dl	0.3 mg/dl	0-0.3 mg/dl
Indirect bilirubin	1.8mg/dl	0.69 mg/dl	0-0.8 mg/dl
SGOT	19.1 IU/L	22 U/L	5-35 IU/L
SGPT	24.5 IU/L	20 U/L	Up to 40 IU/L
Total Protein	6.4 g/dl	7.3 g/dl	6.0-8.0 g/dl
Albumin	3.8 g/dl	4.4 g/dl	3.7-5.3 g/dl
HIV I & II	Negative	Negative	Negative
HbsAg	Negative	Negative	Negative
HCV	Negative	Negative	Negative

THYROID PROFILE – NORMAL,

2D-ECHO – NORMAL STUDY.

TABLE -2

INVESTIGATION	PATIENT'S VALUE 0N ADMISSION	FOLLOW UP	NORMAL VALUE
Serum Iron	31 ug/dl	260.6 ug/dl	70 -180ug/dl
Serum TIBC	296.6ug/dl	310 ug/dl	225-535ug/dl
SerumTransferrin Saturation	87.86%	10 %	13-48%
Serum Ferritin	258ng/ml	174.5 ng/ml	22-322ng/ml
Serum Vitamin B12	<50pg/ml	369 pg/ml	211-911pg/ml
Serum Folic acid	>24ng/ml	NA	>5.38ng/ml
Serum Homocysteine	-	14.3 umol/L	<30umol/L
Serum LDH	1339U/L	196 U/L	135 to 225 U/L
Serum Haptoglobin	-	110 mg/dl	30-200 mg/dl
ANA	Weakly positive 1:100	Negative (0.72)	Negative
Anti ds DNA	Negative	NA	Negative
Direct coombs	Negative	Negative	Negative
Indirect coombs	Negative	Negative	Negative
Hb Electrophoresis HbA HbF HbA_2	 96.5 0.8 2.7	NA	
Serum Intrinsic factor antibody	Negative	Negative	Negative
Glucose 6 phosphate dehydrogenase (G6PD)	22.8 U/gHb	NA	6.6 to 17.2 U/gHb

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Low B12 levels with increased MCV and macroovalocytes on smear suggested B12 deficiency. Low serum Iron and anisopoikilocytosis suggested iron deficiency. However hyperbilirubinemia,elevated LDH and tear drop cells on peripheral blood smear suggested hemolysis probably due to ineffective hematopoiesis which is due to vitamin B12 deficiency.

ETIOLOGIC CLASSIFICATION OF ANEMIA[3]	
PHYSICAL	Burns, Trauma, Prosthetic valves , Frostbite
GENETIC	Thalassemias, Enzyme abnormalities of the glycolytic pathways, Hemoglobinopathies, Defects of the RBC cytoskeleton, Abetalipoproteinemia, Hereditary xerocytosis, Congenital dyserythropoietic anemia, Rh null disease, Fanconi anemia
NUTRITIONAL	Starvation and generalized malnutrition, Vitamin B-12 deficiency, Folate deficiency, Iron deficiency
CHRONIC DISEASE AND MALIGNANCY	Chronic infections, Renal disease, Hepatic disease, Collagen vascular diseases, Neoplasia.
INFECTIOUS	**Bacterial** - Gram-negative sepsis, Clostridia **Protozoal** – Malaria, Leishmaniasis, toxoplasmosis **Viral** - Infectious mononucleosis, Hepatitis, cytomegalovirus

Patient was started on vitamin B12 supplements, folic acid tablets, iron supplements and 4 units of packed cell transfused during the hospital stay. Patient was discharged after 10 days of hospital stay.

Patient was reviewed after one week of discharge from the hospital with significant improvement in his clinical symptoms and his follow up investigations showed Hb of 10.9g/dl with PCV 43.6, normal liver function test, Vitamin B12 369pg/ml, Serum Iron 260ug/dland ANA negative.

Discussion:

Anemia can be of 3 aetiologies 1) blood loss, 2) increased RBC destruction and 3) decreased production of RBC's. Each of these causes includes a number of aetiologies that require specific and appropriate therapy[4].

Anemia requires evaluation to determine the underlying aetiology. Symptoms and signs of anemia are fatigue, dyspnoea on exertion, decreased exercise tolerance, tachycardia, pallor of

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nails and conjunctivae, angular glossitis, angular stomatitis, platonychia and koilonychia[5].

In this case report, our patient presented to us with complaints of easy fatiguability, generalised weakness, dyspnoea on exertion for the past 1 year with progressive worsening of symptoms for 6months and clinical signs of pallor, tachypnea with low Hb confirmed severe anemia.Patient also had jaundice with elevated bilirubin, elevated LDH with tear drop cells in peripheral blood smear which helped as make a diagnosis of hemolytic anemia.

We investigated our patient to work towards the aetiology of anemia. Since he denied history of previous transfusions and childhood history of anemia, we began to focus on acquired causes of hemolysis. Our patient had negative coombs test to argue against autoimmune hemolysis. A weekly positive ANA (which may sometimes occur as a false phenomenon in Megaloblastic anemia) was confirmed with a negative anti ds DNA test. There were no investigations to suggest microangiopathic hemolysis or DIC viz normal renal parameters and adequate platelet count. Also there was no history of any infection, chronic disease or malignancy.

Low serum vitamin B12, low serum iron and smear showing anisopoikilocytes and macroovalocytes helped us conclude the presence of dimorphic anemia with coexisting B12 and iron deficiency anemia. Further evaluation towards aetiology of nutritional deficiency, showed negative intrinsic factor antibody thereby ruling out the possibility of pernicious anemia one of the most common aetiologies of B12 deficiency. Patient not willing for an upper GI endoscopy so it was not done.

Our patient gave history of taking a predominantly vegetarian diet, could probably be the cause for B12 deficiency. Unfortunately we started the patient on B12 supplements before assessing for serum haptoglobin levels and serum homocysteine levels. This could probably explain the reason why these values turned out to be normal.

Our patient gave no history of worm infestation or blood loss, even his stool occult blood was negative. Moreover he was on iron supplements on and off. Despite this he was found to have iron deficiency. This could probably be due to ongoing intravascular hemolysis due to ineffective hematopoiesis leading to iron loss.

Ironically serum ferritin levels were normal, probably because of ferritin rise as an acute phase reactant in the face of anemia & hemolysis. Vitamin B12 is mainly found in milk, meat, egg, fish, shell fish. In india, B12 deficiency is rampant among strict vegans in hindus and jains. But a greater population at risk, if deficiency are in elderly persons and those with malabsorption syndromes. As a significant proportion of B12 absorption depends on enterohepatic circulation of B12 which is lost in malabsorption syndrome.B12 is required for 2 biochemical reactions in the human body namely, 1) methionine synthesis and 2) isomerisation of methyl malonyl CoA. However the loss of one carbon unit transfer reactions that depend on folate require tetrahydrofolate. B12 is required for conversion of methyl tetrahydrofolate to tetrahydrofolate thus B12 deficiency leads to non utilisation of methyl tetrahydrofolate and folate trap[6]. Thus combined B12 and folate deficiency is a common finding in Megaloblastic anemia. However our patient had normal folate levels. B12 deficiency leads to defective myelin synthesis thus patient should always be evaluated for neurodeficits. The neurological examination was normal in our patient. B12 deficiency is diagnosed when serum levels go below 100 pg/ml[7]. we started our patient on oral supplements of B12 and iron and transfused him. Over a few weeks he improved.

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The treatment of cobalamin deficiency requiresreplacement of vitamin B12. High dose oral therapy of 1000 to 2000 mcg per day for daily is as effective as parenteral replacement[7].

This case displays the complexity of anemia presentation with a combined B12 & iron deficiency and hemolysis. Anemia in any age group requires thorough evaluation for aetiology and to guide therapy. Life-long therapy with vitamin B12 is necessary in diseases such as pernicious anemia and malabsorption syndromes. Individuals who are consuming only vegetarian diet should be advised to take supplements as recommended by national guidelines in order to prevent critical hematologic and neurological sequelae[5].

References:

1. Adamko DJ, Agarwal N, Alter BP, Andrews NC, Ansell SM, Aplenc R et al. Wintrobe's clinical hematology. 12th ed. philadelphia: Lippincott Williams & Wilkins; 2009. P. 779.
2. Fauci S, Kasper L, Longo L, Braunwald, Hauser L, Jameson J et al. Harrison's principles of internal medicine. 18th ed. New York: Mc Graw Hill Medical; 2008. p. 844.
3. Anemia. 2014 Dec 1 [cited 2015 Jan 20]; Available from: http://emedicine.medscape.com/article/198475-overview.
4. Dali-Youcef N, Andrès E. An update on cobalamin deficiency in adults. QJM. 2009 Jan;102(1):17–28.
5. Prueksaritanond S, Barbaryan A, Mirrakhimov AE, Liana P, Ali AM, Gilman AD. A puzzle of hemolytic anemia, iron and vitamin B12 deficiencies in a 52-year-old male. Case Rep Hematol. 2013;2013:708489.
6. Northrop-Clewes CA, Thurnham DI. Biomarkers for the differentiation of anemia and their clinical usefulness. J Blood Med. 2013;4:11–22.
7. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013 Jan 10;368(2):149–60.

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