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Anemia by Vitamin B12 and Latent Iron Deficiency

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Abstract: The aim of this work is to illustrate a difficult diagnostic in vitamin B12 deficiency because of using of multivitamin preparations to a patient with unknown etiology of anemia.
History Patient: a 70 year old engineer, following 8 years vegetable – dietary, was admitted to the county hospital, in neurology department, with diagnostic of poli-radiculonevrites, received in ward the treatment with milgama (containing 250 micro-gram multivitamin). After a lipotimia status the patient was transferred to cardiology department. Laboratory examinations showed in peripheral blood: Hb = 6 3 g/dl; Ht = 18.8%; RBC= 290.000/mm³; PLT. = 214000/mm³; WBC = 5300/³mm; Ret. = 3, 7%; Erythrocytes indices = normal values; ESR = 38 mm/h, moderate increase and serum iron decreased, 36 microgram/dl value. On blood smear in optic microscopy was registered: Band = 5% (with nucleus in ring!!!), differential count being normally with aspect flags on Coulter HMX Analyzer with 22 parameters: neutrophilia, lymphopenia, anemia. To microscopic examination of slide from bone morrow, have occurred the hyperplasic series of erythrocytes ~ 45%, deficiency of erythropoiesis, poly-cromathopil and acidophil erythroblasts with megaloblastic character, large metamielocytes and giant band forms. Macrocytes and ovalocytes where also presented. Biopsy results from gastric mucosa showed lesions of chronic gastritis, non-atrophic epithelium.
Conclusions: Megaloblastosis appears in some time with vitamin B12 deficiently in bone morrow but no in peripheral blood because of administration of multivitamin drugs, deleting haematological shape of megaloblastic anemia.

Keywords: Wait blood cells; Erythrocyte sedimentation ratio; Haptocorin; transcobalamin.

1. Introduction

Deficiency of vitamin B12 was a disease that has intrigued numerous investigators for many years. In fact, the history of pernicious anaemia was an “illustrative case” of the development and progress of medicine.

The aim of this work was to illustrate, by one difficult case patient, admitted in hospital, the diagnosis of B12 vitamin deficiency, intrigued with iron deficiency, because of multivitamin drugs, used as an individual treatment of patient, without a previous medical consult.

1.1. History Patient

A 70 year old man, engineer, time of 8 years, eating vegetable diet, was admitted to the County Hospital, Internal Medicine Department, because of weakness, 10 kilo in last two months, dizziness, dyspneea, ataxia and numbress of the hands, with lung disease in evolution.

After screening investigations without a concluded diagnosis, one month later, was transferred to department of Neurology, because of symptoms came to include a loss of sensitivity in extremities, paresthesia, an unsteady gait [ataxia] and loss of balance. Psychiatric symptoms such as memory disturbance, depression and cognitive decline have been also reported.

For a presumptive diagnosis of poly-radiculonevrites, the patient followed, in continue, the treatment with drugs Milgama, contained ciancobalamin vitamin 250 microgr /vial, prednisone, levomepromazin and antibiotics. After outcome from hospital, at home, the patient presented lipotimia status, confusion and, immediately he was admitted in Cardiology department.

1.2. Laboratory Blood Tests

ESR = 38 mm/h, CBC with differential count showed: HGB = 6.3 g/dl; HTC = 18.8%; RBC = 290.000/³mm, Thrombocyte = 214000/.mm³, WBC = 5300/³mm; Reticulocyte = 3.7%; Erythrocyte indices = normal values.

1.3. Blood Smear in Optic Microscopy

Band = 5% [nucleus in ring], Segmented = 75%, Eosinophile = 1%; Basophile = 1%, Lymphocyte = 11%, Monocyte = 3%, .

Suspect flags on coulter HMX: Erythrocyte indices were with abnormal values: Mean corpuscular volume (MCV) = 90.1 fL (reference range = 82 fL-92 fL), Mean cell hemoglobin (MCH) = 30.1 pg (27 pg-31 pg), Mean cell hemoglobin concentration (MCHC) = 33.4 g/dL (32 g/dL-36 g/dL), RDW = 19.1 [n= 9-11], [Figure 1].

Hematologic analyser showed neutrophilia, lymphopenia and the microscopy exam on peripheral blood smears showed the dimorphic pictures, anizocitosis, with poikolocytosis and and ovlaocytes were also presented,

Ancillary tests relieved an increased LDH value = 710 U/L [n = 313 – 618], glucose = 143 mg/dl [n = 75 – 110], urea = 111 mg/dl [n= 25-45 mg/dl], creatinine = 1,3 mg/dl [n= 0.5-1.5 mg/dl], triglyceride = 251 mg/dl [n = 50 – 150], iron = 35 ug/dl [n = 49 – 181], serum ferritn = 15 ng/ dl[30-150], Total bilirubin < 0,2 mg/dl[n=0.5-1.2 mg/dl] and Indirect bilirubin = 0,1 mg/dl [n =0.2-0.75 mg/dl], ALT and AST with normal values.

Other laboratory tests that can help discern the causes of hemolysis include the following: Quantitative Hb electrophoresis, RBC enzyme assays, Flow cytometry, Cold agglutinins and Osmotic fragility.

At examination of bone morrow, on the blood film with May-Grrunwald Giemsa dye, occurred increased erythropoiesis which was megaloblastic in character volume, giant band forms, large metamilocytes

In conclusion, bone morrow was with hyperplasic series erythrocytes ~ 45%, deficiency of erythropoiesis [predominant acidophil and policromatophil erythroblasts]. Biopsy results from gastric mucosa showed lesions of chronic gastritis, non-atrophic.

Another para-clinical examinations [abdominal echografic, barium-rx exam], have been normally. B12 vitamin dosage on the Analyzer Chemi Immulite 2000 in peripheral blood showed 150 pg/m L (biological reference interval =193-982 pg/m L) and folic acid dosage into erythrocytes was in normal value, 1632 nmol/L(biological reference interval =995-2499).

1.4. Patient Diagnosis

Anemia by cobalamin deficiency combined with the iron deficiency The patient followed therapeutic sample [with B12 vitamin, 1000 gamma, im./per day, 2 weeks and than 1000 gamma per week, Omeran 1 tb./day, in morning 10 o'clock, Ferum-gradumet 1 tablet/day, protection of diet.

1.5. Differential Diagnosis

The differential diagnosis for the patient include: glucose-6-phosphate dehydrogenase deficiency (G6PD) which can lead to hemolysis, poikilocytosis, and Heinz bodies in erythrocytes (hemolytic anemia) in the presence of oxidative stress. G6PD deficiency is one of the most prevalent disease-causing mutations worldwide. However, most of the G6PD iso-enzymes with decreased activity are associated with only moderate health risks without a significant effect on longevity. Reticulocytes have five times higher G6PD enzyme activity than the oldest erythrocyte subpopulation [1]. Hereditary spherocytosis, which is characterized by spherocytes, usually is diagnosed via a family history of the condition and a negative direct antiglobulin test result [2]. Sickle-cell anemia [3] and thalassemia [4], which hemoglobinopathic manifestations, are characterized by chronic hemolysis. When iron deficiency is severe, anemia is hypochromic, microcytic cells.

Hemolytic Anemia, Hemolysis may be acute, chronic, or episodic. Chronic hemolysis may be complicated by aplastic crisis (temporary failure of erythropoiesis).Intravascular hemolysis is an important reason for premature RBC destruction and usually occurs when the cell membrane has been severely damaged by any of a number of different mechanisms, including autoimmune phenomena, direct trauma , (eg, defective mechanical heart valves), bacterial toxins and drug administration.

2. Evolution

After therapeutic sample, past 10 days, Hb became 9,8 g/dl, Ht = 29%, Reticulocyte = 11% with IP = 3,48, Leucocyte = 5000/cu-mm, Thrombocyte = 281000/cu.mm, ESR = 18 mm/h.

The peripheral blood picture showed: Neutrophiles = 73%, Eosinophile = 2%, Basophile = 2%, Monocyte = 15%, Lymphocyte = 8%. The blood smear shows anisocytosis: normocytosis with ease macrocytosis.

Urea was normalised = 48 mg/dl, plasma iron = 46 ug/dl, TIBC = 382mg/100 ml, sample of coagulation with normal values [aPTT, fibr, At3, PDF (-), TELCE [-]. In present time the patient there is in treatment with B12 vitamin, 50 gamma/week with the normal level serum ferritin, 122 ng/m L((biological reference interval =25-285 ng/m L for man and 5-148 ng/m L for women. Efficiency of treatment in periodically will be monitored and by performing of metilmalonic acid test (heparnied plasma) and homocystein level (EDTA plasma).

3. Comment

In first time the neurogical manifestation occurred to patients in absence of blood picture in peripheral blood of typical megaloblastic anemia. To the patient with vegetable diet anemia by B12 vitamin is accompanied of neurological syndrome with frequently iron deficiency, specialty to elder men.

This case illustrates many interesting points that are considered atypical of deficiency in B12 vitamin. In first time, the neurological manifestations occurred to this patient in the absence anemia. When a patient with anemia by

B12 vitamin deficiency has the neurological features of disease without the characteristic hematologic abnormalities, the diagnosis is difficult.

On such circumstance, the patient has received B12 vitamin and folic acid in an amount that is sufficient to convert the megaloblastic anemia type of erythropoiesis to the normoblastic type in peripheral blood and raise the erythrocyte count. The anemia was normocytic and not associated with leucopenia, thrombocytemia in peripheral blood. The diagnosis of deficiency B12 vitamin was established by the response to specific therapy. When and iron deficiency is severe the anemia is hypochromic and microcytic but in milder degrees of iron deficiency the anemia is normocytic. A combined deficiency of iron B12 vitamin might result in a normocytic anemia that required both iron and vitamin B12 in treatment [5].

Impaired absorption of vitamin B12 occurs and in other conditions different of diet deficiencies associated with diarrhea or other evidence of the mal-absorption syndrome. Such impairment has been demonstrated to patients with:

- Blind intestinal loops, fistulae, strictures, and diverticula of the small bowel,
- Gastrectomy, because absence of the gastric intrinsic factor, altered gastric secretion, gastric atrophy with degenerative lesions, mal-absorption syndrome, gastro duodenal disease and pancreatic, abnormal bacterial proliferations in bowel, infestation with parasites, failure pancreatic, liver, chronic hepatitis cirrhosis,
- Disease of lymphoma group, myeloproliferative syndrome (MSD) by elevated consummations in neoplasia and hyperthyroid – but a study of the bone morrow usually enable one to establish the diagnosis [6].

In some patient particularly since the advent of folic acid and the widespread use of multivitamin preparations the haematological abnormalities are mild or absent when neurological manifestations are predominant. The bone morrow is usually hyper-cellular. The characteristic feature is the occurrence of the megaloblastic type of erythropoiesis. If anemia is severe, promegaloblastic and basophilic megaloblasts are increased in number and mitotic divisions are numerous [7]. The polychromatophilic megaloblasts which are easiest cells to identify in this serious persist even after the anemia in the peripheral blood has been abolished by transfusion.

Deficiency of vitamin B12 or folic acid also leads to the production of giant metamielocytes and multi-segmented macropolicites. The abnormalities in the granulocytic series do not disappear as promptly as then megaloblasts after specific therapy and their present may be helpful in diagnosis.

There are the conversion of the megaloblastic type of erythropoiesis to the normoblastic type within two day, a rise in reticolocytes during the first week, and a return of the haemoglobin and red count to normal levels in succeeding weeks. The absorption of the vitamin may be affected by atrophic gastritis [around 20% individuals over 60 years this conditions [8].

The recent years the picture has become more complex. For example: 24 – 28% of patients do not have anemia, 17 – 33% have a normal mean corpuscular volume [MCV], there is an apparent normal cobalamin levels to patients with clinical evidence of deficiency in B12 vitamin [9]. In last time, attention has recently been focused on measuring metabolic levels methylmalonic acid [- MMA -], and homocystein [- Hcy -], as these should accumulate when a deficiency stare exists. However, both of these methabolits can be affected by the renal function of the patient and Hcy can be elevated when there is an underling folate deficiency [10].

The situation becomes more warring when abnormal levels of metabolites are detected but the total Hcy are apparently well within normal range. The notion that metabolic levels change before that total Cbl levels decreases this fact not proven. Current made techniques for measuring plasma Cbl that is bond to both haptocorin [HC] and transcobalamin [TC], complex describing Holo-Transcobalamin. Hololotranscobalamin has been suggested as a better marker for cobalamin deficiency because of:

- measures the physiologically relevant fraction of circulating cobalamin,
- It has a short-life and so may be a good early good marker.

It is hoped that the new methods [antibodies and physico-chemical methods] will be enable to the investigators to address the many questions surrounding holo-trancobalamin and also enable carefully designed clinical surveys to be undertaken [11].

4. Conclusions

To the vegetarian elder men, anemia by deficiency of B12 vitamin is accompanied of neurological syndrome. There are frequent and deficiency of iron also to the patient which eats vegetal reached in folic acid, cofactor of B12 vitamin, but poor in B12 vitamin. Megaloblastosis appears in same time with B12 vitamin deficiency, in bone morrow but not in peripheral blood.

Neuropathy was results from accumulations of a metabolised metylmalonic acid [from propionic acid] with decrease of acetyl-coA, ATP and energy cells. Drugs with poli-vitamins administrated more time, without corresponding investigations, can delete haematological shape of megaloblastic anemia.

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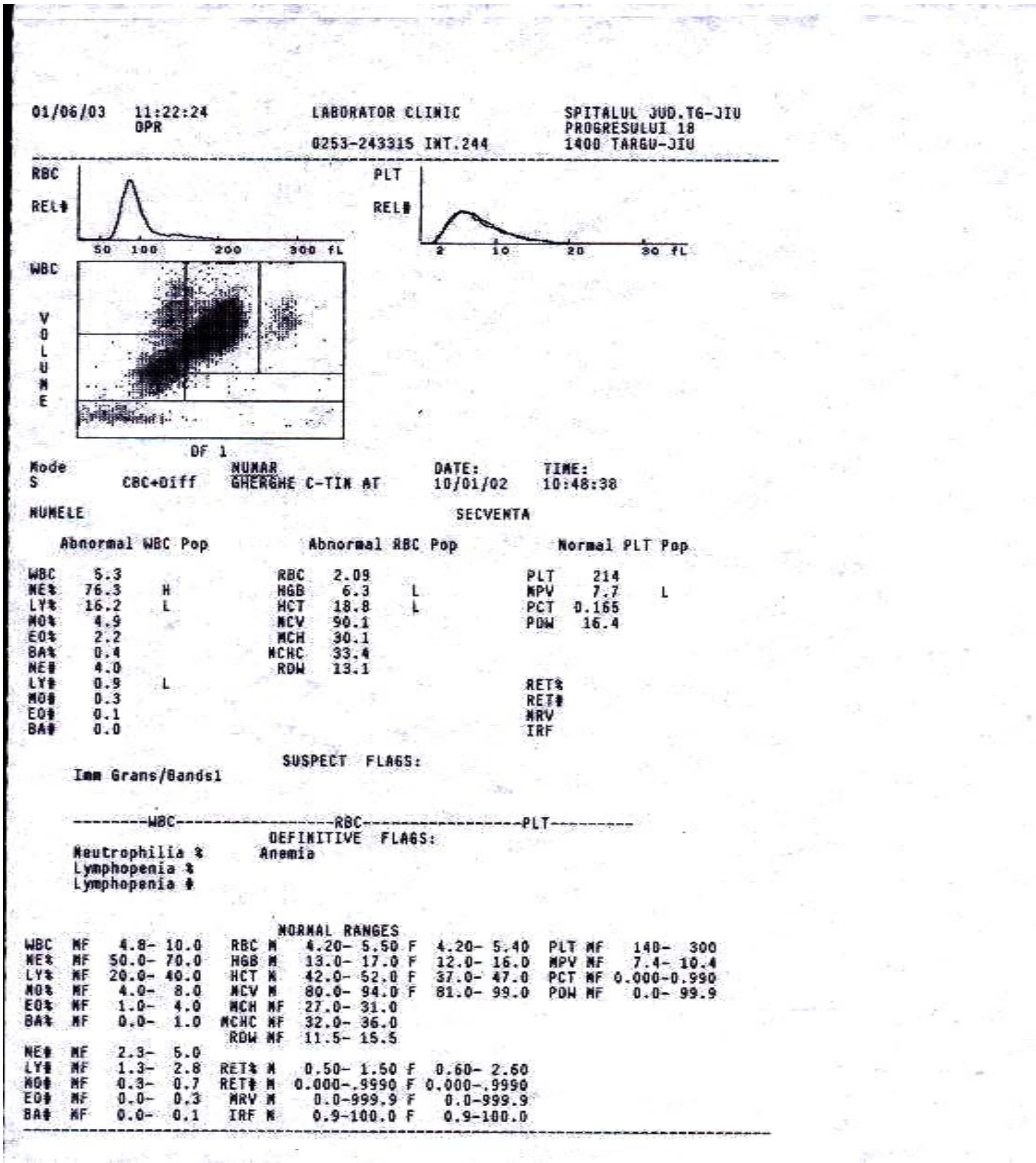
Figure-1. Hematological parameters of Vitamin B12 deficiency, combined with iron deficiency on the Automatic Analyzer Coulter HMX.



01/06/03 11:22:24 OPR LABORATOR CLINIC 0253-243315 INT.244 SPITALUL JUD.TG-JIU PROGRESULUI 18 1400 TARGU-JIU

Mode S CBC+Diff NUMAR GHERGHE C-TIN AT DATE: 10/01/02 TIME: 10:48:38

NUMELE SECVENTA

Abnormal WBC Pop			Abnormal RBC Pop			Normal PLT Pop		
WBC	5.3		RBC	2.09		PLT	214	
NE%	76.3	H	HGB	6.3	L	MPV	7.7	L
LY%	16.2	L	HCT	18.8	L	PCT	0.165	
MO%	4.9		MCV	90.1		PDW	16.4	
EO%	2.2		MCH	30.1				
BA%	0.4		MCHC	33.4				
NE#	4.0		RDW	13.1				
LY#	0.9	L				RET%		
MO#	0.3					RET#		
EO#	0.1					MRV		
BA#	0.0					IRF		

SUSPECT FLAGS:

Imm Grans/Bands1

---------WBC-----------------RBC-----------------PLT---------

DEFINITIVE FLAGS:

WBC	RBC
Neutrophilia %	Anemia
Lymphopenia %	
Lymphopenia #	

NORMAL RANGES

WBC	MF	4.8- 10.0	RBC M	4.20- 5.50	F	4.20- 5.40	PLT MF	140- 300
NE%	MF	50.0- 70.0	HGB M	13.0- 17.0	F	12.0- 16.0	MPV MF	7.4- 10.4
LY%	MF	20.0- 40.0	HCT M	42.0- 52.0	F	37.0- 47.0	PCT MF	0.000-0.990
MO%	MF	4.0- 8.0	MCV M	80.0- 94.0	F	81.0- 99.0	PDW MF	0.0- 99.9
EO%	MF	1.0- 4.0	MCH MF	27.0- 31.0				
BA%	MF	0.0- 1.0	MCHC MF	32.0- 36.0				
			RDW MF	11.5- 15.5				
NE#	MF	2.3- 5.0						
LY#	MF	1.3- 2.8	RET% M	0.50- 1.50	F	0.60- 2.60		
MO#	MF	0.3- 0.7	RET# M	0.000-.9990	F	0.000-.9990		
EO#	MF	0.0- 0.3	MRV M	0.0-999.9	F	0.0-999.9		
BA#	MF	0.0- 0.1	IRF M	0.9-100.0	F	0.9-100.0		