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A strange case of normocytic anemia

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ABSTRACT

This case-report underlines the difficulties of a correct diagnosis in a complex vitamin malnutrition that is seldom suspected in patients living in developed Countries with a good social and economic situation. A 79-year-old woman was admitted to hospital with progressive fatigue, dyspnea till orthopnea, pallor and lumbar pain. On physical examination the patient was awake, conscious and pale with severe dyspnea and the laboratory findings revealed severe anemia normochromic and normocytic; chest radiography shows cardiomegaly. An abdomen echography showed hepatomegaly and an increased gallbladder volume with multiple gallstones and "biliary mud". The patients received infusion of 4 Units of blood and started terapy for secondary congestive heart failure. The third day the temperature increased till 39°C and the urine of the patient shown clear hematuria; considering the hypothesis of hemolytic anemia was started methylprednisolone EV. Blood analysis was made in order to clarify anemia etiology: low blood levels of Vit B12, hypersideremia and very low Unsatured Iron Binding Capacity. A further investigation revealed that her diet had exclusively consisted of potatoes and fresh cheese since years. We started therapy with VitB12 and Folate and the patient was discharge fourteen days after admission. We feel that the importance of this clinical case lies in the diagnostic investigation for the cause of anemia, often more difficult than generally perceived.

Keywords: Normocytic Anemia; Multifactorial Anemia; Nutritional Anemia

1. INTRODUCTION

Anemia, as defined by the WHO criteria [1], affects 1 in every 7 or 8 individuals aged 65 years or over living in the community [2] and above 20% of subjects aged 85 years or older [3-4]. Of these about one-third reveals evidence of coincidental nutritional deficiency (iron, vitamin B12, and folate deficiency) [4].

Folate and vitamin B12 deficient anemia is normally known as machrocytic anemia [5] and is frequently found in elderly patients and in pregnancy. However, when different etiologies and diseases are present simultaneously, correct diagnosis is complex. This case reveals that exist some different situations in which this general classification isn't correct and is need pay attention to all clinical step.

2. CASE REPORT

A 79-year-old Italian woman was admitted to our ward for severe anemia in secondary congestive heart failure: she was suffering from progressive fatigue for 15 days, dyspnea till orthopnea, pallor and lumbar pain.

The patient lived with her sons, showed good hygienic conditions and normal BMI. She denied melena and hematemesis. Her history showed hypertension since she was 50 years old treated with beta-blockade. There was no family history of anemia or thalassemia.

On physical examination the patient was awake, conscious and pale with severe dyspnea, pulse rate was regular, 79 bpm. Blood pressure was 130/70 mmHg and peripheral arterial oxygen saturation 96% while breathing room air. Evidence of diffuse subcutaneous and perimalleolar edema was present. Respiratory system examination revealed that respiratory sounds were diminished in both lower zones. Rectal prolapse associated to external hemorrhoids without bleeding evidence was found by rectal exploration.

The laboratory findings (**Table 1**) revealed severe normochromic and normocytic anemia, mycrohematuria, leucocyturia, batteriuria an increased coagulation time and the bilirubin that was slightly increased both in direct and indirect form.

Chest radiography shows cardiomegaly, diffuse interstitial oedema and bilateral pleural effusion.

The patients received infusion of blood (4 Units) and

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started furosemide (20 mg EV/die), metoprolol (25 mg/die) and Vit K (5 drops/die).

After three days the patient getting physically better: oedema and dyspnea were improved, but blood cell count, bilirubin, platelets and kaliemia worsened (**Table 2**).

Table 1. Blood test screening upon admission.

		Normal value
WBC (10^9/l)	**7.49**	
Neu (%)	78.0	
Lyn (%)	16.8	4.00 – 10.00
Mon (%)	3.7	
Eos (%)	1.5	
Bas (%)	0.0	
RBC (10^{12}/l)	**1.52**	4.00 – 5.20
Hb (g/dl)	**4.1**	12.0 – 15.5
Hct (%)	**13.0**	37.0 – 47.0
MCV (fl)	**85.5**	80.0 – 95.0
MCH (pg)	**27.0**	27.0 – 32.0
MCHC (g/dl)	**31.5**	32.0 – 36.0
PLT (10^9/L)	**266**	140 – 400
Glycaemia (mg/dl)	**120**	60 – 110
Total Bilirubin (mg/dl)	**2.04**	< 1.00
Direct Bilirubin (mg/dl)	**0.87**	< 0.30
AST/GOT (UI/l)	**28**	< 37
ALT/GPT (UI/l)	**10**	< 40
GGT (UI/l)	**10**	5 – 36
Serum Creatinine (mg/dl)	**0.9**	0.70 – 1.20
Serum Sodium (mEq/l)	**138**	135 – 146
Serum Potassium (mEq/l)	**3.6**	3.5 – 5.3
Serum Clorum (mEq/l)	**106**	98 – 110
Total serum Calcium (mg/dl)	**7.7**	8.6 – 10.2
Total Cholesterol (mg/dl)	**53**	< 200
HDL (mg/dl)	**16**	> 40
Triglyceride (mg/dl)	**97**	< 170
C-reactive protein CRP(mg/l)	**2.1**	< 5.0
Total serum Protein (g/l)	**68**	66 – 87
Protein Electrophoresis (%)		
Albumin	58.1	55.8 – 66.1
Alfa 1 globulin	4.1	2.9 – 4.9
Alfa 2 globulin	6.8	7.1 – 11.8
Beta 1 globulin	5.5	4.7 – 7.2
Beta 2 globulin	5.1	3.2 – 6.5
Gamma globulin	20.4	11.1 – 18.8
TSH (mU/l)	**1.34**	0.270 – 4.200
CEA (ug/l)	**1.96**	< 4.0
CA 125 (KU/l)	**12**	< 35.0

Table 2. Blood test following appearance of oedema and dyspnea.

		Normal value
RBC (10^{12}/L)	**2.64**	4.00 – 5.20
HB (g/dL)	**8.4**	12.0 – 15.5
PLT (10^9/L)	**81**	140 – 400
Total Bilirubin (mg/dL)	**5.81**	< 1.00
Direct Bilirubin (mg/dL)	**2.23**	< 0.30
Potassium (mEq/L)	**2.7**	3.5 – 5.3

During the afternoon of the third day a temperature appeared with shiver that increased during the night till 39°C and the urine of the patient showed clear hematuria. Hemocoltures were negative but urinocolture reveals urinary tract infection caused by E. Coli. Blood samples showed a decreasing of Hb (7 g/dl) and an increasing of PCR (33.3 mg/l -nv < 5-) and of LDH (2340 UI/l -nv 230/460-). Aptoglobin was normal (0.3 g/l -nv 0.30/2.00-). Considering the hypothesis of hemolytic anemia was also started a methylprednisolone 40 mg/die EV. An abdomen echography showed hepatomegaly with dyshomogeneous parenchyma, remarkable increase gallbladder volume with multiple gallstones and and "biliary mud". Biliray tract wasn't dilated, spleen, pancreas, kidneys, uterus and other genital organs were normal. Right pleural effusion was confirmed at ultrasonography.

Thorax-abdomen TC excluded thoracic, abdominal and pelvic masses and revealed discreet bilateral pleural effusion, dilatation of cardiac cavities, gallbladder stones and calcification of aorta and renal artery. Patient refused gastrointestinal endoscopy. Other blood analysis showed an unexpected pattern (**Table 3**).

In order to clarify the exact anemia etiology we re-collected the medical history and discovered that the patient's diet have exclusively consisted of potatoes and fresh cheese since years.

We started therapy with VitB12 (1000 mg IM/die for a week), folate (1 injection/week for 3 months) and Prednisone (0,5 mg/Kg/die) for 30 days then gradual tapering. Patient was discharge fourteen days after admission in fairly good condition with an appropriate home therapy.

Table 4 shows laboratory analysis at the follow-up examination executed 2 years after the hospital discharge.

3. DISCUSSION

We consider this case report a good example of a multi-

Table 3. Blood test prior to dismissal.

		Normal value
Vit. B12 (ng/l)	**52**	197 – 866
Folate (ng/l)	**2.59**	3.1 – 17.5
PTH (ng/l)	**85**	10 – 75
Vit. D ng/ml	**< 7**	
fecal occult blood tests	**negative**	Negative
Serum Fe (µg/dl)	**239**	40 – 145
Ferritin (ng/ml)	**70**	30 – 300
Total Iron Binding Capacity (µg/dl)	**248**	228 – 428
Unsatured Iron Binding Capacity (µg/dl)	**9**	150 – 340

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Table 4. 2-year-follow up blood test screening.

		Normal value
WBC (10^9/l)	**9.49**	
Neu (%)	**65.0**	
Lyn (%)	**24.7**	4.00 – 10.00
Mon (%)	**8.0**	
Eos (%)	**1.9**	
Bas (%)	**0.3**	
RBC (10^{12}/l)	**4.32**	4.00 – 5.20
Hb (g/dL)	**15.2**	12.0 – 15.5
Hct (%)	**39.4**	37.0 – 47.0
MCV (fl)	**91.2**	80.0 – 95.0
MCH (pg)	**31.7**	27.0 – 32.0
MCHC (g/dL)	**34.8**	32.0 – 36.0
PLT (10^9/l)	**299**	140 – 400
AST/GOT (UI/l)	**14**	< 37
ALT/GPT (UI/l)	**9**	< 40
GGT (UI/l)	**24**	5 – 36
Serum creatininemia (mg/dl)	**0.85**	0.70 -1.20
Total Cholesterol (mg/dl)	**203**	< 200
HDL (mg/dl)	**44**	> 40
Triglyceride (mg/dl)	**126**	< 170
Serum Fe (ug/dl)	**109**	40 – 145
Ferritin (ng/ml)	**39**	30 – 300
Folate (ug/l)	**7.9**	4.60 – 18.70
Vitamin B12 (ng/l)	**154**	191 – 663
25OH-vit.D (ug/l)	**17.1**	Lack < 10
PTH (ng/l)	**40**	10 – 75
C-reactive protein CRP(mg/l)	**6.5**	< 5.0
Total Protein (g/l)	**69**	66 – 87
Protein Electrophoresis (%)		
Albumin	**50.2**	55.8 – 66.1
Alfa 1 globulin	**5.0**	2.9 – 4.9
Alfa 2 globulin	**12.5**	7.1 – 11.8
Beta 1 globulin	**6.8**	4.7 – 7.2
Beta 2 globulin	**6.4**	3.2 – 6.5
Gamma globulin	**19.1**	11.1 – 18.8

factorial anemia. Anemia is a common situation in elderly population and is very important recognized and treat the causes. Usually, we consider Mean Corpuscular Volume (MCV) an essential diagnostic tool in order to define what kind of anemia we are in front of. Nutritional anemia usually features abnormal MCV. On the contrary most of other anemias affecting the elderly like anem ias of chronic disease or chronic inflammation, renal failure are normocytic [6]. The patient didn't show malnourish aspect and both BMI and albumin were in normal range. On the other hand lipid state could underline a protein-energy malnutrition that is usually accompanied by lipid status decrease in all classical lipid parameters: total cholesterol, HDL cholesterol, apoproteins A1 and B [7]. We didn't investigate enough about patient diet and only in a second moment, after that laboratory exam hadn't revealed iron deficiency and neoplasm, we controlled folate and vitamine B12 values. Medical history of the patient represents the first step in order to suspect a nutritional origin; in this case the patient reveals an important situation of complex vitamin malnutrition that is seldom suspected in developing countries with a good social and economic situation. A severe folate and vitamine B12 deficiency could be explained by her diet which consisted only of potatoes and cream cheese for years. She didn't eat any meat, fish, fruit and green vegetable so that her intake of folate, vitamine B12, vitamine C, vitamine K and a lot of other micronutrients was not sufficient to sustain physiological metabolism. We have also to consider that gastric or ileal disruption of IF-mediated absorption causes 94% of cobalamin-deficiency anemia [8] but unfortunately the patient refused gastrointestinal endoscopy so we didn't confirm it.

Malnutrition causing anemia contributes also to develop Congestive Heart Failure (CHF). This is proved by that fact that CHF improved after therapy and didn't recidivate at two years after discharge.

The second step for a correct diagnosis is correct interpretation of laboratory exams. In this case normocytic anemia divert physician from a rapid correct diagnosis. In old patients anemia could depend by different causes that could overlap. The resolution of anemia only with Folate and vitamine B12 therapy suggest that deficiency of these nutrients was responsible for anemia. This fact makes more difficult interpretation of normocitosis. Some authors suggest that macrocytosis could fail to occur if a microcytic disorder coexists [9]. Most frequent microcytic anemia is due to iron deficiency. In this case one of the earliest biochemical change is a decrease in serum ferritin that our patient didn't show. Even so inflammation and other influences could increase ferritin value [10] so iron deficiency appears probable in the elderly when serum ferritin is below 45 ng/ml and tends to become unlikely only when ferritin exceeds 100 ng/ml [11]. The patient's ferritin was 70 ng/ml so iron deficiency couldn't be excluded. On the other side sideremia is a lot above normal value, Total Iron Binding Capacity (TIBC) is normale and Unsatured Iron Binding Capacity (UIBC) is well below of lower border. In addiction, the MCHC is normal. We concluded that with good probably this iron status was determined by increased delivery of iron in order to produce Hemoglobin which it couldn't be used by the deficiency of Folate and Vitamin B12. During admission the patient developed an urinary tract infection with important fever substained by E. Coli. This further hit developed an hemolytic anemia showed with macrohematuria, hemoglobin decreases from 8.4 g/dl to 7.3 g/dl, as such as platelets which decrease from 176×10^9/l to 81×10^9/l. Bilirubin increaseas till 5.81 mg/dl both in direct and indirect form. At last, hemolysis

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was confirmed by increase of inflammatory indexes like C-reactive protein (CRP), LDH and by low value of aptoglobin.

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