

## CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

### Hematology Quiz – Case 47

A 42-year-old woman was admitted to the hospital, because of persistent fever and severe anemia. The patient first presented fever approximately 30 days before her admission. Since then, she presented spikes of high temperature (39–40 °C) with rigor, almost every four days. The fever dropped spontaneously, with profound perspiration. During this period, she complained of severe fatigue and dyspnea during moderate physical effort. She had no cough or other symptoms or signs of localized infection. During the above period, sometimes she had noticed a dark color of her urine. Her chest x-ray was normal, and the urine cultures were negative. A broad-spectrum antibiotic had been administered, without any improvement. Seven months ago the patient had presented with fever and neck pain. A diagnosis of Hashimoto's thyroiditis was made then, but she had not been given thyroid hormones substitution. In the last six months the patient was not feeling very well. She was feeling tired easily, and therefore she was relaxing several hours every day. She experienced a lack of energy, which was confirmed by her relatives, as well as was a change of personality, becoming somehow depressive. She was also complaining of nocturnal cramps and pain in the upper and lower extremities. The patient was of Thailand origin, and she was working as a housekeeper. She had no particular nutritional habits.

On clinical examination, the patient appeared ill, with pallor and a lemon-tint icterus. Temperature was 38.3 °C, pulse was 105/min and respirations were 22/min. The blood pressure was 145/80 mmHg. Hair and skin appeared dry. Examination of mouth revealed a smooth tongue with one ulcer. In the neck examination the thyroid gland was enlarged. The liver was palpable, non-tender and smooth, and the spleen was also palpable, about 5 cm below the left costal margin. Neurologic examination revealed loss of positional sense in the index toes, and mildly reduced deep tendon, but no other major neurological sign.

Her hematology was as follows: Ht 24%, Hb 7.9 g/dL, MCV 109 fL, reticulocytes 3%, WBC 2.400/μL (neutrophils 65%, some with hypersegmented nuclei, lymphocytes 20%, eosinophils 3%, monocytes 5%, metamyelocytes 4%, myelocytes 3%) and PLT 95.000/μL. Red cell morphology is shown in figures 1 to 4. BUN and creatinine were within normal limits. ESR was 96 mm/h, LDH 1.890 IU/L, ferritin 900 ng/mL, haptoglobin 0.1 g/L, serum vitamin B<sub>12</sub> 300 ng/L, SGOT/SGPT 30/20 IU/L, bilirubin 4.6 mg/dL (conjugated 1 mg/dL), SAP 104 IU/L, γGT 36 U/L. Serum electrophoresis revealed polyclonal hypergammaglobulinemia. Urine: hemoglobin +++, hemosiderin +. Bone marrow morphology is shown in figures 5 to 8. HIV antibodies were negative; HBsAg was negative.

ARCHIVES OF HELLENIC MEDICINE 2016, 33(3):425–427  
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2016, 33(3):425–427

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The patient was started the appropriate therapy for her febrile disease, and hematinics *per os* for her anemia. One week later she was afebrile and a reticulocyte crisis was observed with a rapid increase of the hemoglobin level.

#### Comment

*In human malaria, three species are recognized: Plasmodium falciparum (malignant tertian), P. vivax (benign tertian) and P. malariae (quartan) malaria. In human blood, asexual as well sexual forms can be found. The trophozoite appears as a "blue ring" formation including a red nucleus. As it develops within the erythrocyte, the latter ruptures discharging in this way the daughter merozoites into the blood stream. These are capable of rapidly invading other red cells, thus repeating the parasite cycle.*

*P. falciparum causes a much more intense hemolysis compared to the other species, while all of them preferably affect reticulocytes, as well as younger red cells. The extent of hemolysis and the severity of anemia are greater and lower, than that caused by a single rupture of parasite, including red cells. Plasmodium carrying cells are destroyed (intravascular rupture, extravascular phagocytosis of the corpuscle remnant soon after the parasites are removed).*

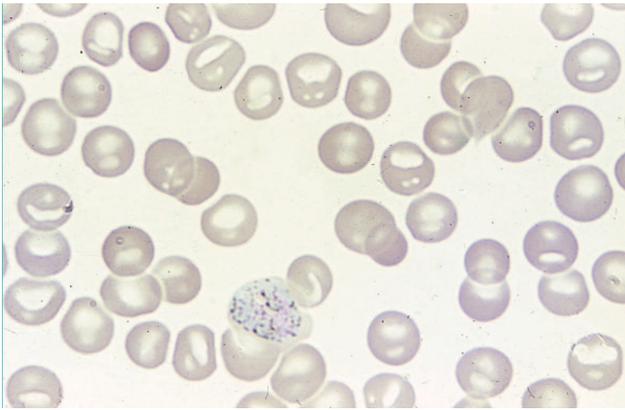


Figure 1



Figure 4

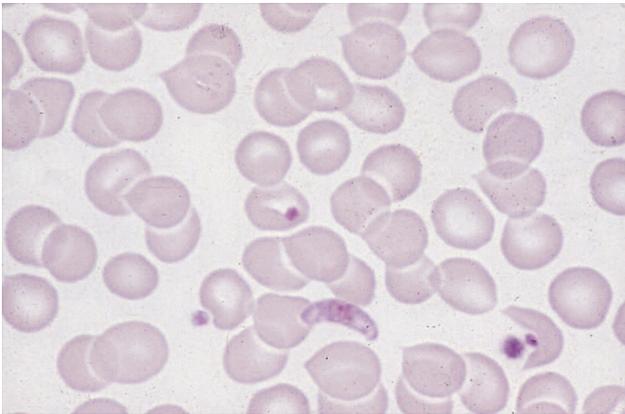


Figure 2

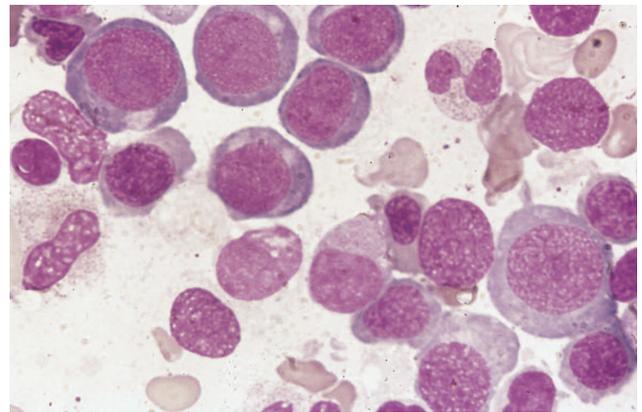


Figure 5

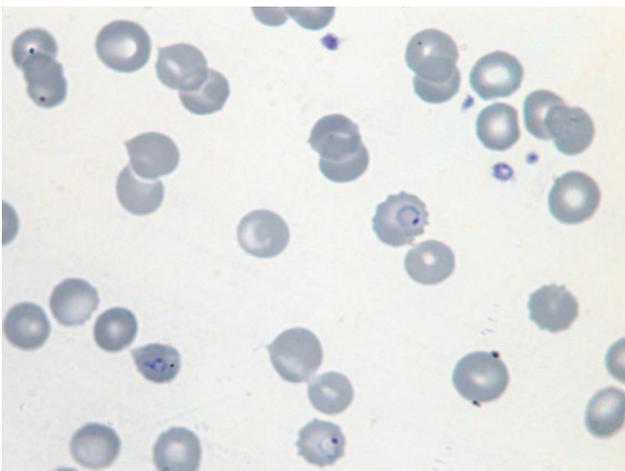


Figure 3

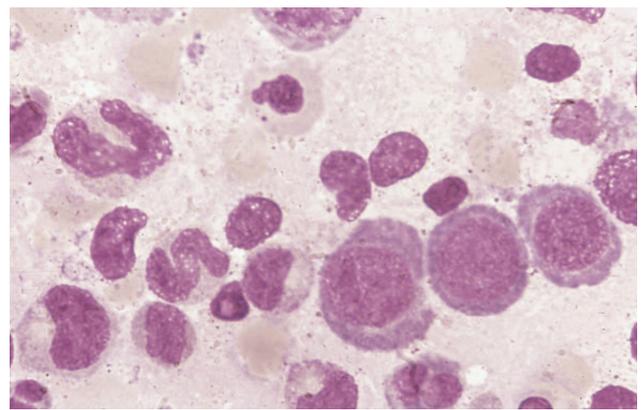


Figure 6

*Erythroblasts and younger erythrocytes are intramedullarily destroyed due to enhanced phagocytic activity, hypersplenism, as well as immune hemolysis and finally, follates usually become insufficient.*

*Vitamins B<sub>12</sub> or follic acid deficiency result in the same disturbances of bone marrow and peripheral blood cell morphology.*

*Follates and vitamin B<sub>12</sub> are implicated in purine and pyrimidine synthesis and in DNA and RNA production as well.*

*Follates (follic acid and its derivatives): The daily requirements are 50–100 µg. In a normal feeding, the follates supply with the alimentation is fairly sufficient. The requirements are highly increased*

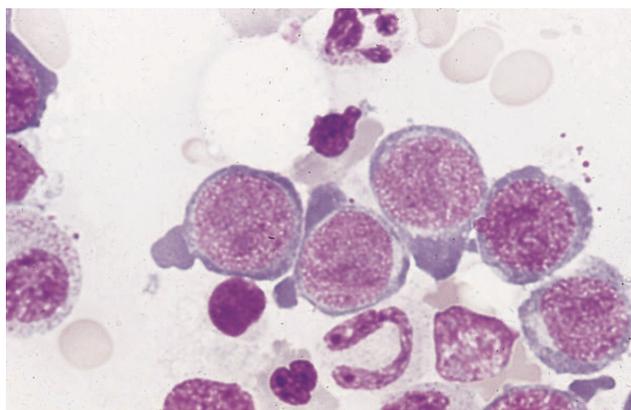


Figure 7

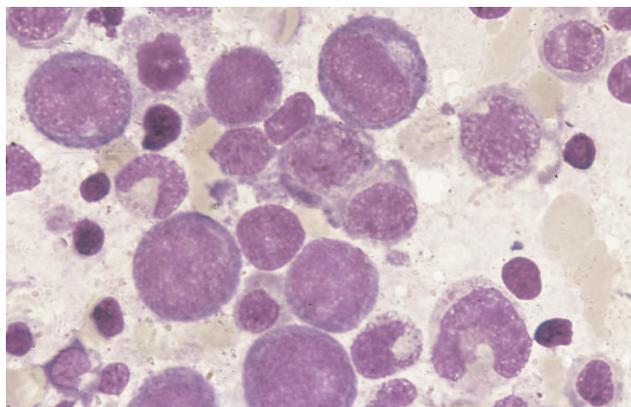


Figure 8

during pregnancy, suckling and infant body development. Serum folates are decreased in patients with folate deficiency but the serum level is affected significantly by recent alimentation; they are also increased in cases of severe vitamin B<sub>12</sub> insufficiency, while they can be false lower in the administration of drugs inhibiting *Lactobacillus casei* growth in vitro (method of folate measurement).

Vitamin B<sub>12</sub> (within this term, there are many cobalamines, with a porphyrin like structure). The daily requirements are 2–4 µg. In normal feeding there is usually much more vitamin quantity according to the normal requirements. There is need of specific proteins of transportation which participate in its absorption and circulation. There are many extracellular proteins (intrinsic factor, transcobalamines I, II and III). For cobalamin release, after feeding a proteolysis of low gastric pH is necessary. The vitamin is released from the protein transporter with pepsin and HCl action in the stomach; following this release, cobalamin is coupled with preference with a protein of saliva (R protein) in the presence of intrinsic factor (IF) released by the parietal cell of the stomach.

Folic acid and vitamin B<sub>12</sub> insufficiency result in decrease of

DNA synthesis with consequences mainly on the cells of quick regenerative tissues.

- Anemia (sometimes severe) normochromic and high macrocytic (often a MCV value up to 130 fL) without reticulocytosis. In the peripheral blood smear macrocytosis (macrocytes and ovaloid macrocytes), anisocytosis, polychromatophilia, basophilic stippling (presence of nucleic acids in the red cells) and Howell-Jolly bodies or Cabot rings are present.
- Leukopenia or neutropenia (with neutrophils of larger size and hypersegmented nucleus). The presence of hypersegmented neutrophils is a useful diagnostic finding, although present rarely and in cases of iron deficiency anemia, and during renal insufficiency with normal vitamin levels.
- Thrombocytopenia with the presence of rare giant platelets.
- Bone marrow: The bone marrow smear is blue after staining (presence of high numbers or primitive cells with increased RNA content) and hypercellular with decrease of adipocytes. The erythroid series is hyperplastic (up to 50% of myeloid cells), a finding which is in contrast with the decreased reticulocytes number (ineffective erythropoiesis) with a predominance of more immature forms (shift to the left of the erythroid series). Despite the increased bone marrow activity, most of erythroid series cells do not arrive in the mature erythrocyte level but there is an intramyelic destruction (ineffective erythropoiesis). This maturation insufficiency is due to a DNA insufficient synthesis during mitosis (the cells in an attempt to divide do not preserve the appropriate DNA content and thus expire their life span).

## References

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**Diagnosis:** Plasmodium falciparum malaria; megaloblastic anemia (folic acid deficiency)