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Authors:	Daniela BADEA Smaranda MITRAN Amelia GENUNCHE-DUMITRESCU Marius Cristian MARINAȘ Aurelian Adrian BADEA Tiberiu ȚENEA COJAN

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ANEMIA OF CHRONIC DISEASE - A DIAGNOSIS NOT ALWAYS EASY

Daniela BADEA[1]
Smaranda MITRAN[2]
Amelia GENUNCHE-DUMITRESCU[3]
Marius Cristian MARINAȘ[4]
Aurelian Adrian BADEA[5]
Tiberiu ȚENEA COJAN[6]

ABSTRACT:
ANEMIA OF CHRONIC DISEASE (ACD)- THE TYPE OF ANEMIA THAT IS THE SECOND MOST COMMON AFTER IRON-DEFICIENCY ANEMIA, AND IS CAUSED BY IMMUNITY[7]. CYTOKINES AND CELLS OF THE RETICULOENDOTHELIAL SYSTEM INDUCE CHANGES IN: IRON HOMEOSTASIS, ERYTHROID PROGENITOR CELLS PROLIFERATION, ERYTHROPOIETIN PRODUCTION AND RED BLOOD CELL LIFE; ALL THIS CONTRIBUTES TO THE PATHOGENESIS OF ANEMIA. PARACLINICAL DIAGNOSIS OF ACD REVEALS NORMOCYTIC NORMOCHROMIC HYPOREGENERATIVE ANEMIA, OR MICROCYTIC HYPOCHROMIC HYPOREGENERATIVE ANEMIA. DIAGNOSIS OF OTHER TYPES OF SUCH ANEMIAS, IS NOT ALWAYS EASY.

KEY WORDS: ANEMIA, ERYTHROPOIETIN, IRON-DEFICIENCY.

INTRODUCTION

Anemia of chronic disease (ACD) is not only associated with infectious, inflammatory or neoplastic diseases, but also with a variety of other pathological conditions, such as: severe trauma, heart failure, diabetes mellitus and anemia in elderly or those with acute or chronic immune activation[7]. This type of anemia is usually a mild (hemoglobin level, 9.5 g/dl) to moderate (hemoglobin level, 8 g/dl) one, hypo proliferative, normochromic, normocytic and

[1] Clinical Hospital of Emergency Craiova, Department of Physiology, University of Medicine and Pharmacy Craiova, Romania
[2] Department of Physiology, University of Medicine and Pharmacy of Craiova
[3] Clinical Hospital of Emergency Craiova, Department of Internal Medicine, University of Medicine and Pharmacy of Craiova
[4] Clinical Hospital of Emergency Craiova, Department of Anatomy, University of Medicine and Pharmacy of Craiova
[5] Clinical Hospital of Emergency Bucharest, resident physician
[6] CFR Hospital, Department of Surgery, University of Medicine and Pharmacy of Craiova

is characterized by: blockage of iron in the macrophages, inability to increase erythropoiesis in response to anemia, a relative decrease in erythropoietin (EPO) synthesis and an abnormal decrease in red blood cell survival[7].

At the same time, the evaluation of anemia in chronic disease must include a determination of the status of whole-body iron in order to rule out iron-deficiency anemia, usually hypochromic and microcytic[8].

MAIN TEXT

Proinflammatory cytokines (IL-1, IL-6, TNF-α, IFN, Hepcidin) are responsible for most of the abnormalities above described. Hepcidin, an acute phase protein, is involved in iron metabolism: it is the factor that causes a decrease in iron absorption in the small intestine, iron transport across the placenta, as well as iron release from macrophages[9]; secondly, it regulates the internalization and degradation of the iron export protein – ferroportin[10]. Hepcidin synthesis is controlled by serum iron concentration, erythropoietic factors and IL-6/bacterial lipopolysaccharides[11] *(figure 1).*

In patients with anemia of chronic disease, the proliferation and differentiation of erythroid precursors - erythroid burst-forming units and erythroid colony-forming units - are impaired[12] and are related to the inhibitory effects of interferon-α, -β şi -γ, TNF-α and IL-1. Interferon-γ appears to be the most potent inhibitor[13], as reflected by its inverse correlation with hemoglobin concentrations and reticulocyte count[14].

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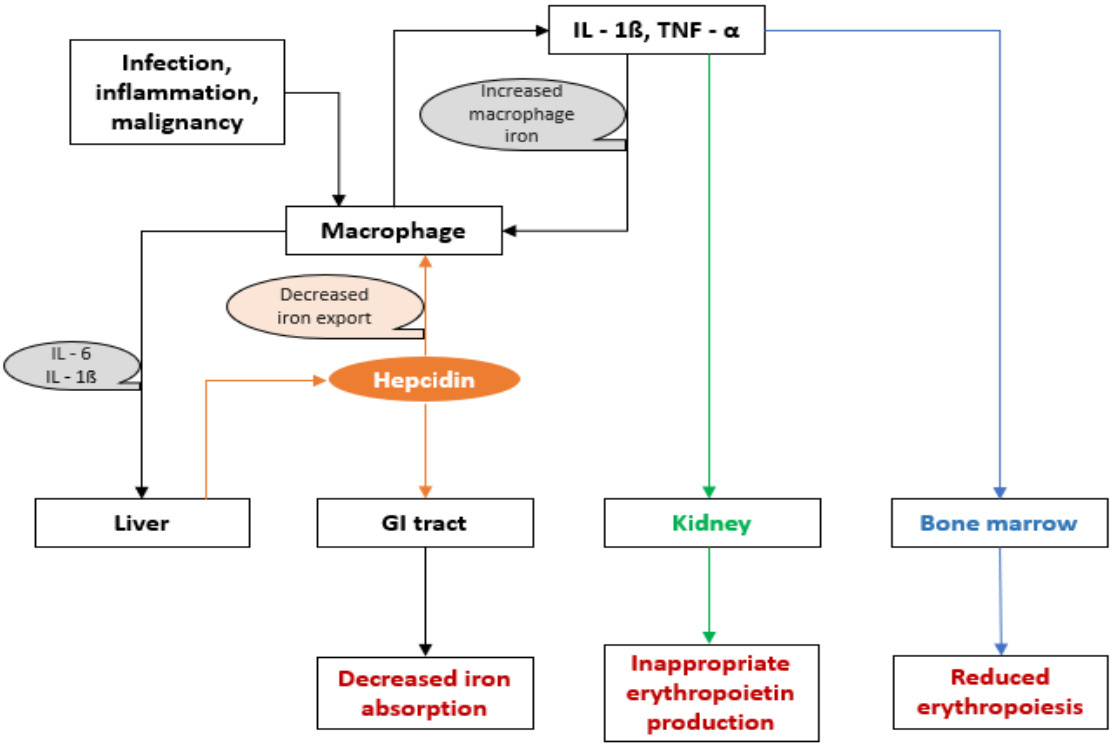

Figure 1. Proinflammatory cytokines responsible for abnormalities in ACD

The pathogenic mechanisms of ACD are represented by: *cytokine-mediated abnormalities* with decreased erythropoietin production, decreased medullary response to erythropoietin and altered iron metabolism[15]; *myelosuppression caused by chemotherapy*, with suppression of erythropoietin production and suppression of hematogenous marrow[16]; *blood loss*; *nutritional deficiencies*; *hemolysis* generated by medication, microangiopathy or autoimmune.

Iron plasma concentration:

INPUT:

- Duodenal iron absorption (1-2 mg/day);
- Recycled iron from the hemoglobin of senescent erythrocytes (20 mg/day);
- Mobilization of iron from warehouses (a few mg/day, depending on needs).

OUTPUT

- Hemoglobin;
- Myoglobin;
- Redox enzymes;
- Other proteins that incorporate iron.

Professional iron exporting cells are represented by: hepatocytes, duodenal enterocytes, cells of the monocyte-macrophage system or placental trophoblastic syncytium.

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Relative decrease in erythropoietin production in ACD.

In ACD, erythropoietin production is slightly increased, but, at the same degree of anemia, below the level shown in case of iron deficiency. The effect of this increase on erythropoiesis is minimal or absent, probably due to increased inhibition/apoptosis of erythroid precursors[17].

Also, proinflammatory cytokines diminish/abolish the effect of increasing EPO gene expression generated by hypoxia; at the same time, erythrophagocytosis is increased[18].

Not all researchers agree with this mechanism (at least in certain situations: *e.g.* in children), considering that, in the foreground, is the reduction of the medullary response to erythropoietin.

The paraclinical diagnosis of ACD highlights a hyporegenerative anemia, with normocytic normochrome or microcytic hypochromia, following the calculation of the corrected number of reticulocytes and the erythrocyte production index. Ferritin level is normal/high, but there are also present: normal/low transferrin saturation (20%), low sideremia and total iron binding capacity (TIBC), reduced percentage of sideroblasts/iron absent in most erythroblasts, presence of iron in medullary macrophages and increased IL-6, protein C, fibrinogen and ESR (Erythrocyte Sedimentation Rate).

The differential diagnosis is made with other types of normocytic normochromic anemias (chronic kidney disease, endocrine diseases - hypo / hyperthyroidism, primary and secondary hyperparathyroidism) and with microcytic hypochromic anemias (iron deficiency anemia, thalassemias, hemoglobinopathy E, congenital or acquired sideroblastic anemia from myelodysplastic syndrome, alcoholism, drugs, lead poisoning).

The difference between anemia of chronic disease and iron-deficiency anemia

Iron-deficiency anemia (IDA) is an anemia caused by low iron stores in the body, while ACD is a functional anemia of iron-restricted erythropoiesis related to diseases such as infections, inflammations, cancer, autoimmune diseases etc.

Thus, in iron deficiency from ACD, level of ferritin is normal or high, reflecting the fact that iron is sequestered within cells, and ferritin is being produced as an acute phase reactant. In iron deficiency anemia, ferritin level is low[19].

The difference between anemia of chronic disease and iron-deficiency anemia relates to the latter, as the result of an absolute iron deficiency, whereas the pathophysiology of anemia of chronic disease is multifactorial. In both, anemia of chronic disease and iron-deficiency anemia, serum iron concentration and transferrin saturation are reduced; this reflects the absolute iron deficiency in iron-deficiency anemia and hypoferremia due to acquisition of iron by the reticuloendothelial system in anemia of chronic disease[20].

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In the case of anemia of chronic disease, the decrease in transferrin saturation is primarily a reflection of low serum iron levels. In iron-deficiency anemia, transferrin saturation may be even lower because serum concentrations of the iron transporter transferrin are elevated, while in anemia of chronic disease transferrin levels remain normal or low[21].

The soluble transferrin receptor (sTfR) is increased in IDA, when the availability of iron for erythropoiesis is low[22]. In contrast, levels of soluble transferrin receptors in ACD are not significantly different from normal, because transferrin-receptor expression is negatively affected by inflammatory cytokines[23]*(table 1):*

Variable	**Anemia of chronic disease**	**Iron-deficiency anemia**	**Both conditions****
Iron	reduced	reduced	reduced
Transferrin	reduced to normal	increased	reduced
Transferrin saturation	reduced	reduced	reduced
Ferritin	normal to increased	reduced	reduced to normal
Soluble transferrin receptor (sTfR)	normal	increased	normal to increased
Ratio of soluble transferrin receptor / log ferritin	low (<1)	high (>2)	high (>2)
Cytokine levels	increased	normal	increased

*Table 1. Serum levels that differentiate anemia of chronic disease from iron-deficiency anemia**
** Relative changes are given in relation to the respective normal values.*
*** Patients with both conditions include those with anemia of chronic disease and true iron deficiency.*

Compared to patients with only anemia of chronic disease, those with anemia of chronic disease and concomitant iron-deficiency, have more frequent microcytic anemia and it tends to be more severe. Some authors have argued that sTfR assessment can distinguish between IDA and ACD, but other studies deny that[24]. The ratio of sTfR to log ferritin (TfR-ferritin index) < 1.0, suggests the diagnosis of ACD, while an index >2.0, suggests either IDA, or IDA associated with ACD *(figure 2).* Reticulocyte hemoglobin content < 26 pg/cell is a reliable indicator of iron deficiency. The bone marrow shows a small number of sideroblasts, in the context of a normal or increased amount of iron stored in macrophages.

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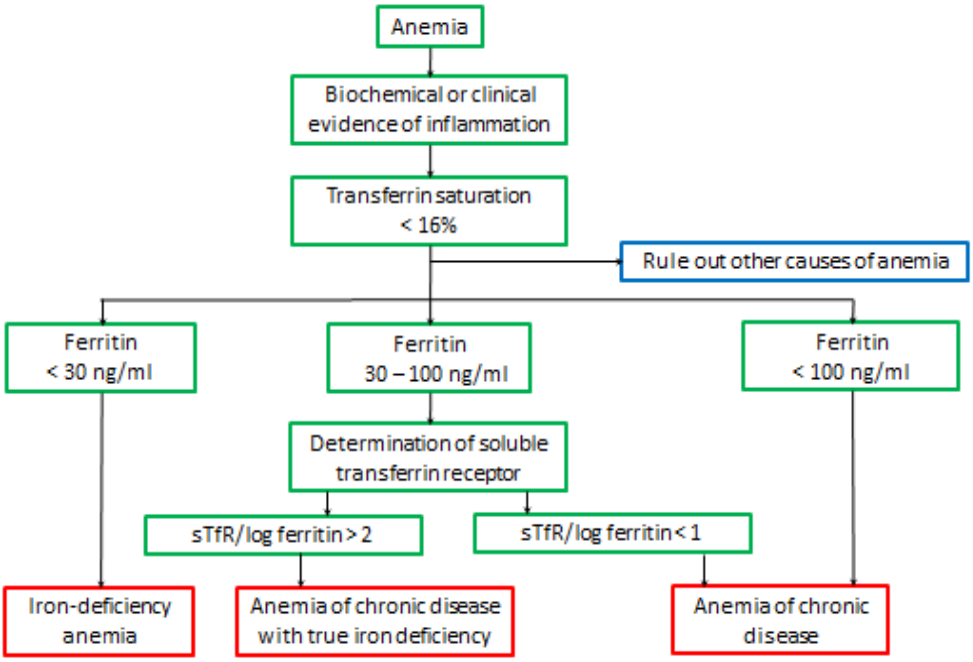

Figure 2. The difference between anemia of chronic disease and iron-deficiency anemia

CONCLUSION

Advances in understanding of the pathophysiology of ACD, including disturbances of iron homeostasis, impaired proliferation of erythroid progenitor cells and erythropoietin response to anemia, have made possible the emergence of new therapeutic strategies. These include treatment of the underlying disease and the use of erythropoietic agents, iron, or blood transfusions.

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