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Anemia of chronic diseases: a verdict or a protective reaction of the body?

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Abstract

Anemia of chronic disease occurs in patients with infectious, autoimmune, kidney diseases, neoplasia, inflammatory bowel disease, obesity, diabetes mellitus, congestive heart failure, and chronic lung disease. This variant of anemia is characterized primarily by impaired iron homeostasis, the suppressive effect of pro-inflammatory cytokines on erythropoiesis, and changes in the erythrocyte membrane that worsen their survival. Anemia of chronic disease is micro- or normocytic anemia with low levels of reticulocytes. In anemia of chronic disease, serum iron and transferrin levels are usually reduced or normal, and serum ferritin levels are within reference values or elevated. The article provides a review of studies on epidemiology, including age aspects, provides information on the etiology and prognosis in patients with anemia of chronic diseases. The issues of the history of anemia of chronic diseases and its place in the structure of all anemias are also covered. Anemia of inflammation is recognized as a widespread pathology; it occupies 40% in the structure of all anemias. It is important to note that anemia of chronic diseases, while accompanying a number of dangerous diseases, actually serves as a natural defense mechanism. This is due to the occurrence of "iron starvation" for microorganisms, since inflammatory reactions increase the synthesis of iron proteins, which quickly extract extracellular and unbound iron. This mechanism allows a person to destroy the infection in time with the help of innate immunity. The article reveals the pathogenetic aspects of anemia of inflammation development and data on the role of iron in the functioning of macro- and microorganisms. Particular attention is paid to the differential diagnosis of anemia of chronic diseases and iron deficiency anemia, key diagnostic hematological markers of anemia, iron metabolism, inflammation and erythropoiesis are given. The pros and cons of therapy options, as well as possible new pathogenetic methods for the treatment of anemia of chronic diseases, are described.

Keywords: anemia of chronic diseases, transferrin, ferritin, ferroportin, hepcidin.

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Background

Anemia of chronic disease (ACD, commonly known as chronic anemia, anemia of inflammation, cytokine-induced anemia, or anemia of iron redistribution) is a body response caused by the release of cytokines (tumor necrosis factor, interleukin-1 and interleukin-6, and interferon), which mediate the inflammatory and immune response. ACD is a well-known disease, accounting for 40% of all types of anemia [1].

According to the literature, ACD occurs in a wide range of patients with long-term immune activation diseases, such as infections, autoimmune diseases, and cancer, and it also develops in chronic kidney disease (CKD), inflammatory bowel diseases, congestive heart failure, chronic pulmonary diseases, and obesity.

Concomitant anemia in chronic disease was first described in 1842 when French researchers found a reduction in the mass of red blood cells in patients infected with smallpox. After further monitoring of patients with typhoid fever, tuberculosis, and syphilis, Maxwell Wintrobe and George Cartwright (1949) introduced the term "anemia of inflammation," [2] and in 1952, ACD began to be regarded as an independent nosological entity.

Eugene Weinberg proposed in the early 1980s that iron is required for the vital functions of all living organisms, including bacteria and tumor cells. On the basis of this theory, we can conclude that anemia of the inflammatory response is a natural protective mechanism aimed at limiting free iron (Fe^{3+}) in the blood when pathogenic microorganisms enter, which is achieved through iron

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binding to lactoferrin and iron deposition (ferritin). The synthesis of ferritin and lactoferrin increases during inflammatory processes, resulting in iron deficiency, which reduces the growth of pathogenic microorganisms [3–7].

Epidemiology

According to the World Health Organization, anemic syndrome affects one out of every three people globally. ACD is the second most common cause of anemia after iron deficiency anemia (IDA) and appears more often in the elderly [8]. According to McCranor et al. (2013), inflammation is responsible for 10%–32% of anemia in elderly patients due to increased levels of circulating interleukin-6 with age [9].

Joosten and Lioen (2015) revealed that ACD was diagnosed in 70% of hospitalized elderly patients with anemia ($n = 191$). In this patient group, the most common cause was acute inflammation (71%), followed by chronic infection (16%) and cancer disease (12%) [10].

In a retrospective study, V.V. Cherepanova found an increase in the proportion of anemia in elderly patients ($n = 1,789$). ACD accounted for 62.5% of all cases of anemia. Analysis of anemia structure by etiology showed that ACD was diagnosed in 39.4% of patients hospitalized in the therapeutic department, whereas the etiology of anemia was not established in 26.5% of patients, with IDA and megaloblastic anemia accounting for 27.3% and 8.6%, respectively [11].

Etiology

The classification by etiology should be used to determine the position of ACD in the structure of all types of anemia. Group 1 anemia is characterized by a lack of iron, vitamin B_{12}, and folic acid. ACD is classified as group 2, anemia associated with diseases characterized by low-grade inflammation (autoimmune, infectious inflammatory, and neoplasms). Group 3 anemias are known as "hematological" anemias because they are associated with reduced bone marrow function or increased erythrocytosis. This grading of anemia is intended to determine the treatment approach, where patients with "deficient" anemia are often handled by a general practitioner, patients with group 2 anemia are treated by a specialist in the specialty of the underlying disease, and patients with group 3 anemia are treated by a hematologist [12].

The most common causes of ACD are acute and chronic infectious processes of viral, bacterial, fungal, or parasitic etiology. Tumors, particularly hemoblastosis, are the second leading cause of ACD. Autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, have a specific role in the structure of ACD etiology. ACD occurs less often in patients with chronic transplant rejection, CKD, chronic heart failure (CHF), and diabetes mellitus [13–16].

ACD in patients with CKD is caused by chronic inflammation associated with a high incidence of infectious diseases, increased levels of pro-inflammatory cytokines, and a uremic environment. It is also worth noting that the severity and prevalence of anemia increase with the CKD stage [17].

Anemia in CHF patients is caused by several pathogenetic mechanisms, including deficiency of alimentary iron and reduced absorption due to chronic inflammation, decreased erythropoietin synthesis, and poor sensitivity. IDA is most commonly diagnosed in CHF; however, ACD is detected in several patients with severe heart failure due to iron salvage from macrophages, suppression of erythropoiesis by pro-inflammatory cytokines that suppress the action of erythropoietin, and inadequate production of erythropoietin [18–20]. Several studies have found that the prevalence of anemia in CHF patients ranges from 15% to 55%, and it is related to renal dysfunction and decreased erythropoietin secretion [21]. According to a meta-analysis, the prevalence of anemia in CHF patients ($n = 153,180$) was 37.2% [22].

According to the literature, ACD can coexist with iron deficiency in some cases, which impairs the functioning of the cardiovascular system in patients with CKD and congestive heart failure [23]. In CHF and CKD, the development of anemia worsens the prognosis. Silverberg et al. [24] proposed the term "cardiorenal anemic syndrome," with each of the three components aggravating the course of the other two.

ACD is given special consideration in obese patients. With high levels of pro-inflammatory cytokines and acute phase proteins, adipokine production in such patients stimulates hepcidin synthesis, whose pathogenetic role is to reduce iron absorption in the intestine and iron sequestration in macrophages. Consequently, iron redistribution occurs, which is not involved in hemoglobin synthesis but in cell activation in the case of inflammation, resulting in "relative iron deficiency," characteristic of ACD [25].

Anemia of inflammation is a common cancer manifestation. Anemia was observed in 63.4% of 888 patients with carcinomas in a study. The severity of anemia has been shown to correspond with the stage of a cancer disease [26].

Pathogenesis

ACD is multifaceted, including changes in iron metabolism, impaired erythropoiesis, decreased

regulation of the response to erythropoietin, and a combination thereof [15]. Iron is responsible for erythropoiesis due to abnormal iron metabolism, which traps it in reticuloendothelial cells. Impaired erythropoietin secretion and shortened erythrocyte lifespan also contribute to ACD pathogenesis. Notably, the contribution of each of the mechanisms above may vary in different patients, depending on several factors, such as the cause of inflammation, the patient's somatic status, and the presence of concomitant diseases [27].

The main pathogenetic pathways mediated by immune system mediators are as follows. Changes in iron metabolism are component 1 of the pathogenesis of ACD. Iron response element (IRE) and iron response protein (IRP) ensure iron homeostasis at the posttranscriptional level. During iron deficiency (which occurs with IDA), the association of IRE with IRP in cells is stimulated, preventing ferritin synthesis. The interaction of IRE with IRP is significantly reduced in cells with high metabolically active iron [28].

Immune cells release multiple inflammatory cytokines and alter systemic iron metabolism in response to microbial agents, autoantigens, or tumor antigens, resulting in iron retention in macrophages and decreased dietary iron absorption. Interleukin-6 and interleukin-1β are important cytokines that mediate the effects of inflammation on developing red blood cells. Thus, interleukin-6 stimulates the synthesis of hepcidin, the main regulator of iron metabolism, by hepatocytes. The hepcidin gene is activated as the labile iron pool increases. This has the following effects [29]:

– decreased iron absorption in the duodenum,

– the inability of macrophages to release iron, and

– a reduction in the ability of the bone marrow's erythroid lineage to metabolize iron.

As a result, low iron concentration impairs erythroid cell maturation, resulting in impaired haem synthesis.

Given those mentioned above, increased hepcidin levels in the blood cause iron deficiency. This is also facilitated by increased ferritin levels and iron retention in macrophages caused by pro-inflammatory cytokines. Interleukin-1β has also been implicated in the production of lactoferrin, which binds free iron and is subsequently deposited in macrophages. However, the primary source of iron for macrophages is aging red blood cells. Cytokines, radicals produced from the focus of inflammation, and complement factors damage red blood cells while promoting erythrophagocytosis by stimulating receptors that detect aging red blood cells [30].

The impaired proliferation and differentiation processes of erythropoiesis cells are also critically important factors in the development of ACD. As receptor expression decreases, cytokines reduce erythropoietin formation. Interleukin-6 and activin B increase hepcidin expression.

It is also vital to consider the negative impact of acute phase proteins, which can bind transferrin and reduce iron binding to transferrin by erythropoiesis precursors. Ferritin also has an antiproliferative effect. However, its mechanism is unknown; it is believed to be related to iron availability for erythroid precursors. Reduced cobalamin and folic acid levels in the human body can also contribute to the progression of anemia. In cancer patients, in addition to the factors mentioned above, the degree of anemia is also affected by chemotherapy treatment, which worsens its course [31].

It has been demonstrated that patients with cancer disease have a higher concentration of soluble transferrin receptor (sTFR) in the presence of anemia than patients without it. Maximum sTFR levels are found in comparing laboratory parameters (hepcidin, ferritin, C-reactive protein, and sTFR), indicating a lack of iron for erythropoiesis. Park, Jung, and Kim [32] propose that the pathogenetic mechanism described above is critical in the development of ACD.

The most important factor in anemia is a decrease in the formation of erythropoietin and a reduction in its bioactivity. It can be induced by cytokines, which cause the formation of toxic radicals that prevent the production of erythropoietin [12].

Thus, ACD is caused by altered iron metabolism, pro-inflammatory and anti-inflammatory cytokine activity, shortened erythrocyte survival, reduced erythropoietin response to anemia, impaired formation of erythroid colonies in response to erythropoietin, and abnormal mobilization of reticuloendothelial iron stores [31].

Diagnostics

In most cases, ACD is normochromic and normocytic in nature; it is less often hypochromic and microcytic; not all hypochromic anemias are iron deficient. This must be considered because the treatment approach for ACD and IDA differs [33].

The presence of hypochromia can be determined by an automatic hematological analyzer using such parameters as the mean corpuscular volume and mean corpuscular hemoglobin, which does not deviate from reference values in the case of ACD (the mean corpuscular hemoglobin is 27.0–34.0 pg and the mean corpuscular volume is 80.0–100.0 fl). ACD develops hypochromic (mean corpuscular hemoglobin of <27.0 pg) with a long underlying disease course.

In addition, other hematological indices that reflect the hemoglobin content in mature ery-

Table 1. Laboratory parameters for diagnosing anemia of chronic diseases (ACD) and iron deficiency anemia (IDA)

Indicator	ACD	IDA	ACD + IDA
Hemoglobin level	Reduced	Reduced	Reduced
Serum iron level	Normal or reduced	Reduced	Reduced
Total iron-binding capacity	Normal or reduced	Increased	Reduced or lower limit of normal
Transferrin saturation	Reduced	Reduced	Reduced
Serum ferritin level	Normal or increased	Reduced	Increased
sTFR level	Normal	Increased	Normal or increased
Ratio of sTFR to the logarithm of ferritin (sTFR index)	Low or normal (<1)	Increased (>2)	Increased (>2)
Blood serum level of pro-inflammatory cytokines (C-reactive protein and procalcitonin)	Increased	Normal	Increased
Serum hepcidin level	Increased	Reduced	Normal
Growth differentiation factor 15	Increased	Normal	Increased
Erythropoietin level	Normal or slightly increased	Increased	Normal or increased

Note. ACD, anemia of chronic diseases; IDA, iron deficiency anemia; sTFR, soluble transferrin receptor.

throcytes and reticulocytes exist, including the proportion of hypochromic erythrocytes (%), the proportion of erythrocytes with a hemoglobin concentration of less than 280 g/L (%), the proportion of erythrocytes containing less than 17 pg of hemoglobin (%), the proportion of erythrocytes with low hemoglobin density (%), reticulocyte cellular hemoglobin content, average hemoglobin content in a reticulocyte, and reticulocyte hemoglobin equivalent. Iron deficiency is indicated by an increase in the content of hypochromic erythrocytes of more than 5%–6% or a decrease in the hemoglobin content in reticulocytes of less than 29 pg [34].

When obtaining a final diagnosis of ACD, it is necessary to rule out other causes of anemia, such as internal blood loss and traumatic hemorrhage. ACD is characterized by reduced serum iron levels and inadequate iron saturation of transferrins. The count of sideroblasts in bone marrow puncture samples is reduced to 5%–20%, with the norm being 30%–50%. The count of hemosiderin-containing macrophages increases, except for the combination of ACD and IDA. The serum ferritin level is increased in ACD patients; however, with concomitant iron deficiency, it can decrease without reaching low levels, as in IDA.

A decrease in serum ferritin levels of less than 30 μg/L in ACD patients may indicate iron deficiency. ACD and IDA differentiation is complex and performed based on several parameters. An important diagnostic criterion is the detection of sTFR in blood serum, whose content decreases in ACD and increases in IDA. Another criterion is increased pro-inflammatory cytokine (C-reactive protein and procalcitonin) levels in ACD patients, which is not observed in IDA. It should also be noted that the total iron-binding capacity of the blood serum is normal or reduced in ACD, which is not typical for IDA wherein this parameter increases.

Determining the etiology of anemia in a patient (ACD or IDA) is extremely important in practice because incorrect interpretation of the results can result in the prescription of ineffective iron treatment, which can lead to the development of complications in the form of iron overload (Table 1) [35].

Treatment

In most cases, effective treatment of a chronic disease that contributes to the development of anemia results in the normalization of altered hematological parameters. When treatment for the underlying disease is ineffective, treatment for anemic syndrome is performed in three directions.

Direction 1 is blood transfusion, which is recommended for all patients with severe anemia (hemoglobin level of less than 70 g/L). Even in the most severe cases of ACD, there is often no need for blood component transfusion associated with the duration of the ACD course and patient adaptation. This ACD treatment is only advised in life-threatening cases, such as cardiovascular system decompensation, acute blood loss, and hematological diseases. It is important to remember that hypervolemia can cause an increase in the severity of anemia [36].

However, others question the validity of transfusion treatment. First, its effect is short-term, with a sufficient number of complications, such as al-

lergies and anaphylactic shock. Second, as with any blood transfusions, there is a risk of infection from the human immunodeficiency virus and viral hepatitis. Third, repeated blood transfusions inhibit erythropoietin production, which is detrimental to erythropoiesis [14].

Direction 2 is the prescription of iron supplements, which rationality cannot be stated unambiguously. Ferrotherapy is known to produce highly toxic hydroxyl radicals. They can damage tissues and cause endothelial dysfunction. These changes increase the risk of developing cardiac diseases [14]. At the same time, iron is an essential component of the cell's most important metabolic processes, and it should be used promptly in treating ACD in cases of an absolute iron deficiency. Simultaneously, active infectious agents require iron for their growth and reproduction [36].

It is important to remember that iron treatment suppresses the immune system. Excess iron in the body impairs neutrophil function, which can contribute to developing infections in ACD patients [36]. At the same time, if ACD has developed in a patient with any autoimmune disease, iron's immunosuppressive effect may be beneficial. It has been revealed that a decrease in the formation of tumor necrosis factor α by iron contributes to a reduction in the severity of this pathology in patients with rheumatoid arthritis and end-stage CKD [33, 35].

Direction 3 is the use of erythropoiesis stimulants. Erythropoietin suppresses cytokine antiproliferative effects, improves iron absorption, and increases the haem synthesis in erythropoiesis precursor cells [36, 37]. ACD patients should use erythropoietin if their hemoglobin level is less than 100 g/L [31, 38]. Erythropoietin therapy corrects anemia and reduces the need for blood transfusions in ACD patients [37].

The response rate to such therapy in ACD patients varies; however, there is a clear correlation between erythropoietin dosage and efficiency. The erythroid lineage of the bone marrow is progressively restored. Therefore, the efficiency of erythropoietin use can only be assessed after a month. It is important to monitor and achieve an optimal hemoglobin level (110 g/L) during erythropoietin treatment to avoid an uncontrolled increase in its content even after erythropoietin discontinuation [31].

In the pathogenetic treatment of ACD, new experimental approaches target the activities of interleukin-6 and the hepcidin–ferroportin axis. Siltuximab, which contains chimeric monoclonal antibodies against interleukin-6, has been shown to improve the condition of ACD patients. The efficiency of tocilizumab, an antibody drug targeting the interleukin-6 receptor, has been shown to reduce hepcidin levels in blood serum and improve the course of ACD. These drugs have received clinical approval. Hepcidin-binding agents, including monoclonal antibodies that target the hepcidin peptide, as well as hepcidin synthesis inhibitors [inactivation of hepcidin matrix ribonucleic acid (mRNA), inactivation of transferrin receptor mRNA, and heparin derivatives], are being investigated [39–43].

Prognosis

The importance of the issue under discussion is due to the unfavorable prognosis of ACD patients.

According to large-scale population-based studies, the incidence of anemia is less than 10% in patients with CKD stages I and II, 20%–40% in stage III, 50%–60% in stage IV, and more than 70% in patients with end-stage renal disease (stage V). Other studies show that anemia is as high as 90% in CKD patients on dialysis [17].

Maggioni et al. reported that mortality in patients with anemia was 26% higher than in CHF patients without anemia (hazard ratio of 1.26; 95% confidence interval, 1.04–1.52). According to the New York Heart Association, the clinical manifestation of anemic syndrome in CHF patients is associated with a higher functional class [44]. A meta-analysis revealed that anemia increased the risk of mortality in CHF patients, with an adjusted odds ratio of 1.46 ($p < 0.001$) [22].

It has been demonstrated that a decrease in hemoglobin concentration leads to a worsened prognosis in patients with cancer and concomitant anemia. Hypoxia of tumor tissue has been associated with resistance to chemotherapy and stimulation of genetic mutations, making it challenging to regulate tumor development [26].

Conclusion

Anemia of chronic disease has a multifactorial pathogenetic mechanism and develops in chronic diseases accompanied by low-grade inflammation, such as CKD, CHF, and oncological neoplasms.

Although ACD is concomitant to many diseases, such anemia may also be considered an evolutionarily developed protective mechanism. This mechanism is used by the human body to prevent free iron from being used by hazardous agents, such as microorganisms and tumor cells.

In most cases, effective treatment of the underlying disease that causes anemia leads to normalizing hematological disorders. If treatment for a chronic disease is ineffective, therapy aimed at correcting anemia is used. It is important to assess the role of anemia in each patient and the impact of anemia treatment on prognosis under different disease conditions.

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