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THE COURSE OF ANEMIC SYNDROME IN RHEUMATOID ARTHRITIS

Madasheva Anajan Gazkhanovna*; Abdiev Kattabek Makhmatovich; Alikulov Davron Eshmatovich*****

*Teacher,
Department of Hematology,
Samarkand State Medical Institute,
Samarkand, UZBEKISTAN

**Associate Professor,
Department of Hematology,
Samarkand State Medical Institute,
Samarkand, UZBEKISTAN

***Teacher,
Department of Hematology,
Samarkand State Medical Institute,
Samarkand, UZBEKISTAN
Email id: ozoda.madasheva@mail.ru
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ABSTRACT

This article discusses the course of anemia syndrome in rheumatoid arthritis and its consequences, causes, diagnosis, and prevention. Rheumatoid arthritis (RA) is one of the most common inflammatory diseases of the joints, occupying about 10% in the structure of rheumatological pathology. It is not only a medical but also an economic problem, since the onset of the disease in most cases is observed in people of working age.

KEYWORDS: *Anemia Syndrome, Rheumatoid Arthritis, Consequences, Causes, Diagnosis, Prevention, Articular Syndrome.*

INTRODUCTION

Recent studies have shown the leading role of cytokines and other mediators of inflammation in the development of not only the articular syndrome, but also the entire range of systemic manifestations of this disease. Based on the data obtained, fundamentally new and more effective drugs were developed and introduced into clinical practice, the action of which is based on the anticytokine principle **[1,2].** However, despite these advances, a number of questions regarding the pathogenesis of individual manifestations of RA and especially their treatment remain open. These include the problem of anemic syndrome - a frequent companion of rheumatoid inflammation.

Main part

Epidemiology According to the literature **[3],** anemia develops in 30–70% of patients with RA. In this case, anemia of chronic disease (ACD) is most often diagnosed - 25-64% of cases **[4, 5],**

iron-deficiency anemia (IDA) - 36-48.4% **[6]** and B12-deficiency - 24-29% **[7]**. Cases of development of mixed, aplastic and hemolytic anemias are also described **[8, 9].** The results of our study showed that 57 (64%) of the 89 examined patients with RA were diagnosed with anemia. At the same time, IDA was detected in 32 (56%) patients, ACD - in 14 (25%), mixed - in 11 (19%). Pathogenesis Change in iron metabolism It is believed that the leading role in the development of anemia in RA is played by a change in iron metabolism, a shortening of the life of erythrocytes, and their inadequate production by the bone marrow (BM) **[10].** This may be due to exposure to various pro-inflammatory cytokines such as interferon-γ, interleukins (IL), tumor necrosis factor-α (TNF-α) (tumor necrosis factor (TNF)). The level of these cytokines and activity significantly increase in RA. In recent years, it has been established that hepcidin, a 25-amino acid peptide synthesized in the liver, plays the role of a universal humoral regulator of iron metabolism **[11, 12].** The relationship between hepcidin and iron metabolism was first described by C. Pigeon et al. [**4].** It has been noted that under the action of pro-inflammatory cytokines, in particular IL-6, hepcidin hyperproduction occurs, which blocks the receptors of ferroportin, a transmembrane protein that transports iron adsorbed by enterocytes into the blood. This assumption was confirmed in an in vitro experiment, in which the regulatory functions of ferroportin and hepcidin were studied. The authors used 59Fe-labeled rat erythrocytes that were phagocytosed by macrophages. The results showed that about 70% of 59Fe is released into the blood, which is associated with the regulatory function of ferroportin. It was noted that the effect of hepcidin on macrophages led to a decrease in the level of ferroportin and a decrease in the amount of 59Fe in the blood. A similar effect was found when mice were injected with synthetic hepcidin.

Changes in iron metabolism can also occur as a result of an increase in the phagocytic activity of macrophages. There is evidence that this is facilitated by IL-1, which, acting on neutrophils, leads to the release of lactoferrin from them; the latter binds free iron and delivers it not to erythrocytes, but to macrophages. Shortening the life span of erythrocytes A certain role in the development of anemia in patients with RA is played by a shortening of the life span of erythrocytes, which is probably associated with an increase in the activity of the reticuloendothelial system and increased phagocytosis. The results of studies have shown that the inflammatory mediator prostaglandin E2 activates Ca2+ permeable cationic and Ca2+ sensitive K+ channels, resulting in hyperpolarization of the erythrocyte membrane. This leads to a shift of phosphatidylserine from the inner to the outer cell membrane, where it acts as a receptor that attracts macrophages. This is followed by recognition of erythrocytes by macrophages with their subsequent phagocytosis. In an experiment on mice, it was shown that the introduction of TNF-α or endotoxin also shortens the life of erythrocytes **[13].**

The role of pro-inflammatory cytokines The results of a number of studies have shown that the development of anemia in RA may be associated with the ability of pro-inflammatory cytokines to disrupt the formation of erythrocytes. One of the mechanisms for this may be the redistribution of iron (decrease in the amount of Fe2+ required for the synthesis of heme in the blood serum with its sufficient content in the depot). It is known that the main source of iron for heme synthesis in erythroblasts is iron-containing macrophages (siderophages), which receive Fe2+ ions from phagocytized old erythrocytes or from transferrin protein circulating in the blood. It is under the influence of pro-inflammatory cytokines IL-1 and TNF-α that excessive activation of siderophages occurs, which enhances phagocytosis and blocks their ability to

transfer iron to erythroblasts. The direct toxic effect of cytokines on erythropoietin can also lead to the development of anemia. In particular, macrophage inflammatory protein 1α has such an effect, the level of which in the blood serum of RA patients with anemia is significantly higher than in patients without anemia. It was also shown that in patients suffering from RA and anemia, an increase in the level of TNF-α in the blood was accompanied by a decrease in the concentration of serum erythropoietin. This allowed the authors to suggest that TNF-α inhibits the production of this colony-stimulating factor. There is evidence that inflammatory cytokines also have an inhibitory effect on erythropoietin receptors and related intracellular signal transduction mechanisms (mitogen and tyrosine kinase phosphorylation) and thus inhibit cell proliferation. Papadaki H.A. et al. in patients with RA and anemia, an increase in the number of apoptotic and a decrease in the number of normal CD34+/CD71+ and CD36+/glycoprotein A+ cells was found in the BM [24]. At the same time, a decrease in the number of colony-forming erythroid units (CFUe) was also observed. At the same time, a positive correlation was found between the level of TNF-α and the number of apoptotic cells, and a negative one – with the number of CFUe and the level of hemoglobin. On this basis, the authors concluded that TNF-α causes apoptosis of erythroid precursors in the BM, which leads to a decrease in hemoglobin levels. The results of our study also showed an increase in the levels of pro-inflammatory cytokines in RA patients with reduced hemoglobin levels, which can trigger a cascade of pathological reactions leading to the development of anemia. Thus, in patients with RA and anemia, an increase in the concentrations of TNF-α (32.54±9.71; 7.69±3.45 pg/ml, respectively) and IL-1 (166.32±18.54; 102.28 ±16.34 pg/ml, respectively) compared with patients with normal hemoglobin levels. **[14]**

The influence of medicines The development of anemia may also be due to the effects of medications used to treat RA. Methotrexate, which is the "gold standard" for the treatment of RA, can have a toxic effect on CM and blood cells, causing anemia. Especially often methotrexate, being a powerful inhibitor of dihydrofolate reductase, causes megaloblastic anemia. This drug disrupts the methylation process of deoxyuridine monophosphate, as a result of which the latter is phosphorylated and converted into deoxyuridine triphosphate, which accumulates in the cell and is integrated into DNA. As a result, defective DNA appears, in which thymidine is partially replaced by uridine, which leads to megaloblastic anemia. According to some data, even small doses of methotrexate (12.5±5.0 mg/week) can cause anemia. At the same time, there is evidence of the safety of low doses of methotrexate and even an increase in hemoglobin levels in the treatment of elderly patients (mean age 78.8 years) suffering from RA. So, in 33 patients taking methotrexate for 2 years at a dose of 7.5 mg/week, an increase in hemoglobin concentration from 124 to 130 g/l was registered. The results of our study revealed a phase relationship between the duration of methotrexate intake and the level of hemoglobin. It was found that with a duration of methotrexate intake ≤1 g, the hemoglobin concentration remains within the normal range. At the same time, with the duration of methotrexate intake for 1–3 years, a significant decrease in hemoglobin concentration is observed, which may be associated with the toxic effect of the drug, and when taken for >3 years, this indicator normalizes, probably due to inhibition of the production of pro-inflammatory cytokines and decrease in RA activity. The use of sulfasalazine and gold preparations can also lead to anemia (often aplastic). Nurmohammed M.T. et al. registered severe pancytopenia in a patient taking sulfasalazine for 4 months; while the hemoglobin level barely exceeded 54 g/l. Another study

noted the development of pancytopenia in 7 out of 10 RA patients taking gold preparations. Inhibition of CM function can also be provoked by azathioprine. This drug is also capable of causing displacement of phosphatidylserine into the outer shell of the erythrocyte, shrinkage of the cell, and later its death. The use of aminoquinoline drugs, on the one hand, can lead to disruption of erythropoietin production and, accordingly, to the development of anemia, on the other hand, these drugs have an anti-inflammatory effect, causing a decrease in the concentration of IL-1, IL-6, which reduces the activity of RA, the severity of articular manifestations and anemia.

Diagnostics As already mentioned, most often with RA, either ACD or IDA develop. Since they have similar clinical and laboratory features, this complicates the differential diagnosis. At the same time, it is believed that ACD is, as a rule, normocytic and moderately hypochromic in nature, the serum iron content in this anemia can be slightly reduced, and the total serum iron-binding capacity (TIBC) is usually within the normal range or moderately reduced, the ferritin concentration corresponds to normal or slightly increased. With true iron deficiency, anemia is always hypochromic microcytic, it is accompanied by an increase in TIBC and a decrease in the concentration of ferritin. The results of our study also showed that in the blood serum of patients with RA and IDA, microcytosis and hypochromia of erythrocytes, a decrease in iron and ferritin levels, an increase in TIBC, transferrin and erythropoietin concentrations are observed. With ACD, the normal sizes of erythrocytes, the levels of color index, iron, TIBC, transferrin, elevated / normal ferritin levels, an increase in the concentration of erythropoietin and its relative insufficiency are recorded. The greatest difficulty in diagnosis is mixed anemia, since it combines the signs of IDA and ACD. So, according to Simek M. et al., the level of serum iron in patients with mixed anemia (4.4±5.3 mmol/l) did not differ from its indicators in patients with IDA (3.4±1.69 mmol/l) and AChZ (4.6±2.7 mmol/l). At the same time, the iron concentration in blood serum in patients with ACD (4.6±2.7 mmol/l) was significantly higher compared to that in IDA (3.4±1.69 mmol/l). The results of our study showed that mixed anemia is normo-/hypochromic, normo-/microcytic in nature, characterized by a decrease in iron levels, a reduced/normal level of ferritin, an increase/normal FBC, an increased/normal concentration of transferrin, and a relative deficiency of erythropoietin. Since most laboratory parameters in mixed anemia are multidirectional (combining signs of IDA and ACD), we came to the conclusion that for its early diagnosis it is necessary to use the following criteria: a combination of low iron levels with a reduced / normal ferritin concentration and a relative deficiency of erythropoietin in the blood serum .

Prevention In the prevention of anemia in RA, one of the main places is occupied by adequate treatment of the underlying disease. According to some authors, the use of a new generation of drugs for the treatment of RA - disease-modifying drugs - allows you to increase the concentration of hemoglobin. Thus, when infliximab, a TNF-α antagonist, was added to the basic therapy with methotrexate, in patients with RA and anemia, the hemoglobin level significantly ($p=0.0001$) increased by 10–20 g/l. Another TNF-α antagonist, etanercept, also has a positive effect on hemoglobin levels. Folic acid is prescribed to patients receiving methotrexate both in the case of the development of folic acid deficiency anemia and for its prevention, which not only eliminates its deficiency, but also reduces the toxicity of the cytostatic. Calcium folinate, an antidote for folic acid antagonists, can be used to treat and prevent megaloblastic anemia in RA patients. It contributes to the restoration of folate metabolism, prevents damage to CM cells,

protects hematopoiesis, restores the biosynthesis of nucleic acids and compensates for the deficiency of folic acid in the body. Treatment Given the high incidence of anemia in patients suffering from RA, the development of methods for its correction is an urgent issue. Successful treatment of the underlying disease that caused the development of anemia, as a rule, allows to normalize the existing hematological disorders. If effective treatment of the underlying disease is not possible, therapy aimed at correcting anemia is used. Correction of low iron levels primarily consists in eliminating the possible causes of its occurrence. In the presence of IDA, patients are prescribed oral or parenteral forms of iron preparations. The latter are used when oral forms are poorly tolerated or their absorption in the intestine is limited (for example, inflammatory changes in the gastrointestinal tract (GIT)). To prevent the development of IDA, it is recommended to eat foods containing a large amount of iron, and vitamins that improve its absorption.

Currently, the issue of choosing an iron preparation remains relevant, the oral forms of which can be represented by ionic salt forms of Fe2+ or non-ionic ones - developed on the basis of the hydroxide-polymaltose complex (HPC) Fe3+. There is a fundamental difference in the metabolism of these drugs. Thus, due to its low molecular weight, the absorption of salt forms of Fe2+ is a passive uncontrolled process, which can lead to their excessive accumulation and overdose. At the same time, due to the Fe2+ oxidation reaction, free radicals are formed, which can damage the gastrointestinal mucosa, which can subsequently block the absorption of many trace elements, incl. and the iron itself. The features of HPA Fe3+ are its high molecular weight, the presence of an iron hydroxide core surrounded by a polymaltose shell, which limits its absorption, and therefore their overdose becomes almost impossible. When they are used, there is also no stage of oxidation with the transition of Fe2+ to Fe3+, and, accordingly, the release of free radicals. All this significantly reduces the risk of adverse reactions characteristic of iron salt preparations. So, Jacobs P. et al. compared the effectiveness of IDA treatment with preparations containing ferrous sulfate (Group 1) and GPA (Group 2). The results of the study showed that there were no significant differences in the increase in hemoglobin levels between the groups (group 1 - 121±11 g/l, group 2 - 123±15 g/l, $p>0.05$). At the same time, the ferritin concentration was significantly higher ($p<0.05$) in patients of the 1st group (12.1±11.3 ng/ml) compared with the 2nd (5.5±4.9 ng/ml). The incidence of side effects from the gastrointestinal tract was also significantly higher ($p<0.05$) in the 1st group (44.7%) than in the 2nd (17.5%). Human recombinant erythropoietin (HRE) is successfully used in the treatment of ACD. According to some authors, the clinical effect of erythropoietin therapy is not only in the correction of anemia and a decrease in the need for blood transfusions, but also in a possible positive effect on the course of the underlying disease due to interaction with the cytokine signaling cascade. So, in the observation of Kaltwasser J. et al. treatment of RA patients with TRE resulted not only in an increase in hemoglobin levels, but also in a decrease in the activity of the underlying disease.

CONCLUSION

The results of our study also showed that the use of iron preparations in the treatment of IDA, TRE in the treatment of ACD, and a combination of these groups of drugs in the treatment of mixed anemia allowed normalization of hemoglobin levels and iron metabolism in most patients. However, despite the normalization of the hemoglobin level, the objective data of RA activity did not significantly change after the therapy, while after 3 months. maintenance therapy, a significant decrease in both clinical and laboratory-instrumental indicators of RA activity was noted.

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