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Anemia of Chronic Diseases

Xalimova Yulduz Salokhiddinovna
Department of Clinical Sciences, Asian International University, Bukhara, Uzbekistan

Abstract
Anemia that occurs in infectious and inflammatory processes, non-infectious inflammatory diseases, and tumors is called "anemia in chronic diseases" (AHZ). With all the variety of pathogenetic mechanisms of anemia in these situations, one of the main ones is the redistribution of iron into the cells of the macrophage system, which is activated during various inflammatory (infectious and non-infectious) or tumor processes. According to the prevalence of AHZ, they occupy the 2nd place after iron deficiency anemia (IDA). The isolation of AHZ into a separate pathogenetic variant and awareness of it is important due to the similarity of this variant with IDA and some sideroachrestic anemia, although the essence and therapeutic approaches for these anemia are different.

Keywords: anemia of chronic diseases; iron deficiency anemia; prevalence.

Anemia is detected in 4% of men and 8% of women, and among middle—aged and elderly people - in 8-44%. One of the common variants of anemia is anemia of chronic diseases (AHZ), or anemia of chronic inflammation, or iron-distributing anemia, which occurs in patients with chronic activation of cellular immunity and lasts more than 1-2 months. AHZ ranks 2nd among anemia in terms of prevalence after iron deficiency anemia (IDA) [3].

Morbidity in the elderly and senile age is characterized by polymorbidity, i.e. the accumulation of diseases, among which anemia occupies a significant place.

The main pathogenetic mechanism in AHZ is considered to be the redistribution of iron in the cells of the macrophage system, which is activated during various inflammatory or tumor processes. Anemia is very diverse in etiology, pathogenesis and clinical and hematological signs. In the clinical and pathogenetic classification of anemia, a section is allocated concerning iron metabolism disorders (iron deficiency, iron distribution, sideroachrestic anemia).

In the morphological classification of anemia, AHZ refers to normocytic anemia, and according to

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the degree of regeneration — to regenerative. Clinical manifestations in a patient with anemia are determined by the pathology causing anemia and the severity of tissue hypoxia. AHZ is one of the symptoms of a common disease, often masking the underlying disease or masking it. There is a direct relationship between the degree of AHZ and the severity of the underlying disease. Anemia increases clinical manifestations in case of damage to the arteries supplying the brain and lower extremities, exacerbates heart failure, and in lung diseases anemia exacerbates hypoxic syndrome. The body adapts to low levels of hemoglobin (Hb) and red blood cells, and patients often get used to their malaise, explaining it by overwork at work, psychoemotional overload, and other factors. Changes on the part of internal organs appear when the Hb level drops to 80-70 g/l, and with a decrease in the Hb concentration of less than 40 g/l, the probability of developing an anemic coma is high [6]. In normocytic anemia, the MCV is 81-100 fl. Regeneration is observed in the bone marrow — the number of reticulocytes is 1.5—5%. The number of leukocytes corresponds to the concomitant pathology. In case of infection and severe intoxication, toxic neutrophil granularity is detected. To make a diagnosis, it is necessary to assess the adequacy of the state of iron metabolism: serum iron (LC), serum ferritin (FS), the degree of saturation of transferrin with iron (NTJ) and the serum level of transferrin receptors (TfR). The ferritin level is the gold standard for estimating the amount of iron stored in the body: it is directly proportional to the accumulation of iron in macrophages and hepatocytes, if there is no infection or inflammatory process. Its reduction has a 100% specificity in relation to the detection of iron deficiency conditions. The concentration of ferritin may increase in AHZ associated with the infectious process, inflammation and malignant disease. The Hb content in reticulocytes of more than 28 pg indicates sufficient iron reserves for the synthesis of Hb and erythropoiesis. It should be borne in mind that transferrin (Tf) has the qualities of a "negative" acute phase protein, i.e. acute inflammation contributes to a decrease in its level. Malignant neoplasms, liver diseases, nephrotic syndrome and poor nutrition can reduce the concentration of serum Tf, while pregnancy and oral contraceptives can increase this indicator. The total iron binding capacity of blood serum (OGSS) reflects the degree of "starvation" of serum and correlates with the level of Tf. With iron deficiency (J), an increase in heart rate is observed. A decrease in this indicator is observed in diseases accompanied by significant loss or increased protein intake (nephrotic syndrome, chronic renal failure, severe burns, chronic infections and active inflammatory processes, malignant neoplasms, severe liver diseases). There is no data on the effect of inflammatory reactions on the concentration of TfR [7]. A distinctive feature of AHZ is the combination of J and, accordingly, a lack of iron in the hematopoietic bone marrow tissue with intensive iron uptake by macrophages and dendritic cells of the reticuloendothelial system (RES). Iron released from decaying erythrocytes, which under normal conditions is reused in the synthesis of new hemoglobin molecules, enters an iron-containing depot. As a result, the content of FS increases. AHZ is diagnosed in the presence of hypoferremia and elevated or normal FS levels. This occurs as a result of stimulation of iron

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accumulation in the RES and immune activation of ferritin synthesis. With IDA and AHZ, there is a decrease in the concentration of LC and saturation of Tf with iron. A decrease in Tf saturation with iron in AHZ reflects a decrease in serum iron concentration, whereas in IDA there is an increase in Tf content (in the first case, this indicator is within the normal range or increased), which makes the decrease in Tf saturation with iron more pronounced. With the combination of AHZ with concomitant IDA, microcytosis and a more severe degree of pathological changes are more often noted. To identify functional damage during erythropoietin (EPO) therapy in patients with AHZ, it is proposed to determine the percentage of erythrocyte hypochromia and Hb levels in reticulocytes [8].

Private forms of AHZ

Anemia in chronic inflammatory (infectious) diseases. Anemia most often develops with purulent diseases of the lungs, kidneys and other organs a month after the onset of the disease. Hb decreases to 110-90 g/l. AHZ can become the leading symptom of a latent disease. With such AHZ, special corrective therapy is not required, treatment should be directed at the underlying disease.

Anemia on the background of HIV infection. The viral load in HIV infection is inversely correlated with all hematological parameters. The disease can cause anemia by affecting cytokine production and inhibiting erythropoiesis, reducing EPO concentrations and increasing the risk of opportunistic infections. The therapy used in the treatment of HIV is also the cause of a decrease in the number of red blood cells (myelotoxic effect). Anemia is associated with a decrease in life expectancy and a deterioration in the quality of life of HIV-positive patients [9].

Anemia in chronic kidney disease (CKD). Diabetes mellitus and hypertension are the main causes of end-stage CKD. For patients with a newly diagnosed CKD, the main task is to slow the progression of the disease by optimizing the treatment of the underlying disease. Anemia in CKD develops due to the inability of the kidneys to secrete a sufficient amount of EPO to stimulate adequate erythropoiesis and is aggravated by J, severe hyperparathyroidism, acute or chronic inflammatory diseases, shortening of the lifespan of red blood cells. Anemia worsens as CKD progresses. Anemia in systemic connective tissue diseases is caused by a violation of the synthesis of EPO, J due to blood loss from ulcers and erosions of the gastrointestinal tract, developing with prolonged use of anti-inflammatory drugs. Rheumatoid arthritis is accompanied by anemia in 16-65% of cases. In the group of patients with anemia, 77% of patients have AHZ and 23% have IDA.

The development of anemia in rheumatoid arthritis is facilitated by an increased level of inflammatory cytokines. Approximately half of patients with systemic lupus erythematosus have anemia with an Hb content of less than 100 g/l, it is either hypochromic or normochromic. In all cases of anemia against the background of connective tissue diseases, treatment of the underlying disease is necessary.

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Diagnostic criteria for anemia in chronic hepatitis and cirrhosis of the liver. Clinical signs (anemia is secondary to impaired liver function, the most common cause of non-megaloblastic macrocytic anemia, observed in about half of cases of liver disease), pathology is diverse (hemolysis, decreased bone marrow response, folic acid deficiency; blood loss, disorders in the lipid composition of the erythrocyte membrane).

Endocrine pathology is quite common. At the same time, it is possible to develop all morphological variants of anemia: normal, hypo-, macrocytic. Thus, with primary hyperparathyroidism, AHZ is observed in every second patient. Hypothyroidism is accompanied by anemia in 30-60% of patients. Anemia in hypopituitarism occurs in 32-46% of cases. The number of diabetic patients continues to grow worldwide. As diabetes mellitus progresses, the glomerular basement membrane thickens as a result of glycosylation, which leads to an increase in intrarenal pressure. This damage leads to a decrease in EPO production and the development of anemia [12]. Diagnostic criteria for anemia in endocrine diseases. Clinical signs (symptoms are specific: hyperthyroidism, hypothyroidism, hyperfunction of the adrenal cortex, hypofunction of the adrenal cortex, hypoandrogenemia, diabetes mellitus), pathology (hyperthyroidism — increased total mass of red blood cells due to accelerated proliferation; hypothyroidism — a decrease in the total mass of red blood cells due to a decrease in oxygen demand; hyperfunction of the adrenal cortex is a moderate polycythemic condition due to an increased level of androgens; hypofunction of the adrenal cortex is a state of hemoconcentration with normal or slightly elevated hematocrit levels due to a lack of mineralocorticoids; hypogonadism is anemia due to a reduced level of androgens; diabetes mellitus is a falsely elevated hematocrit level, acute hemolysis may develop with ketoacidosis) [13].

Anemia in malignant neoplasms (ZN). The prevalence of anemia in patients with ZN varies from 5 to 90%. Mild anemia after chemotherapy is observed in 100% of patients, and the frequency of moderate to severe anemia can reach 80%. The occurrence of anemia contributes to the progression of the underlying disease. Anemia in ZN is the result of cytokine—mediated regulation of erythropoiesis: impaired iron utilization, suppression of differentiation of erythroid progenitor cells and inadequate production of EPO and a decrease in the life expectancy of erythrocytes. Approximately 75% of patients with ZN complain of fatigue symptoms (weakness, apathy), problems with starting and ending tasks, and the need to sleep during the day (61% of patients noted that fatigue has a more adverse effect on their lives than pain associated with ZN). Other side effects associated with anemia include palpitations, impaired cognitive function, nausea, decreased skin temperature, impaired immune system function, dizziness, headache, chest pain, shortness of breath, depression and impaired performance. The presence of anemia in patients with ZN increases the risk of death. Anemia has an adverse effect on the quality of life and prognosis in patients with heart disease. Treatment of anemia reduces the need for blood transfusions by 7-47%. Only 50% of cancer patients have a full-fledged therapeutic response to the usual doses of EPO. Intravenous iron

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administration significantly improves the response to EPO therapy [14].

The algorithm of examination in the presence of normocytic anemia. If a patient with anemia has erythrocytes of normal appearance and size, first of all, it is necessary to count the number of reticulocytes. With an increased level of reticulocytes, differential diagnosis between posthemorrhagic and hemolytic anemia is necessary. If the level of reticulocytes is normal or decreased, the LC is determined. With a decrease in its content, it is necessary to differentiate early J and AHZ. With normal or elevated levels of HC, first of all, an examination should be carried out to exclude diseases of the kidneys, liver or endocrine system. With a normal level of LC and the absence of chronic diseases, it is necessary to examine the bone marrow. This will make it possible to detect possible infiltration of the bone marrow by leukemic cells, tumor metastases, fibrous tissue proliferation, identify myelodysplastic syndrome, masked megaloblastic anemia, as well as to establish aplastic anemia or a rare type of hereditary dyserythropoietic anemia, in which there are multinucleated erythroblasts. In normocytic anemia, first of all, CRF, nutritional defects, as well as hemolytic anemia should be excluded [16]. Anemia is not a diagnosis, but a syndrome. After conducting a laboratory study and detecting AHZ, it is necessary to conduct a comprehensive examination of the patient to diagnose the underlying disease. In infectious and inflammatory lung diseases (bronchiectasis, abscesses, pleural empyema), the main methods are X-ray and tomographic examination of the lungs, bronchological examination (bronchography, bronchoscopy). Diseases of the abdominal cavity (cholangitis, liver abscesses, subdiaphragmatic abscess, interdigital abscess, peritonitis, inflammatory processes in the pelvis) are detected by ultrasound, laparoscopy of the abdominal cavity, gynecological examination.

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