Lecture

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ANEMIA OF CHRONIC DISEASE

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The lecture deals with one of the commonest forms of anemia which develops secondary to systemic illnesses as an inflammatory response. Main causes, pathogenesis, clinical manifestation of anemia of chronic disease and basic approaches to its diagnostics and treatment are described.

KEY WORDS: anemia of chronic disease, etiology, clinics, diagnostics, treatment

АНЕМІЯ ХРОНІЧНИХ ЗАХВОРЮВАНЬ

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В лекції розглянуто одну з найпоширеніших форм анемій, що розвивається як запальна реакція внаслідок системних захворювань. Наведені дані про основні чинники розвитку, патогенез, клінічні прояви анемії, а також базові підходи до діагностики та лікування цього захворювання.

КЛЮЧОВІ СЛОВА: анемія хронічних захворювань, етіологія, патогенез, клініка, діагностика, лікування

АНЕМИЯ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ

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В лекции рассматривается одна из самых распространенных форм анемий, которая развивается как воспалительная реакция в ответ на системное заболевание. Приведены данные об основных причинах возникновения, патогенезе, клинических проявлениях анемии, а также основные подходы к диагностике и лечению этого заболевания.

КЛЮЧЕВЫЕ СЛОВА: анемия хронических заболеваний, этиология, патогенез, клиника, диагностика, лечение

DEFINITION

Anemia of chronic disease (ACD), or anemia of inflammation, is the term used to describe the hypoproliferative anemia seen in response to systemic illness or inflammation [1]. ACD is the second most common form of anemia worldwide after anemia caused by iron deficiency and the commonest type of anemia among patients with chronic diseases [1, 2].

ETIOLOGY

ACD was initially considered to be associated with inflammatory, neoplastic or infectious diseases. However, later other diseases such as major trauma, critical illnesses, heart failure were added to possible causes of ACD [1, 2].

Main etiological causes of ACD are the following:

- Chronic and acute viral, bacterial, parasitic or fungal infections (e.g., tuberculosis, chronic fungal infections, hepatitis, osteomyelitis, HIV, pneumonia, pyelonephritis, endocarditis, cellulitis, and soft tissue infections);
- Systemic connective tissue diseases, vasculitis and autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematous, dermatomyositis, scleroderma,

giant cell arteritis, inflammatory bowel disease, sarcoidosis);

• Chronic diseases (e.g., chronic kidney disease (CKD), congestive heart failure, diabetes mellitus, major thrombosis, chronic pulmonary disease);

• Malignancy (hematologic and solid tumors, e.g., lymphoma, multiple myeloma, renal cell carcinoma);

• Critical illness and major trauma;

• Chronic rejection after solid-organ transplantation [2].

EPIDEMIOLOGY

Because ACD is a result of immune system activation secondary to different causes, there are no available epidemiologic data specific for this condition. Approximately 30 % of all cases of anemia are considered to be associated with chronic disorders, including CKD [3]. The estimated prevalence of anemia in rheumatoid arthritis varies from 39 % to 53 %; over 75 % of these people are believed to have ACD [4]. About 65 % of hospitalized patients develop new cases of anemia while being in the hospital, and 57 % of them are also believed to have ACD [5].

PATHOGENESIS

As mentioned above, ACD develops as a result of immune system activation secondary to different causes. A range of underlying conditions results in release of proinflammatory cytokines, as well as activation of the reticuloendothelial system [6]. These processes have a number of implications:

- *Dysregulation of iron homeostasis* which is a hallmark of pathogenesis of ACD. This abnormality along with increased uptake and accumulation of iron within storage sites in the reticuloendothelial system result in a distraction of iron from the blood into cells of the reticuloendothelial system, following decreased availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis [2]. Acute phase protein hepcidin plays a pivotal role in the development of ACD because of its property to inhibit intestinal iron absorption. Furthermore, intensification of iron uptake by macrophages and block of iron export from macrophages primarily to the bone marrow occur simultaneously. As a result, serum irons concentration drops (with normal total amount of iron in the organism), retarding erythropoiesis and causing anemia [7]. However, sometimes this fall in serum iron concentration can be beneficial, because it makes iron less available for microorganisms retarding their growth.

Patients with CKD have additional mechanisms of development of iron deficiency. Those who are undergoing hemodialysis may develop it as a result of significant blood loss during the procedure (loss of iron can reach more than 1,000 mg per year). Contact with dialysis fluid during hemodialysis results in breakdown of folic acid. Uremic thrombocytopathy can cause gastrointestinal bleedings [8].

- *Reduction of survival of circulating red blood cells (RBCs)* due to increased erythrophagocytosis by macrophages and damage by cytokine-generated free radicals.
- *Violation of erythropoiesis* due to inhibited differentiation and proliferation of erythroid progenitors in the bone marrow. Erythropoiesis may be additionally impaired when microorganisms involve the marrow (as in HIV, hepatitis C, and malaria) or tumor cells infiltrating marrow produce proinflammatory cytokines and free radicals that have local effect on erythroid progenitor cells [2].
- *Reduced production of erythropoietin and reduced response of erythroid cells to erythropoietin* because of downregulation of erythropoietin receptors [9].This mechanism is of great importance in patients with CKD. Secondary hyperfunction of parathyroid gland in patients with chronic renal failure causes additional suppressive effect on erythropoiesis.

DIAGNOSTIC APPROACH

The diagnosis of ACD is based on the presence of the disease, causing anemia, with excluding of other possible causes of anemia at the same time (iron, vitamin B_{12} or folic acid deficiency, hemolysis). *Thus, diagnosis is made primarily by laboratory findings but supported by the clinical setting.*

Clinical features. In most cases, symptoms of the underlying disease prevail over anemia, but sometimes anemic syndrome may be the first manifestation of the causative disease.

General manifestations of *anemic syndrome* include pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise and are common to all types of anemia regardless of its etiology.

Clinical manifestation of *underlying disorders* may be general less specific, which can be seen in many diseases, and specific for the given cause of ACD.

General presenting features of underlying disorders which are more but less specific include fever, night sweats, anorexia, weight loss, weakness, myalgias, or arthralgias.

Findings *specific* for each type of ACD are the following:

- *those suggesting infection*: neck stiffness; tenderness of joints, shoulder girdle, abdomen, or bones; decreased breath sounds or rales;
- *those suggesting tumor:* the presence of a mass, adenopathy, hepatomegaly, splenomegaly;
- *those suggesting autoimmune disorder:* tenderness of joints or shoulder girdle, presence of a rash.

Uncommon findings are not expected in ACD and should prompt consideration of an alternative cause for the anemia. Such findings include symptoms of bleeding (e.g., melena, hematochezia, menorrhagia, metrorrhagia), positive history of high alcohol intake or of poor nutrition, history of exposure to radiation or to drugs known to be associated with the risk of anemia.

Laboratory tests. The ACD syndrome may be defined by the following constellation laboratory test results [1, 2]:

- Mild to moderate anemia with non-severe decrease in hemoglobin (Hb) level (Hb 80 g/L to 110 g/L).

Severe anemia should prompt consideration of an alternative or coexisting cause (e.g., blood loss, iron deficiency anemia, or a primary hematologic disorder).

- Anemia is either normocytic normochromic or microcytic hypochromic.

Generally, RBC indices that are normocytic and normochromic suggest ACD of fairly recent onset. RBC indices and blood smear that are microcytic and hypochromic suggest ACD has been present some weeks or months [10, 11].

- Otherwise normal RBC morphology.
- Elevated serum ferritin (sFt).

sFt is induced in response to inflammation and in ACD, with absent iron deficiency, it is typically > 100 ng/mL, and often significantly higher, thus reflecting its dual roles in iron storage and as an acute phase reactant [12] It is generally considered a marker of iron stores. Generally, when sFt is < 30 ng/mL in an anemic patient, iron deficiency can be diagnosed. However, in many patients, a combination of iron deficiency and ACD may exist [13].

- Transferrin saturation < 15 %.

The transferrin saturation is typically 5 % to 15 % in ACD indicating that the iron supply to the erythron is limited [14].

- Total iron-binding capacity (TIBC) may be normal or reduced.

Typically < 250 micrograms/dL. If it is increased (> 400 micrograms/dL), it is suggestive of iron deficiency anemia.

- Absolute reticulocyte count is low for the degree of anemia.

Indicates underproduction by the marrow which is typical in ACD.

- Elevated C-reactive protein (CRP).

It remains a fairly nonspecific measure of inflammation which helps to confirm presence of inflammation, and therefore ACD, if cause of anemia is uncertain [14].

- Significantly elevated erythrocyte sedimentation rate (ESR).

It helps to confirm presence of inflammation, and therefore ACD, if cause of anemia is uncertain. ESR is widely used as a marker of disease activity in certain diseases that are associated with ACD (e.g., rheumatoid arthritis, polymyalgia rheumatica).

- Serum erythropoietin level is usually lower than it is expected for the given degree of anemia.

Measurement of erythropoietin levels is useful only for anemic patients with Hb < 100 g/L, since erythropoietin levels at higher Hb concentrations remain well in the normal range. Furthermore, any interpretation of an erythropoietin level in ACD with Hb < 100 g/L must take into account the degree of anemia [2]. It may also be helpful in predicting patients who will respond to erythropoietin (patients with serum erythropoietin levels < 500 milliunits/mL are more likely to respond).

Biochemically anemia of chronic disease remains a clinical diagnosis of exclusion. The key test is to rule out iron deficiency:

- Soluble transferrin receptor levels – normal in ACD, elevated in iron deficiency.
- Ratio of soluble transferrin receptor to log ferritin - low (<1) in ACD, high (>2) in iron deficiency or coexisting iron deficiency and ACD.

Other laboratory tests which may be useful in ACD:

- Serum creatinine level is useful for ruling out anemia associated with renal insufficiency, although ACD may complicate anemia that is primarily due to renal disease.
- A lactate dehydrogenase (LDH) serum level is useful for ruling out hemolysis or another bone marrow disorder (elevated LDH).
- Liver function tests are used to exclude liver disease as a cause of ACD.
- Serum B12 helps to rule out B12 deficiency.
- Serum folate is useful for ruling out folate deficiency.
- Thyroid function tests are used to exclude hypo- or hyperthyroidism that can lead to anemia.
- Bilirubin (both indirect and direct) is useful for ruling out hemolysis as the cause of the anemia.

Bone marrow biopsy. Usually performed if there is suspicion of a primary hematologic disorder (e.g., myelodysplasia or a hematologic malignancy). Also may be performed, when necessary, to determine if iron deficiency is present. In ACD results are positive for iron presence and negative for evidence of tumor, dysplasia, or other abnormalities [15].

TREATMENT

Rationale for treatment of ACD is based on two considerations: (1) anemia can be generally deleterious in itself, requiring a compensatory increase in cardiac output in order to maintain systemic oxygen delivery; (2) anemia is associated with a poorer prognosis in a variety of conditions.

Thus, moderate and severe anemia warrants correction, especially in patients older than 65 years of age, those with additional risk factors (such as coronary artery disease, pulmonary disease, or CKD), or a combination of these factors [2].

Principles of treatment of ACD:

1. When possible, treatment of the underlying disease is the best approach to solve the problem of ACD. Improvement in Hb levels has been demonstrated, for example, in patients with rheumatoid arthritis who were receiving therapy with anti-TNF antibodies [2, 16].
2. In cases in which treating of the underlying disease is not feasible, for example in patients with incurable cancers or chronic renal or cardiac failure, alternative strategies are necessary [1, 2].
3. Correction of as many contributory factors as possible is also desirable, for example correction of nutritional deficiencies [1, 17].
4. Iron supplementation is recommended in patients with ACD and concomitant absolute iron deficiency [18]. Supplemental iron is not recommended for patients with ACD with normal or high ferritin levels (> 100 ng/mL) [2, 19].

Alternative strategies of therapy include RBC transfusion and erythropoiesis-stimulating agents (ESAs).

RBC transfusion is widely used for its rapid and high efficacy. It is indicated in severe anemia (Hb < 80 g/L) or life-threatening anemia (Hb < 65 g/L), particularly when the condition is aggravated by bleeding [2]. Long-term blood transfusion therapy is not recommended in patients with cancer or CKD because of iron overload and sensitization to HLA antigens that may occur in patients before renal transplantation.

Erythropoiesis-stimulating agents (ESAs). There are five ESAs currently available: epoetin-alpha (Epogen®, Procrit®, Eprex®), epoetin-beta (Recormon®), epoetin-omega (Epomax®), epoetin-delta (Dynepo®), and darbepoetin-alpha (Aranesp®). These agents all have the same amino-acid sequence, but glycolysation varies as a result of type- and host cell specific differences in the production process. The clinical efficacy of both epoetin-alfa and epoetin-beta is similar. Darbepoetin-alpha is an erythropoietin analogue, which has a longer half-life and potency. In Ukraine the only available erythropoietin is epoetin-alpha [20].

The basis for the usage of ESAs in the ACD is decreased erythropoietin response (the serum levels of erythropoietin is significantly lower than it must be for the

given level of Hb), deceased sensitivity of erythroid progenitors to erythropoietin, ability of treatment with erythropoietin to attenuate cytokine-mediated inhibition of erythropoiesis and to stimulate iron uptake and heme biosynthesis in erythroid progenitor cells [1, 2].

ESAs are currently approved for treatment of ACD in patients with cancer who are undergoing chemotherapy, patients with CKD, and patients with HIV infection who are undergoing myelosuppressive anti-retroviral medication [2]. The efficacy of therapy with ESAs significantly varies depending on underlying cause of ACD: from 25 % in patients with myelodysplastic syndromes up to 95 % in those with rheumatoid arthritis and CKD [21, 22].

There are some controversies regarding the target levels of Hb for patients with ACD and CKD who are undergoing treatment with ESAs. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend a target level of Hb in the range of 110 to 120 g/L, and the Hb should not exceed 130 g/L [23]. These goals are associated with lower mortality and less frequent hospitalization rates. The Food and Drug Administration has approved that the target Hb levels in erythropoietin-treated patients should not exceed 120 g/L [24].

Epoetin-alpha is prescribed in wide range dose of 75 – 150 mg/kg every 1-2 weeks. The standard starting dose is 100 mg/ kg every 2 weeks. Dosing should be adjusted to reach and maintain the Hb goal of 100-120 g/L.

A rise in the Hb concentration of at least 5 g/L in 2-4 weeks of treatment indicates a positive response to therapy. In the absence of elevation in the Hb concentration within 5-8 weeks, the regimen can be intensified to daily therapy or 300 U/kg 3 times weekly. In the absence of clinically meaningful positive response in 12 weeks the treatment should be discontinued [25].

Adverse effects of ESAs. Epoetin may increase the risk of serious cardiovascular events and death when it is dosed to achieve a target Hb > 120 g/L [24].

In people with ACD caused by CKD, Hb should be monitored:

- every 2–4 weeks in the induction phase of ESA therapy
- every 1–3 months in the maintenance phase of ESA therapy
- more actively after an ESA dose adjustment [26].

Long-term treatment with ESAs has been associated with increased systemic blood pressure (BP) and occurrence of seizures; hypertension has been documented to be a common side effect of intravenous use of ESAs. The possible mechanism is an imbalance between endothelin and proendothelin that leads to hyper-responsiveness to vasoconstrictive effects of norepinephrine and hyporesponsiveness to vasodilative effects of nitric oxide. For this reason, BP should always be closely monitored in patients administered with such agents [27].

ESA resistance. The working definition of ESA resistance is the requirement for greater than 150 units/kg of ESA at least 3 times per week or the sudden development of refractoriness to a previous stable maintenance dose, such that Hb level falls below target levels [28].

The common causes of ESA resistance are:

- iron deficiency (the commonest cause). Therefore, it is imperative that iron stores are adequate during ESA treatment;
- chronic infection/inflammatory state, which is attributed to inflammatory cytokines (interleukin-1);
- hyperparathyroidism (the mechanism appears to be related to bone marrow fibrosis);
- severe malnutrition [28].

Supplemental iron is prescribed with any type of ESA because sufficient body iron stores are required to achieve and maintain the target Hb. Although oral iron tablets are easily available and are of low cost, but their effectiveness is diminished due to hepcidin mediated iron block in the intestine. Hence, intravenous iron therapy is more effective [29]. Parenteral iron has been demonstrated to enhance rates of response to therapy with erythropoietic agents in patients with cancer who are undergoing chemotherapy and in patients undergoing dialysis [2]. Supplemental iron should be administered, as needed, to maintain a transferrin saturation of 20 %, and a serum ferritin level of 100 ng/mL [30].

People with ACD caused by CKD should not have iron levels checked earlier than 1 week after receiving intravenous iron. The

length of time to monitoring of iron status is dependent on the product used and the amount of iron given. Routine monitoring of iron stores should be at intervals of 4 weeks to 3 months [28].

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