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APLASTIC ANEMIA. WHAT IS THIS AND HOW TO LIVE WITH IT?

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Abstract: Damage or inhibition of bone marrow cells (stem cells) that develop into mature blood cells and platelets can cause the bone marrow to stop producing enough cells. This bone marrow disorder is called aplastic anemia. Bone marrow failure leads to a significant decrease in the number of red blood cells, white blood cells and platelets.

The term aplastic anemia is used to describe anemia that occurs when the production of most or all types of blood cells is suppressed. If only the production of red blood cells is affected, the disorder is called pure red cell aplasia.

Key words: aplastic anemia, bone marrow transplantation, immunosuppressive therapy, hematopoietic growth factors, antilymphocyte globulin, cyclosporine.

Aplastic anemia (AA) is a rare blood disease that develops as a result of arrest of proliferation and death of hematopoietic stem cells. It is characterized by an almost complete cessation of hematopoiesis, which is morphologically manifested by the replacement of functionally active red bone marrow (BM) with inert adipose tissue and pancytopenia (a decrease in the number of cells of all hematopoietic germs) of the peripheral blood. In 80% of cases, AA is an acquired disease and only in 20% of cases it occurs due to hereditary genetic disorders. According to large-scale studies conducted in Israel, Europe and Thailand, as well as a number of smaller studies, the incidence of AA in both children and adults is 2 per 1 million per year in the West; in Asia this figure is 2–3 times higher [1, 10].

Etiology

The reasons for the development of AA may be:

- chemicals (arsenic, aromatic hydrocarbons, in particular benzene, heavy metal salts, mercury vapor, nitric acid, various dyes, pesticides);
- physical factors (ionizing radiation, high frequency currents, vibration);
- medications (nonsteroidal anti-inflammatory drugs, cytostatics, Mercazolil, analgin, chloramphenicol, penicillin, tetracycline, streptomycin, sulfonamides, antithyroid, anticonvulsants, antihistamines, antidiabetics, anthelmintics, barbiturates, gold salts), as well as toxins, vaccines;
- infectious diseases (influenza, infectious mononucleosis, tuberculosis, viral hepatitis, pneumonia, staphylococcal infection, mycoses, parasitic infestations);
- autoimmune processes (systemic lupus erythematosus, Sjogren's syndrome);
- immunodeficiencies;
- genetic predisposition [2, 10].

Pathogenesis

The concept of AA pathogenesis, developed in 1970, remains relevant to this day and suggests a connection between the development of hematopoietic aplasia and:

- functional or anatomical defect of stem cells with a violation of their proliferative activity of a congenital or acquired nature;
- disruption of hematopoiesis by immunocompetent lymphoid cells;
- damage to the bone marrow stroma, i.e. hematopoietic microenvironment [5, 10].

It has been established that in AA there is a decrease in the colony-forming and cluster-forming ability of granulomonocytopoiesis precursor cells (COE-GM). Such changes in AA indicate that in most patients the development of AA is associated with damage to pluripotent stem cells, which is confirmed by the established connection with clonal diseases, such as paroxysmal nocturnal hemoglobinuria, myelodysplasia and acute myeloid leukemia [7].

The next important aspect of the pathogenesis of AA is the pathology of the hematopoietic microenvironment. The fundamental role of stromal cells in the regulation of hematopoiesis (differentiation and maturation of hematopoietic cells) is ensured by the local production of cytokines, extramedullary matrix proteins and direct intercellular contacts. By synthesizing collagen, glycosaminoglycans and other biologically active substances, reticular cells are able to influence the processes of proliferation and differentiation of hematopoietic precursors. Endothelial and fat cells are a powerful source of colony-stimulating factor.

Evidence of the involvement of the immune system in the pathogenesis of AA is the improvement of hematopoietic function after immunosuppressive therapy with antilymphocyte and antithymic globulins, the mechanism of action of which is based on the international criteria for the severity of AA on the lymphocytotoxic effect in relation to the population of activated T- suppressors [6].

Thus, the development of AA is based on multifactorial pathophysiological mechanisms. An intrinsic defect in pluripotent stem cells is a primary disorder that manifests or intensifies when exposed to various etiological factors [9].

Classification

Congenital (present at birth) AA:

- hereditary (passed from parents to children) AA with a general lesion of hematopoiesis (the formation of blood cells) and congenital developmental anomalies (disturbances in the structure of organs) – Fanconi anemia;
- hereditary AA with a general lesion of hematopoiesis without congenital developmental anomalies - Estren-Dameshek anemia;
- partial red cell aplasia (Diamond–Blackfan syndrome) – reduction only in the number of red blood cells (red blood cells).

Acquired during life:

- with general damage to hematopoiesis (blood cell formation):
- acute (suddenly occurs, develops quickly);
- subacute (develops more gradually, lasts from 1 to 6 months);
- хроническая (развивается постепенно, длится >6 мес);
- with selective damage to erythropoiesis (red blood cell formation) - partial red cell aplasia [3].

Based on severity, severe and non-severe AA are distinguished:

- severe AA – in which the number of granulocytes is <0.5•109/l, platelets <10•109/l, and reticulocytes – <1%; there are few cells in the bone marrow punctate; non-hematopoietic cells account for >65%; - non-heavy AA – with the best performance.

Clinical signs

The disease is characterized by 3 syndromes:

- anemic syndrome – general weakness, pallor of the skin and visible mucous membranes, increased fatigue, decreased performance, darkening and spots before the eyes, nausea, dizziness, arrhythmia, tachycardia, shortness of breath, tinnitus, systolic murmur over the apex of the heart;
- hemorrhagic syndrome – petechiae on the skin, hemorrhages in the eyes, bleeding from the nose, gums, gastrointestinal, uterine and renal bleeding, slow cessation of bleeding, thrombocytopenic purpura, easily formed bruises, hematuria; signs: leuko- and neutropenia - increased body temperature, possible presence of infectious foci on the skin, in the lungs and other organs, stomatitis;
- toxic-infectious syndrome - weak immune status of the body, severe mild viral diseases, slow healing of wounds, suppuration of scratches.

Fanconi anemia, which is familial, is more common in boys. The first symptoms of the disease usually appear at the age of 6–8 years.

Up to 80% of patients are born with the following bodily abnormalities:

- from the musculoskeletal system - additional, missing or fused fingers, underdevelopment or absence of shoulder blades, non-closure of the hard palate, absence of auricles, deformation of nasal cartilage, additional vertebrae, scoliosis, etc.;
- from the nervous system - microencephaly or anencephaly, macrocephaly, spina bifida, blindness, deafness, myasthenia gravis, paraparesis and tetraparesis, mental retardation;
- from the genitourinary system - underdevelopment or absence of kidneys, accessory kidneys, renal polycystic disease, S-shaped kidney, horseshoe kidney, ectopic ureters, exstrophy of the bladder, uterine agenesis, bicornuate uterus, complete fusion of the hymen, anorchia, agenesis of the urethra and penis, etc.;
- from the cardiovascular system - non-closure of the foramen ovale and interatrial septum, open botal duct, aortic stenosis at different levels, inversion of the great vessels of the heart, etc.;
- from the digestive system - intestinal stenosis and aneurysms, diverticulosis, intestinal atresia, bronchoesophageal fistulas at different levels.

75% of patients have café au lait skin. There are also vitiligo - areas of skin with increased or decreased pigmentation. The only way to maintain the patient's life is to transfuse the missing blood components. For this reason, after 4–5 years of illness, the skin of patients acquires a grayish tint due to excess iron during the destruction of red blood cells. In cases where congenital anomalies are compatible with life, bone marrow transplantation is permitted as a treatment method. However, the prognosis of the disease is unfavorable. Most patients die at an average age of 7 years.

Congenital partial AA Joseph–Diamond–Blackfan develops in early childhood. It may be associated with an autoimmune process that occurs during fetal development, or with a congenital metabolic defect. Anemia of varying degrees is combined with deep erythro- and normoblastopenia against the background of myelokaryocytopenia. Leukopoiesis and thrombopoiesis are preserved, no bleeding is observed. The disease is characterized by selective damage to erythropoiesis; sometimes accompanied by damage to the skeleton and eyes. Upon examination, attention is drawn to a grayish tint of the skin, as well as hepato- and

splenomegaly due to hemosiderosis. A general blood test reveals severe plastic or hypoplastic anemia. Hemoglobin content decreases to 14 g/l; the number of leukocytes and platelets remains normal, but with hypersplenism these indicators also decrease. In the myelogram, already at the beginning of the disease, the content of erythrokaryocytes is reduced; The leukocyte/erythrocyte ratio in Diamond–Blackfan anemia increases sharply – up to 100:1.

Acquired AA with general damage to hematopoiesis

Acute AA. The onset is violent, hemorrhagic syndrome is pronounced (nasal, skin, intestinal, renal bleeding). High fever is caused by the addition of necrotic processes (angina, destructive pneumonia, etc.). Within a few days, pancytopenia develops, reaching extremes. In the myelogram there is a delay in the maturation of granulocyte lineage cells, megakaryocytes are absent, the number of erythrokaryocytes is sharply reduced. Subsequently, a reduction of all hematopoietic germs develops with an increase in the number of reticular cells, plasma cells, and relative lymphocytosis. Death occurs 4–8 weeks from the onset of the disease.

The subacute form of AA is characterized by a slower development of cytopenic syndrome and less pronounced bleeding; life expectancy – from 3 to 13 months.

Chronic hypoplastic anemia begins gradually; First, asthenic syndrome, dizziness, pallor of the skin, and mild hemorrhagic syndrome appears. The size of the spleen remains normal; peripheral lymph nodes can be enlarged due to the inflammatory process (for example, with angina, the submandibular lymph nodes become enlarged). Anemia is hypoplastic in nature, but as it progresses it becomes aplastic. Reticulocytosis indicates latent hemolysis. The leukocyte content is moderately reduced due to granulocytes; thrombocytopenia is observed. Gradually pancytopenia becomes pronounced. The overall cellularity in the bone marrow punctate is either reduced or remains normal; the content of granulocytes is moderately reduced with a delay in their maturation; erythropoiesis may be “irritated”; the number of megakaryocytes is reduced, and the content of lymphocytes, plasma cells, and bone marrow stromal cells, on the contrary, is increased.

The disease can begin at any age, but most often develops in adults; provoked by infectious processes. The course is chronic; sometimes a long-term remission occurs (several years); a relapse can be triggered by a stressful situation or an accidental infection, even many years after an apparent recovery.

Laboratory indicators:

anemia is usually normo- or slightly macrocytic, moderate anisocytosis and poikilocytosis, the number of reticulocytes is normal or reduced; Hb concentration may be <70 g/l;

- the content of leukocytes and blood platelets is reduced;
- the number of SEPs has been increased; in children with AA there is an increase in HBF levels;
- when calculating the leukocyte formula, relative lymphocytosis and neutropenia are revealed, but with significantly pronounced leukopenia (0.2–1.5•109/l), absolute lymphopenia is observed;
- bleeding time is moderately prolonged;
- coagulation parameters are usually normal;
- serum iron concentration is increased;
- immune disorders: detection of autoantibodies to blood and bone marrow cells; development of auto and allosensitization in 35% of patients;
- inhibition of the phagocytic reaction of neutrophils; decrease in the content of CD4+ and increase in the level of CD8+ lymphocytes [7].

Treatment

Hemocomponent therapy:

- if there is a risk of bleeding, platelet transfusions can be performed; platelets from one donor should be used to prevent the development of sensitization;
- To prevent sensitization, it is necessary to use blood products that are maximally purified from leukocytes;
- if the Hb content is <70–80 g/l, red blood cell transfusions are performed.

Bone marrow transplantation:

- HLA typing of patients and close relatives as possible donors is necessary; In patients undergoing bone marrow transplantation, all transfusions should be limited or completely eliminated. If there is a need for blood transfusions, immediate relatives should not be used as donors;
- BM transplantation is indicated for patients under 40 years of age; in the presence of a suitable donor in patients who have not previously undergone transfusions, the positive effect of transplantation is achieved in 75–85% of cases, whereas after multiple transfusions the effect is achieved in 55–60% of cases.

Immunosuppressive therapy

Antilymphocyte globulin (ALG) can be used in different therapeutic doses: small doses of ALG - 1-5 mg/kg for 4-9 days; large doses (10–30 mg/kg) are administered over 4–6 days. A dose of 15–40 mg/kg is given daily intravenously for 4–10 days. When using small doses of ALG, remissions are achieved in 70% of patients (15% of them with severe disease). When large doses are prescribed, a response to therapy is observed in 40% of patients (90% of them with severe AA).

Cyclosporine (Sandimmune):

- prescribed for patients refractory to ALG;
- the initial daily dose of cyclosporine is 10–12 mg/kg daily; after achieving remission, long-term maintenance therapy is prescribed (1.6–6.0 mg/kg);
- side effects – dysfunction of the kidneys, liver, adrenal glands;
- therapy is effective in 25% of patients (the level of sensitivity to therapy ranges from 0 to 80%).

The combination of ALG + cyclosporine increases the effectiveness of treatment.

Hematopoietic growth factors can be used to correct neutropenia. A temporary increase in neutrophil counts has been observed with GM-CSF and G-CSF therapy in some patients. Interleukin-3 promotes a temporary increase in the absolute number of neutrophils [8].

References

1. Idelson L.I. Acquired hemolytic anemia. Guide to hematology / Edited by A.I. Vorobyov. – M.: Newdiamed, 2005. – C.261–274.
2. Nagornaya N.V., Vilchevskaya E.V., Bordyugova E.V. Aplastic anemia in children. Child's health. 2013; 7: 50.
3. Сараева Н.О. Новые взгляды на апластическую ане- мию. Сибирский медицинский журнал. 1999; 18 (3).
4. Guseva S.A., Goncharov Ya.P. Anemia. Kyiv: Logos, 2004; 408.

5. Clinical hematology. Guide for doctors / Ed. A.N. Bogdanova, V.I. Mazurova. – St. Petersburg: Foliot, 2008. – P. 206–222.
6. Rational pharmacotherapy of diseases of the blood system. Guide for practicing doctors / edited by A.I. Vorobyov. – M.: Publishing house “Litterra”, 2009. – P.509-541.
7. Guseva S.A., Voznyuk V.P., Dubkova A.G. Anemia: principles of diagnosis and treatment. Directory. M., 1998.
8. Skvortsov V.V., Nedogoda V.V.. Use of the Mustang-2000 apparatus for pancytopenia syndrome in a patient with chronic iron deficiency anemia. Advances of modern natural science. 2003; 5: 85.
9. Hoffman R., Benz E.J., Sanford J. et al. Hematology Basic Principles and Practice. 5-rd Edition. London: Churchill Livingstone, 2005. – 2678 p.
10. Petz L.D., Garratty G. Immune hemolytic anaemias. 2-rd Edition – Philadelphia: Churchil Livingstone, 2004. – 458 p.