AUTOIMMUNE HEMOLYTIC ANEMIA CLINICAL-LABORATORY DIAGNOSTICS AND TREATMENT METHODS

Kurbonova Z.Ch
Babadjanova Sh.A
Xo'shboqova G.O
Yusupov B.N
Tashkent Medical Academy

Autoimmune hemolytic anemia is a heterogeneous group of diseases characterized by the uncontrolled production of antibodies against one's own red blood cells and subsequent hemolysis of the red blood cells.

Autoimmune hemolytic anemia frequently affects up to 41 out of 80,000 individuals in any age group, with a female to male ratio of 2:1.

The underlying mechanism of autoimmune hemolytic anemia is the disruption of immunological tolerance to one's own antigen. Depending on the mechanism of erythrocyte destruction, hemolysis can occur within the cell, on the membrane, or in the interstitial variants.

The serological characteristics of autoantibodies are crucial for the classification of autoimmune hemolytic anemia into four types:

- Incomplete warm agglutinins
- Warm hemolysins
- Incomplete cold agglutinins
- Cold biphasic hemolysins

Approximately 80% of cases of autoimmune hemolytic anemia are classified as incomplete warm agglutinins.

Autoimmune hemolytic anemia can manifest as an idiopathic condition or as a syndrome associated with other diseases. It can occur in systemic lupus erythematosus, lymphoproliferative disorders (such as chronic lymphocytic leukemia), and in diseases affecting the reticuloendothelial system, liver, and bone marrow (e.g., Fisher-Evans syndrome). Autoimmune hemolytic anemia associated with viral infections is also known.

The development of autoimmune hemolytic anemia is attributed to the breakdown of immunological tolerance to self-antigens. The exact mechanism of this process is not fully understood. Genetic defects in T lymphocytes, which may enhance their suppressor function, contribute to the expansion of B lymphocyte populations that produce antibodies against their own structures.

The characteristics of autoantibodies determine the specific features of different forms of autoimmune hemolytic anemia. Incomplete autoagglutinins induce agglutination of erythrocytes only in a saline environment, while the effect of complete autoagglutinins is observed in any environment. Warm antibodies attach to

erythrocytes and interact with Fc receptors on immunoglobulins. As a result, macrophages remove a portion of the erythrocyte membrane, altering its biophysical properties and affecting ion channels. This leads to the formation of microspherocytes and rapid sequestration of erythrocytes in the spleen and occasionally in the liver.

Cold agglutinins cause temporary agglutination of erythrocytes in cold temperatures, leading to complement fixation and subsequent membrane destruction.

Hemolysins activate the complement system, resulting in membrane damage within the blood vessels. In this form of autoimmune hemolytic anemia, the infectious agent may mimic the antigenic structures of erythrocytes or modify them slightly in the initial stages, subsequently leading to autosensitization.

Two classes of antibodies are commonly involved in the development of autoimmune hemolytic anemia: IgG and IgA or IgG and IgM. Complement is also implicated in the pathophysiology and treatment of this disease. IgM actively fixes complement, and the direct Coombs test is usually negative in these cases. Splenectomy is not effective in patients with this type of disease because hepatic phagocytes play a significant role in the removal of erythrocytes.

Autoimmune hemolytic anemia usually begins suddenly. Patients experience yellowing of the skin and sclera, abdominal pain, dark urine, and increased body temperature. Splenomegaly is observed in 40-80% of patients, while hepatomegaly is observed in 20-50% of cases.

Clinical manifestations of the disease vary depending on the serological variants.

- The warm autoimmune hemolytic variant is usually accompanied by hemoglobinuria and other signs of intravascular hemolysis.

- Cold agglutinin disease, associated with cold agglutinins, manifests as chronic hemolytic anemia and continues with intravascular hemolysis and acrocyanosis, extremity pain, Raynaud's syndrome, and peripheral blood circulation disorders under the influence of low temperatures.

- In autoimmune hemolytic anemia associated with warm antibodies, the destruction of red blood cells primarily occurs in the spleen.

- Cold antibody-mediated hemolysis is mainly caused by phagocytosis of red blood cells by mononuclear cells of the liver.

Blood tests indicate normochromic or macrocytic anemia. Hemoglobin levels range from 30 to 90 g/l. Anisocytosis, poikilocytosis, spherocytosis, and increased numbers of nucleated erythroid cells and reticulocytes of various maturation stages are detected. In some cases, it is difficult to determine the number of red blood cells, and in other cases, the group affiliation of the patient becomes challenging due to pronounced hemolysis. Panagglutination, similar to cold agglutinins, occurs in the presence of cold antibodies. Osmotic fragility of erythrocytes is often reduced. The left shift of the leukocyte formula and neutrophilic leukocytosis with thrombocytosis are possible. Sometimes, a decrease in the average number of leukocytes and platelets is observed.

Erythroid hyperplasia occurs in the bone marrow. Myelogram may reveal changes specific to the underlying disease (chronic lymphocytic leukemia, etc.).

During hemolysis, unconjugated bilirubin mainly accumulates. The iron content in the blood serum usually increases, while haptoglobin levels decrease. In patients with Donath-Landsteiner syndrome, the amount of direct bilirubin and free hemoglobin in plasma increases. Haptoglobin levels also decrease. The diagnosis of autoimmune hemolytic anemia can be confirmed by a positive Coombs test.

Intracellular hemolysis mechanisms include:

- Increased unconjugated bilirubin
- Reticulocytosis
- Urobilin in the urine
- Increased iron content in the blood and stercobilin in the feces
- Erythronormoblastic appearance in the bone marrow

Extracellular hemolysis mechanisms include:

- Formation of hemoglobin in the blood plasma and urine
- Hemoglobinemia
- Hemoglobinuria
- Hemosiderinuria

Diagnostic algorithm for patients with autoimmune hemolytic anemia. List of mandatory medical services:

- Initial referral to a general surgeon (examination, consultation)
- Complete blood count, including platelet and reticulocyte counts
- Determination of total bilirubin level in the blood
- Determination of conjugated and unconjugated bilirubin levels in the blood
- Coomb’s test
- Direct antiglobulin test (Coomb’s test)
- Agglutination test
- Detection of warm hemolysins in the blood
- Detection of cold

Autoimmune hemolytic anemia-specific laboratory indicators:

1. In peripheral blood:

- Decreased red blood cells and hemoglobin levels;
- Normal coloration of red blood cells;
- Normal size of red blood cells;
- Increased reticulocyte count;
- Increased unconjugated bilirubin in the blood;
- Increased iron levels in the blood.

During hemolytic crisis:

- Increased number of nucleated normocytes;

- Reticulocyte count exceeding 30%.

2. Bone marrow examination reveals normoblastic hematopoiesis and erythroid hyperplasia.

When the information in the mandatory range is insufficient or treatment is ineffective, additional medical services are used (a series of tests are performed in specialized hematological clinics):

- Cytological examination of bone marrow (myelogram);
- Free plasma hemoglobin and haptoglobin levels;
- Determination of glucose-6-phosphate dehydrogenase level in erythrocyte hemolysate;
- Determination of AST level in the blood;
- Determination of ALT level in the blood;
- Determination of γ-glutamyltransferase level in the blood;
- Determination of alkaline phosphatase level in the blood;
- Bone marrow puncture (erythroid hyperplasia and morphology, lymphocyte count and morphology, metastatic cell complexes);
- Trepanobiopsy (if necessary);
- Immunophenotyping of lymphocytes (with peripheral blood lymphocytosis and suspected leukemia);
- Determination of vitamin B12, folate, and homocysteine levels in the blood;
- Determination of iron metabolism indicators (including transferrin, serum ferritin, and erythrocytes);
- Extended coagulogram + red clot anticoagulant;
- Rheumatological tests (antibodies to native DNA, rheumatoid factor, antinuclear antibodies, antibodies to cardiolipin antigen);
- Chest X-ray (if necessary, CT);
- Esophagogastroduodenoscopy;
- Irrigoscopy / sigmoidoscopy / colonoscopy;
- Ultrasonographic examination of abdominal organs and abdominal lymphatic pathways;
- Spleen, bone marrow, prostate gland;
- Determination of parathyroid hormones if necessary,

prostate-specific antigen, tumor markers.

The differential diagnosis of autoimmune hemolytic anemia is carried out based on hemolytic syndrome. Lymphoproliferative diseases (lymphomas, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, and others), toxic effects of various chemical agents, autoimmune diseases, including systemic autoimmune diseases, diseases associated with monoclonal gammopathies, interactions with Plasmodium parasites, hereditary hemolytic anemias, and PNH (Table 1).

Table 1. Differential diagnosis of autoimmune hemolytic anemia

Diagnosis	Query	Criteria for confirming diagnosis

Autoimmune hemolytic anemia with incomplete hot agglyutinin (primary)	Direct Kumbs test, red bone marrow punctiation (morphology and hyperplasia along with red blood cells, number and morphology of lymphocytes, complex of metastatic cells); immuno-phenotyped lymphocytes (lymphocytosis in peripheral blood analysis and removed spleen); Rheumatological tests (local DNA antibodies, rheumatoid arthritis factor, antinuclear factor, antibodies to cardiovascular antigen); immunoglobulin whey (A, G, M) + cryoglobulins; thyroid hormones, prostate specific antigens, oncomarkers; abdominal organs and abdomen ultrasonic examination of the lymph nodes, small lungs, prostate gland, thyroid gland; X-ray of the lungs (if necessary KT); colonoscopy.	Direct Kumbs test jobless, no information on the secondary nature of anemia
Autoimmune hemolytic anemia with full cold agglyutinin	The vibration of cold agglyutinins; general urine analysis (definitely evaluating the color of urine); analysis of hemosiderin, immunoglobulins in the whey (G, A, M) + cryoglobulins	Clinical appearance is resistance to constipation (hand, foot, ear nose fingers subsequent whitening, severe pain in the limbs) is the seasonality of the disease. Inability to detect blood group and count red blood cells, high vibration of M-gradient, High vibration of cold antibodies at +4°C
Genetic hemolytic anemia	Direct Cumbs test, ultrasonic examination of spleen and gallbladder, morphology of red blood cells, determination of activity of red blood cells enzymes, hemoglobin electrophoresis	Childhood history, heredity, stigmas of embryogenesis in objective vision, direct Kumbs test response negative.
Vitamin B_{12} - deficiency anemia	Determination of vitamin B_{12}	Funicular myelosis, a_{12} decrease in blood vitamin B, negative is the direct Cumbs test response.
Wilson's disease	Direct Cumbs test, copper detection in urine, blood seruloplasmin, neurologist, ophthalmologist consultation	Symptoms of nerve tissue damage, presence of Kaiser Flaysher rings in the liver, decreased seruloplasm levels in blood plasma, decreased copper in the bloodstream, and increased copper separation in the urine

PTG	Determination of PTG - red blood cells clone protein in peripheral blood analysis immunofenotypiprotoclin cytoplasm method	Sakharoza and Hema tests positive, uv writing - expression Immunophenotypi of Express GPI-linked proteins

For a general blood test for hemolytic anemia, an example is: hemoglobin - 51 g/l, erythrocytes - 1.7 × 1012/l, hematocrit index - 28%, MCV - 89 fl, MCH - 28.4 pg, leukocytes - 8.9 × 109/l. Leukocyte formula: neutrophils - 80%, lymphocytes - 15%, monocytes - 5%, platelets - 170 × 109/l, reticulocytes - 40%, ESR - 35 mm/hour.

During the outpatient stage, they continue the treatment that started in the hospital, monitoring the clinical and laboratory parameters. The first direction of therapy is corticosteroid hormone drugs. Prednisolone is prescribed at a daily dose of 1.5-2 mg/kg of body weight. The dose should be gradually reduced as the hemoglobin level normalizes. In patients with autoimmune hemolytic anemia associated with IgG antibodies, higher doses of corticosteroid hormones are effective in 90% of cases. However, they are gradually tapered off. This tactic involves taking prednisolone for a period of 3-4 months.

During the course, the hemoglobin and reticulocyte levels are monitored. If remission lasts for 3-4 months with a daily dose of 5 mg of prednisolone, it is necessary to completely discontinue the medication. Due to the non-specific effect, the normalization of hemoglobin levels leads to a rapid decrease in the dose, which always leads to a relapse of hemolysis. In addition to the main treatment, supportive therapy may include bisphosphonates, vitamin D, calcium, and folic acid. Monitor the blood glucose level and actively treat diabetes; prevent the risk of thromboembolism, especially in patients with autoimmune hemolytic anemia and red cell anticoagulants or in patients with relapse after splenectomy.

After splenectomy, there is an increased risk of severe infections caused by Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae. Therefore, 2-4 weeks before splenectomy, patients are vaccinated with polyvalent pneumococcal, meningococcal, capsular polysaccharide (PRP type) vaccines, and tetanus toxoid (TT) conjugate.

In recent years, rituximab has been recommended for patients who do not respond well to prednisolone therapy.

Indications for prescribing rituximab:

- Resistant forms of autoimmune hemolytic anemia with an increasing number of symptoms;
- Starting after splenectomy;
- In cases with high-risk symptoms;
- Indications against splenectomy, high risk of venous thromboembolism.

Contraindications for prescribing rituximab:

- Uncontrolled viral hepatitis B and C;
- Acute viral or bacterial infection.

The standard regimen is 375 mg/m2 on days 1, 8, 15, and 22. Patients who have been receiving treatment with glucocorticoids before starting rituximab should continue the glucocorticoid therapy until the first sign of a response to rituximab appears.

When choosing an immunosuppressive drug (cyclophosphamide, azathioprine, cyclosporine A), the main factor should be the safety of the patient, as the expected effectiveness of all drug options is low, and treatment may be more risky for the patient than managing the disease. Long-term treatment can be carried out under the supervision of a specialist in outpatient conditions (Table 2).

Table 2. Preparations used in autoimmune hemolytic anemia

Name of the international non-patented name	Average delivery frequency	Unit	Average daily dose	Average course dosage
Hormonal preparations belonging to the endocrine system				
Non-sexual hormones with synthetic substances and antigormons,				
Prednizolon	1,0	Tablet	80	2400
Anti-tumor, immunodepressive and additional preparation				
Cytostatic drugs				
Cyclophosphamide	0,01	Tablet	100	1500
Azatioprin		Tablet	150	1200
Monoclonal Antibodies				
Rituksimab	0,02	Ampoule	700	2800
Blood-reproductive drugs				
Anti-anemia preparations				
Folic acid	0,7	Tablet	3	90

Indicators of the effectiveness of treatment for autoimmune hemolytic anemia.

Remission criteria: complete resolution lasting at least 2 months:

Hemogram parameters (hemoglobin >120 g/l, reticulocytes <20%);

Unconjugated bilirubin level within normal range;

Normal LDH activity.

Partial remission criteria (lasting at least 2 months):

Hemoglobin >100 g/l;

Reticulocytes decreased by at least 2-fold;

Unconjugated bilirubin level below 25 μmol/l.

Lack of response to therapy is defined as insignificant positive dynamics or response lasting less than 1 month.

Long-term therapy with glucocorticoids requires regular physical exercises, prevention of steroid-induced osteoporosis, discontinuation of smoking, and avoidance of risk factors for thrombosis.

In autoimmune hemolytic anemia, it is necessary to avoid hypothermia with cold antipyretics.

Glucocorticoid-induced osteoporosis requires sufficient intake of calcium and vitamin D and avoidance of alcoholic beverages.

Therapy for autoimmune hemolytic anemia is currently based only on retrospective and a few prospective studies, as randomized trials are lacking and high-quality evidence is limited. There is no official consensus on the definition of complete or partial remission. Therefore, the following recommendations regarding treatment of this disease are based on the appropriate level of evidence for vitamin D.

The outpatient card should include monitoring of treatment effectiveness, overall patient condition, parameters of complete blood count, including reticulocytes and platelets, biochemical indicators such as bilirubin and LDH levels, monitoring of immunoglobulin levels using immunoglobulin enzymes, evaluation of erythrocyte membrane, and recording the results of the Coombs test (Table 3).

Table 3. Autoimmune hemolytic anemia screening plan

Patients' category	General blood test with reticulotsitis	Blood biochemical analysis (with bilirubin fractions, LDG)	Direct Cumbs test	Determining the number of immunoglobulins in the membrane of erythrocytes in immunoferment mode	Hematologist consultation
Conservative cure	During treatment - at least 1mahal for 10 days; 1 time for 1 month after remission	During treatment - at least 1mahal for 10 days; 1 time for 2 months after remission	1 time in 3 - 6 months	1 time in 2 months	Staying under the care of a residential hematologist for 5 years

Instructions for admission to the hematology department:

- Correction of therapy;
- Conducting courses of pathogenetic therapy;
- Preparation for splenectomy.
- Hemolytic crisis;
- Uncompensated anemia.

Algorithm of actions in emergency situations.

If there is suspicion of a hemolytic crisis (fever, jaundice, dark urine, enlarged spleen, anemic shock, anemic coma) - depending on the severity of the condition, immediately seek urgent assistance from the hematology department or the intensive care unit.

Monitoring vital functions: respiratory rate and nature, heart rate and rhythm, systolic and diastolic blood pressure indicators, urine volume and color.

If there are signs of impairment of vital functions (acute respiratory distress, signs of shock, renal failure) - provide emergency assistance: ensure venous access,

administer colloidal preparations; if intravascular hemolysis is suspected - correct renal function (furosemide), provide oxygen with oxygen.

70% of patients have a good prognosis. The prognosis in secondary autoimmune hemolytic anemia depends on the treatment course and effectiveness of the underlying disease.

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