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Review Article

Autoimmune Hemolytic Anemia: A Review

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Abstract: Autoimmune hemolytic anemia (AIHA) is defined as an anemia caused by the destruction of red blood cells by antibodies directed against the patient's own red blood cell surface antigens. Different forms of AIHA are distinguished based on the characteristics of the antibody responsible for the disease. The most common form (70% of cases) is warm antibody autoimmune hemolytic anemia. These antibodies become active at temperatures between 35°C and 40°C. This type of hemolysis occurs mainly within tissues, particularly in the spleen. The diagnosis of AIHA relies on rigorous interpretation of immunohematological parameters, as well as additional tests to exclude associated diseases. In "idiopathic" cases, it is recommended to continue monitoring elderly patients beyond remission to detect the possible occurrence of lymphoma or myelodysplastic syndrome. Corticosteroid therapy is the standard treatment, but it can lead to numerous side effects. The efficacy of rituximab appears particularly promising in "refractory" forms of AIHA, and its use in the early phase of management to spare corticosteroid therapy should be evaluated in a prospective and randomized study.

Keywords: Autoimmune hemolytic anemia (AIHA), idiopathic, refractory.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is defined as an anemia caused by the destruction of red blood cells by antibodies directed against the patient's own red blood cell surface antigens. Under normal conditions, the lifespan of red blood cells is 120 days. However, in the case of AIHA, their lifespan is shortened due to premature destruction (hemolysis).

AIHA can occur at any age, but it is more common in individuals aged 60 to 70 years, with a slight female predominance (60%) [1]. In about half of the patients, AIHA is associated with another disease, which can also be autoimmune (such as lupus) or related to an excess of lymphocytes due to lymphatic system dysfunction (lymphoid hemopathy).

The diagnosis of AIHA is based on the demonstration of variable degrees of anemia and the presence of autoantibodies directed against the surface antigens of red blood cells [2, 3].

I. CLASSIFICATION OF AUTOIMMUNE HEMOLYTIC ANEMIA

Different forms of AIHA are distinguished based on the characteristics of the antibody responsible for the disease. The most common form (70% of cases) is warm antibody autoimmune hemolytic anemia [4]. These antibodies become active at temperatures between 35°C and 40°C. This type of hemolysis occurs mainly within tissues, particularly in the spleen [5].

On the other hand, there are cold antibody autoimmune hemolytic anemias (25% of cases), in which the destruction of red blood cells is triggered by exposure to cold temperatures (red blood cell activity peaks at around 4°C) [6]. This type of agglutinin causes the lysis of red blood cells through complement activation, primarily in the liver [2].

Other rare forms of AIHA (Table 1) can also be observed. In addition to this classification based on the characteristics of the involved autoantibodies, a distinction is also made between primary or "idiopathic" AIHA and secondary AIHA based on the presence or absence of an underlying disease (Table 2).

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Table 1: Classification and main characteristics of AIHA

Type of AIHA	Typical Population/Clinical Presentation	"Secondary" Forms	Ig Class Cold agglutinin	Optimal temperature	Specificity of TDA	Eluate
Warm autoimmune hemolytic anemia (WAHA) with auto-antibodies	**Adults > Children Intra-tissue hemolysis (spleen), subacute onset**	**50-60% of cases 30% in children**	**IgG >> IgA, IgM Absent or low levels of cold agglutinins**	**37°C**	**IgG + C3d**	**IgG**
Cold agglutinin syndrome	**Age > 50 years Intra-tissue hemolysis (liver)**	**90% of cases have monoclonal IgM kappa**	**IgM >>> IgA or IgG Cold agglutinins > 1/64**	**4°C**	**C3**	**Negative**
Other cold antibody autoantibodies	**Children, young adults Intra-vascular hemolysis**	**Infections (Mycoplasma, EBV, etc.)**	**Polyclonal IgM Cold agglutinins > 1/64**	**4°C**	**C3**	**Negative**
Paroxysmal cold hemoglobinuria	**Exceptional in adults Acute intra-vascular hemolysis**	**Infections (Mycoplasma, syphilis, viruses)**	**IgG**	**>30°C**	**C3**	**Negative**
Mixed AIHA	**Adults**	**Associated with lymphoproliferative disorders**	**IgG, IgM + Cold agglutinins 1/64 to 1/500**	**4°C – 37°C**	**IgG + C3**	**IgG**

Miscellaneous:
- **Pregnancy**
- **IgG4-related disease**
- **Post-bone marrow transplantation**
- **Di George syndrome**

Table 2: Main diseases or conditions that can be associated with warm antibody AIHA at diagnosis or during its course

Main diseases or conditions that can be associated with warm antibody AIHA at diagnosis or during its course:	
Lymphoid Hemopathies and Other Hemopathies:	- Chronic lymphocytic leukemia - Other B-cell non-Hodgkin lymphomas (marginal zone lymphoma) - B-cell acute lymphoblastic leukemia - Chronic lymphoproliferative disorder with large granular lymphocytes - Angioimmunoblastic T-cell lymphoma - Hodgkin lymphoma - Myelodysplastic syndromes - Myelofibrosis
Other Tumors:	- Thymoma - Castleman disease - Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) - Ovarian dermoid cyst - Carcinomas
Autoimmune or Inflammatory Diseases:	- Systemic lupus erythematosus - Primary antiphospholipid syndrome - Rheumatoid arthritis - Sjögren's syndrome (primary or secondary) - Ulcerative colitis, Crohn's disease - Pernicious anemia - Myasthenia gravis - Autoimmune hepatitis - Infantile giant cell hepatitis - Thyroiditis (Hashimoto's thyroiditis, Graves' disease)

	- Lymphocytic interstitial pneumonitis - Sarcoidosis - Shulman's fasciitis
Infectious Diseases:	- Infectious mononucleosis (EBV) - Chronic infection with HCV, HIV - CMV, Parvovirus B19 - Tuberculosis - Brucellosis - Syphilis
Primary Immunodeficiencies:	- Common variable immunodeficiency - Autoimmune lymphoproliferative syndrome (ALPS) and "ALPS-like" syndrome - IPEX syndrome - Genetic syndromes: Wiskott-Aldrich syndrome, Kabuki syndrome - Combined humoral and cellular immunodeficiencies - Syndromes with autoimmunity and/or lymphoproliferation and/or immunodeficiency due to mutations in CTLA4, LRBA, or STAT3 genes
Miscellaneous:	- Pregnancy - IgG4-related disease - Post-bone marrow transplantation - Di George syndrome

II. DIAGNOSTIC OF AUTOIMMUNE HEMOLYTIC ANEMIAS

1. Clinical Diagnosis

Anemia develops when the number of red blood cells and hemoglobin levels decrease. This is manifested by pallor, fatigue, shortness of breath, exertional tachycardia, dizziness, and ringing in the ears [7].

Hemolysis is commonly associated with bilirubin, a breakdown product of hemoglobin, leading to a yellowing of the skin and whites of the eyes (jaundice). The excretion of undegraded hemoglobin in the urine can result in dark-colored urine.

2. Laboratory Diagnosis

2.1. Complete Blood Count + Reticulocyte Count

It reveals a regenerative normochromic anemia with mild macrocytosis due to reticulocytosis. However, the reticulocyte count may be normal or low during the early days. Varying degrees of thrombocytopenia and/or neutropenia may be observed in Evans syndrome [8, 9]. Note that the presence of high titers of cold agglutinins (cold agglutinin disease) can cause agglutination in the test tube, making it impossible to count red blood cells and measure hematocrit. In such cases, the tubes should be promptly sent to the laboratory and transported at 37°C [10].

2.2. Examination of Red Blood Cells on Blood Smear:

This is a fundamental examination that should be performed urgently in cases of hemolysis, regardless of the suspected cause. In autoimmune hemolytic anemias, it provides important elements for positive and differential diagnosis.

During AIHA, it is common to observe polychromatophilia, anisocytosis, and poikilocytosis. The presence of spherocytes, indicating incomplete phagocytosis of erythrocyte membrane fragments by splenic macrophages, is not specific to hereditary microspherocytosis and is observed in 45% of AIHA cases [11].

The presence of schistocytes, especially in the presence of thrombocytopenia, should raise suspicion of thrombotic thrombocytopenic purpura (TTP), which requires urgent management with appropriate therapeutic modalities. Other causes of congenital hemolytic anemia (G6PD deficiency, etc.) or acquired hemolytic anemia (malaria, etc.) can be confirmed by blood smear examination and exclude the diagnosis of AIHA.

2.3. Confirmation of the Autoimmune Nature of Anemia (Coombs Test):

This confirmation is based on a semi-quantitative test called the direct Coombs test, where a positive result indicates the presence of autoantibodies and/or complement fixed to the surface of red blood cells [12].

In cases of suspected autoimmune hemolytic anemia (AIHA) with a negative direct antiglobulin test, it is recommended to systematically search for the presence of IgA antibodies. If the only positive direct antiglobulin test is for complement (anti-C3d), a specific search and titration of cold agglutinins should be performed [13]. The indirect antiglobulin or indirect Coombs test is positive in approximately 50% of cases of "warm" AIHA, and as a result, the indirect antiglobulin test for irregular antibodies is also positive in these cases due to the presence of autoantibodies in the serum [13, 14]. Although antibody elution and titration tests may be useful in defining the specificity of antibodies against blood group antigens, they are not

available in all laboratories and are not essential for the diagnosis in routine practice [14].

2.4. Search for Associated Diseases:

The result of the direct antiglobulin test (DAT) determines the etiological assessment. In adults, it is important to differentiate warm autoimmune hemolytic anemias with autoantibodies, where an associated disease is present in approximately 50% of cases (Table 2), from cold agglutinin disease, which is most often associated with a monoclonal IgM kappa immunoglobulin [15].

In children, autoimmune hemolytic anemias with cold agglutinins, which represent only 15-20% of cases, are mostly post-infectious.

In 10 to 15% of cases, an infection may be present in AIHA with warm antibodies at the time of the initial diagnosis. They may also be associated with other immunological abnormalities, either present at the time of diagnosis or appearing during the course of the disease, in approximately 35% of isolated AIHA cases.

Based on the patient's history and clinical context, the recommended additional tests to search for an underlying associated condition in adults or children with warm antibody autoimmune hemolytic anemia are shown in Tables 3 and 4.

Table 3: Additional tests to be performed in adult cases of cold antibody autoimmune hemolytic anemia

Disease to be investigated	Systemic examinations	Context-dependent examinations
Infections		Mycoplasma testing Serology for HIV, HCV, CMV, Parvovirus B19, EBV
Lymphoid lineage hematopathies	Serum protein electrophoresis (SPEP) Thoracic and abdominal CT scan B-cell immunophenotyping	CH50, C3, and C4 complement levels Lymph node biopsy Bone marrow biopsy

Table 4: Diagnostic investigations for warm antibody autoimmune hemolytic anemia with autoantibodies

Suspected Disease	Systematic Examinations	Context-dependent Examinations
Autoimmune Disease (systemic lupus erythematosus, antiphospholipid syndrome)	Antinuclear antibodies (ANA) testing, and if ANA+, testing for anti-extractable nuclear antigens or anti-ENA and native anti-double-stranded DNA antibodies	Antiphospholipid antibodies testing: IgG and IgM anticardiolipin antibodies, anti-β2-glycoprotein 1 antibodies, and lupus anticoagulant testing in cases of lupus, history of thrombosis, and/or prior to splenectomy Complement fractions C3, C4, and CH50
Lymphoid hematopathy*	Serum protein electrophoresis (SPEP) | Circulating B-cell immunophenotyping Thoracoabdominopelvic CT scan	Bone marrow biopsy if there is a monoclonal spike, deep lymphadenopathy, disproportionate splenomegaly compared to the degree of hemolysis, or hypogammaglobulinemia Lymph node biopsy
Solid tumors	Thoracoabdominopelvic CT scan	
Immune deficiency	| Quantitative immunoglobulin levels (IgG, IgA, IgM) T, B, NK cell phenotyping	If hypogammaglobulinemia is present: Vaccination serologies (tetanus, etc.) ± viral serologies B and T naive and memory cell phenotyping
Infection	HCV, HIV serologies HBV serology (pre-treatment before rituximab due to the risk of reactivation)	CMV, EBV serologies (if mononucleosis-like syndrome and/or suggestive context) Parvovirus B19 serology ± PCR (if low reticulocyte count) Syphilis serology

2.5. Differential Diagnosis

Other causes of hemolysis, both constitutional (membrane abnormalities, hemoglobinopathies, enzyme deficiencies) and acquired, constitute the differential diagnosis with autoimmune hemolytic anemias. The presence of spherocytosis on blood smears is common in autoimmune hemolytic anemias. If the direct antiglobulin test (DAT) is negative, the diagnosis of hereditary microspherocytosis (Minkowski-Chauffard disease) should be excluded [16].

Isolated positive DAT can also be observed in patients with autoimmune diseases (such as lupus) or malignant hematologic disorders (most commonly chronic lymphocytic leukemia) or during HIV infection, in which case the diagnosis of AIHA cannot be established.

Patients with constitutional hemolytic anemia (such as sickle cell disease) who have undergone repeated blood transfusions may have a positive DAT

due to the presence of allo-erythrocyte antibodies, without having AIHA.

Evans syndrome may be confused with thrombotic microangiopathy (TMA), particularly autoimmune thrombotic thrombocytopenic purpura (TTP), which is the main differential diagnosis. In cases of hemolytic anemia with thrombocytopenia, the presence of significant schistocytes (>5%) on blood smears strongly suggests TMA, either typical TTP or atypical hemolytic uremic syndrome (HUS) in the presence of renal involvement [17, 18].

However, the diagnosis can be challenging because a weakly positive direct antiglobulin test may sometimes be present in the context of authentic autoimmune TTP, while a few schistocytes may be observed in authentic Evans syndrome. In such cases, the presence of neurological manifestations (TTP) and/or renal manifestations (HUS) and/or fever (TTP), as well as the absence of evident cutaneous-mucosal hemorrhagic syndrome despite sometimes profound thrombocytopenia, favor a diagnosis of TMA rather than Evans syndrome [17].

III. TRAITEMENT DES ANEMIES HEMOLYTIQUES AUTO-IMMUNES

La stratégie thérapeutique des anémies hémolytiques auto-immunes est en fonction de la forme de la maladie.

Dans le cas des AHAI à anticorps chauds, le traitement repose sur les corticoïdes qui permet d'empêcher la destruction des hématies, le traitement se prend par voie per os et la dose initiale est maintenue pendant 4 à 6 semaines, puis réduite progressivement [19]. Ce traitement est maintenu pendant au moins 1 an avec une efficacité chez environ 85 % des cas.

Dans le cas d'inefficacité ou de rechute, des immunosuppresseurs ou un anticorps monoclonal peuvent êtres proposés. La splénectomie peut être envisagée si la corticothérapie n'a pas été efficace [20-22].

Dans le cas des AHAI à anticorps froids, l'anémie est généralement modérée et des mesures de protection contre le froid suffisent. Dans ce cas, il est recommandé aux patients, pendant l'hiver, de porter des vêtements chauds. Dans les formes sévères, les immunosuppresseurs peuvent être envisagés. Des transfusions de globules rouges réchauffés peuvent parfois êtres indiquées.

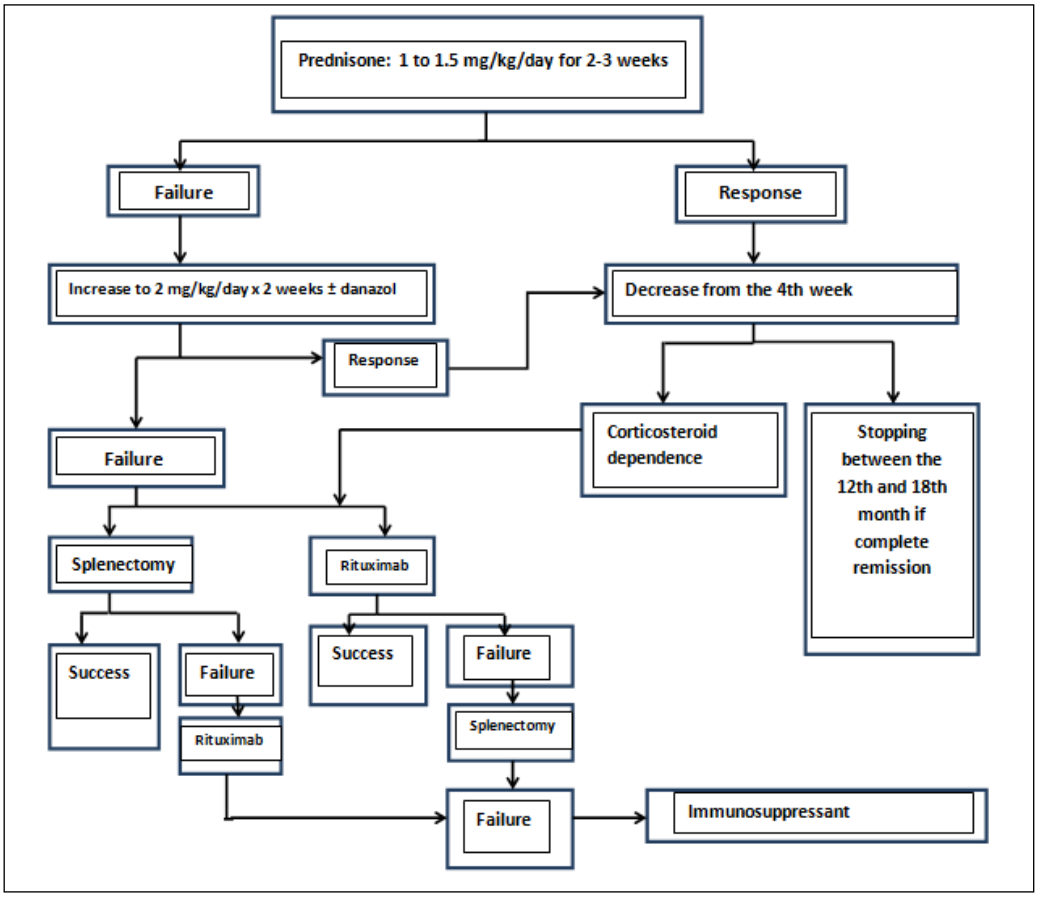

Figure 1: Decision tree. Therapeutic strategy for the management of warm autoimmune hemolytic anemia in adult idiopathic cases [16]

IV. SURVEILLANCE OF AUTOIMMUNE HEMOLYTIC ANEMIAS

1. Clinical Monitoring

- Monitoring of AIHA and underlying diseases.
- Monitoring of infections and secondary organ pathologies (such as digestive malabsorption).
- Monitoring of growth and weight development in children.

2. Laboratory Monitoring

2.1. Monitoring of hemolytic anemia:

2.1.1. Complete blood count

Regular monitoring of complete blood count, including reticulocyte and platelet counts: Every 2 weeks at the beginning of treatment, then gradually spaced out after a favorable response to treatment [16].

2.1.2. Hemolysis parameters:

- Measurement of unconjugated plasma bilirubin levels.
- Measurement of LDH levels ± haptoglobin levels.
- In cases of persistently elevated levels of free bilirubin, with normal complete blood count and other hemolysis parameters, Gilbert's disease should be considered.

2.1.3. Direct antiglobulin test (DAT)

The DAT remains positive in the majority of cases even after remission, and the presence of free antibodies in the serum and its negativization is not a therapeutic goal in itself [16].

2.2. Treatment Monitoring

- Monitoring of potassium levels, fasting blood glucose, and glycosylated hemoglobin to detect corticosteroid-induced diabetes [11].
- Measurement of immunoglobulin levels to screen for the development of secondary hypogammaglobulinemia [11].

CONCLUSION

Autoimmune hemolytic anemia (AIHA) is a rare event in adults but has a relatively poor prognosis. The diagnosis of AIHA relies on rigorous interpretation of immunohematological parameters, as well as additional tests to exclude associated diseases. In "idiopathic" cases, it is recommended to continue monitoring elderly patients beyond remission to detect the possible occurrence of lymphoma or myelodysplastic syndrome. Corticosteroid therapy is the standard treatment, but it can lead to numerous side effects. The efficacy of rituximab appears particularly promising in "refractory" forms of AIHA, and its use in the early phase of management to spare corticosteroid therapy should be evaluated in a prospective and randomized study.

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