

Autoimmune Hemolytic Anemia - A Short Review of the Literature, with a Focus on Elderly Patients

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Abstract

Autoimmune hemolytic anemia (AIHA) is the most common extracorporeal hemolytic anemia. AIHAs are related to the presence of autoantibodies directed against components of the erythrocyte membrane. To date, data related to AIHA are rare, primarily from retrospective studies of small effective. To our knowledge, data related to AIHA in elderly subjects are almost non-existent. Thus, we report our experience of 10 consecutive patients older than 75 years with a documented AIHA.

Keywords: Autoimmune hemolytic anemia; Elderly; Lymphoproliferative disorder; Steroid

Introduction

Autoimmune hemolytic anemia (AIHA) is the most common extracorporeal hemolytic anemia [1]. AIHAs are related to the presence of autoantibodies directed against components of the erythrocyte membrane [2].

The prevalence of AIHAs is estimated at 1 to 3 per 100.000 inhabitants (orphan disorder), being less common than immune primary thrombocytopenia. AHAI is usually reported in middle age adult patients.

The thermal optimum of reactivity allows us to distinguish warm antibody AIHAs (the most frequent form, mostly of the IgG type) from

cold antibody AIHAs (of the IgM type), which has a completely different etiological and therapeutic profile (Table 1) [2,3].

Their sudden onset, potential seriousness, and unpredictable nature impose both rapid and well-codified management [1,3]. Furthermore, the treatment initiated must take account of the wide range of etiologies responsible for these disorders.

To date, data related to AIHA are relatively rare, primarily from retrospective studies of small effective. To our knowledge, data related to life-threatening AIHA or AIHA in elderly subjects are almost non-existent.

Thus in the present paper, we realize a short review of AIHAs and report our experience of 10 consecutive patients older than 75 years with a documented AIHA.

	Warm antibody AIHA	Cold antibody AIHA
Incidence	+++	+
Direct Coombs' test	Positive (IgG, IgG+complement, IgA)	Positive (isolated complement or IgM+complement)
Elution test	Positive (IgG)	Non-reactive
Indirect Coomb's test	Positive (IgG)	Positive (high levels IgM at 30°C)
Context	Adult	Child or adult
Etiologies	Drugs, acute disseminated lupus erythematosus, lymphoproliferative disorders, viruses	Infectious diseases (EBV, CMV, Mycoplasma sp), cold agglutinin disease (other lymphoproliferative disorders)
Investigations	Blood count and blood smears, lymphocyte phenotype, bone marrow examination, B and C virus serology, HIV serology, antinuclear antibodies, thoracic X-ray, abdominal, ultrasound	Blood count and blood smears, lymphocyte phenotype, serum protein electrophoresis, bone marrow examination, EBV and CMV serology, Mycoplasma serology, chest x-ray

Treatment	Symptomatic (red cell transfusions) and treatment of underlying cause, steroids (oral or intravenous), intravenous immunoglobulin, rituximab, splenectomy, immunosuppressive agents,	Symptomatic (red cells transfusions) and treatment of underlying cause, rituximab, plasmapheresis
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Table 1: Characteristics of AIHA [1,3,5,10].

Clinical Picture of AIHA

The clinical picture of AIHA, especially in elderly patients, include: 1) manifestations related to anemia i.e. pallor, tachycardia, polypnea, asthenia, and excessive fatigability under stress, these latter are difficult to interpret in elderly patients; and 2) those of hemolysis including jaundice, dark urine and splenomegaly [1,3].

AIHAs most often present as acute intravascular hemolysis, in which jaundice and splenomegaly may be absent, while fever, hemoglobinuria, acute lumbalgia, renal insufficiency, and

hemodynamic instability may predominant. In the emergency setting, such AIHAs can progress to hypovolemic shock [1].

Specific data related to AIHA in population of elderly patients are rare or quit specifically nonexistent in the literature (case-reports or small series). Clinical characteristics of such patients are described in Table 2 [4]. These patients, older than >75 years with documented AIHA, have been extracted from the database of AIAH, in the University Hospitals from Reims and Strasbourg (France).

Patient	Sex	Age (years)	Hemoglobin level at admission	Clinical manifestations of hemolytic anemia	Coombs results	Type of warm antibodies	Presence of agglutinins	Associated disorders	First line therapy	Failure of first therapy	Second line therapy	Death
			(d/dL)				(titer >1/64)					
1	M	88	7.3	Yes	D/I +	IgG/C3d +	None	Chronic lymphoid leukemia	Steroid	-	-	-
2	F	81	7.8	Yes	D/I +	IgG +	None	Non-classified autoimmune disorder	Steroid	Yes	Immunosuppressive agents	No
3	M	85	9.5	Yes	D/I +	IgG +	None	Lymphoma	-	-	No	Yes
4	F	92	6.5	Yes	D +	IgG/C3d +	None	Chronic lymphoid leukemia	Steroid	-	No	Yes
5	F	85	5.8	Yes	D/I +	IgG/C3d +	Yes	Lymphoma	Steroid	Yes	Immunosuppressive agents	-
6	F	82	6.1	Yes	D -	IgG/C3d +	None	Idiopathic	Steroid	-	No	-
7	F	76	9.3	None	D +	C3d +	Yes	Cold agglutinin disease with lymphoma	Avoidance of cold	No	No	No
8	M	83	10.7	None	D +	-	None	Idiopathic	None (wait and see).	No	No	No
9	F	91	7.,1	Yes	D +	IgG/C3d +	Yes	Cold agglutinin disease	Avoidance of cold	No	No	No
10	F	93	12.3	None	-	C3d+	Yes	Idiopathic	-	No	No	No

Table 2: Characteristics of AIHA in 10 elderly patients at least 75 years old [4]. - : not available.

The mean age of these patients is 85.6 years (range, 76 to 93); the sex-ratio F/H is 2.7. As reported in Table 2, severe clinical manifestations related to hemolytic anemia are observed in 70% of cases, such as: chest pain (n=4), tachycardia (n=4), cardiac failure (n=3), confusion (n=3) and excessive fatigability (n=6). These

symptoms, as the depth of anemia, led to a transfusion requirement in a majority of patient (n=7) [4].

In the presence of an acrosyndrome and when a hemolytic crisis is triggered by cold exposure, a cold antibody AIHA must be considered

[1,3,5]. Such a clinical picture is much more common in cold antibody AIHAs.

Three of our aforementioned patients have symptomatic manifestations of acrosyndrome [4]. In secondary AIHAs, the clinical presentation may be dominated by clinical signs of the primary condition, such as arthralgia and cutaneous signs (vespertilio, photosensitivity, etc.) as observed in cases of systemic lupus erythematosus or tumoral syndrome (lymphadenopathy, splenomegaly, etc.) as observed in lymphoproliferative disorders [6-8].

Positive Diagnosis of AIHA

The positive diagnosis of AIHA is based upon confirmation of hemolysis as well as detection of autoantibodies [1,5-7].

Hemolytic anemia should be suspected if the following signs are present: 1) acute-onset anemia (hemoglobin <120 g/l), with normocytosis or macrocytosis (mean erythrocyte cell volume >100 fl) and high level of reticulocytosis (reticulocyte count >120000/mm³); 2) decreased haptoglobin (the most constant sign), hyperbilirubinemia with a predominance of unconjugated bilirubin, and raised LDH levels [1,9].

In addition, thrombocytosis and hyperleucocytosis may also be observed [6-8]. Peripheral blood film may be useful, as this examination is likely to provide additional indicators of hemolysis and its cause.

A direct Coombs' test is the gold standard examination for diagnosing AIHA (Table 1) [1-3]. Using specific anti-globulins, this test allows detection of antibodies and/or complement fraction fragments fixed on red cell surfaces. Most often, IgG immunoglobulins are detected, and more rarely, IgA or IgM immunoglobulins [2,5,9]. A direct Coombs' test may be performed at a temperature of either 4°C or 37°C.

Low antibody density (<200 antibody molecules per red cell) may result in false negative results, whereas false positive test results may be linked to a transfusion history, foeto-maternal incompatibility or nonspecific immunoglobulin adsorption in the case of monoclonal or polyclonal gammopathy.

In the case of a positive direct Coombs' test with complement alone, the presence of cold agglutinins must be sought [1,3,9].

In our aforementioned cohort of elderly patients with AIHA, the mean hemoglobin level is 82 d/l (range, 58 to 123) (Table 2) [4]. In these patients, AIHA related to warm antibodies are documented in 70% of the cases.

Further diagnostic tests include the Elution test and indirect Coombs' test. An Elution test, (which is not essential for diagnosis), is performed by removing antibodies from the red cell surface membrane and bringing them into contact with a specific erythrocyte panel [1,9].

Alternatively, the indirect Coombs' test may be used. This can be carried out at different temperatures and circulating autoantibodies are detected and identified using a control erythrocyte panel [1-3].

Associated and/or Causative Disorders of AIHA

Depending on whether cold or warm antibodies are identified, the causes of AIHA vary [1,3,5,8]. Predominant etiologies of warm antibody AIHAs include: systemic lupus erythematosus, certain viruses and lymphoproliferative disorders.

The main causes of cold antibody anemia include: Mycoplasma, Cytomegalovirus, and Epstein Barr Virus infections (in transient adult AIHAs) and biphasic hemolysin (Donath-Landsteiner) in young children, as well as lymphoproliferative disorders [10-12].

The main causes of AIHAs as well as laboratory findings and recommended management steps are summarized in Table 1 [1-3]. In all cases, common immune variable deficiency must be excluded as a matter of routine [12].

In elderly patients, lymphoproliferative disorders are the main causes, as observed in the aforementioned case-report series (Table 2) [1,4].

The combination of both AIHA and immune primary thrombocytopenia refers points to the diagnosis of Evans syndrome, which is mainly caused by systemic lupus erythematosus and lymphoproliferative syndromes [13,14].

Differential Diagnosis of Hemolytic Anemia

In the emergency setting, all other causes of acute anemia must be differentiated from AIHA [1]. Severe active hemorrhage can easily be ruled out. Patient history and clinical examination may reveal signs in favor of sepsis, toxin or allergy-mediated immune hemolysis [1-3,5].

Based on the results of the full blood count and blood film, the differential diagnosis must include other conditions potentially associated with spherocytosis, e.g. inherited microspherocytosis, Wilson's disease and, in particular, septic hemolytic anemia caused by *Clostridium perfringens*. When considering infectious causes, babesioses must be excluded.

Examination of the blood film allows the physician to exclude hemolysis, and the percentage of schistocytes also needs to be assessed to rule out thrombotic microangiopathy [1,3,10].

In frailty or too sick elderly patients, especially in malnourished context, vitamin B12 (cobalamin) and vitamin C deficiencies must be ruled out [15].

It should also be noted that all causes leading to jaundice with fever, notably those conditions where jaundice is the predominant feature, should also be considered in the differential diagnosis [1,10,12].

Criteria for Assessing the Severity of AIHA

Once AIHA has been diagnosed in the acute stage, its degree of severity must be assessed [3,5,10-12]. The deep and the extent of the anemia, the clinical condition of the patient and acute onset generally mean that prompt therapeutic intervention is required – particularly in elderly patients (frailty or too sick) or patients with underlying organic diseases, i.e.: cardiac insufficiency, ischemic cardiopathy, gastric ulcer, etc. [12,16,17].

It's also imperative to determine the drugs taken by patients, such as anticoagulant or antiplatelet agents. These are indeed responsible for an increased bleeding risk.

Certain etiologies such as HIV, systemic lupus erythematosus and lymphoproliferative disorders are likely to result in a worse prognosis due to their systemic effects in conjunction with AIHA, or due to complications which arise from opportunistic infections in states of immunodeficiency [12-16].

In elderly patients, especially in frailty or too sick patients, it's necessary to list all the comorbidities to integrate these latter in the diagnostic and therapeutic approach. It is indeed essential not to generate iatrogenic complications and successfully integrate in the therapeutic decision the potential side effects of drugs.

Management of AIHA

General measurements

A summary of the main therapeutic principles for AIHAs is given in Table 1 [1,5,16,18]. Clinically, if the anemia is poorly tolerated, urgent treatment is required. Oxygen therapy is generally necessary, particularly if signs of hypoxia are observed.

Although careful attention to hydration status and avoidance of intravascular volume depletion is necessary, frequent administration of large volumes of crystalloid should be avoided, due to the risk of hemodilution [1,3].

Hemofiltration may be required in cases of anuria secondary to acute hemolysis [19].

The indication for blood transfusion must be carefully considered, particularly in AIHA cases with complement alone, as the transfused red blood cells are extremely fragile due to the active hemolytic process [16,18]. Moreover, alloantibody test results may be falsely negative because of the presence of masking autoantibodies.

In AIHAs, transfusion is only considered in combination with other treatments, for example in cases of severe, poorly tolerated acute anemia [1,18].

Treatment of Warm Antibody AIHA

As shown in Table 1, for warm antibody AIHAs, corticosteroid therapy in the form of methylprednisolone pulse therapy at a dose of 15 mg/kg/day for 3 days is administered as emergency treatment [1,5,10,16]. Thereafter, oral prednisone at a dose of 1 or 1.5 mg/kg/day is given.

Splenectomy and other immunosuppressant medications, notably rituximab (Mabthera[®]), are indicated should there be any resistance to corticosteroids [10,20,21].

Polyvalent immunoglobulins are far less effective than for immune primary thrombocytopenia treatment [10].

Since plasmapheresis has a targeted action on plasma, its efficacy is much lower in warm antibody AIHAs where hemolysis is chiefly interstitial, than in cold agglutinin disease, where hemolysis is mostly intravascular [19,20].

In the acute setting, the additional use of simple treatments must not be underestimated, and patients should be supplemented with folate (vitamin B9), iron, and if necessary, vitamin B12 and vitamin C to promote medullary regeneration [15].

In cases of treatment failure and in the absence of a reticulocytosis, infection with parvovirus B19 must be excluded [1-3].

AIHA related to warm antibodies are documented in 70% of our aforementioned cohort of elderly patients (Table 2) [4]. Five patients present a lymphoproliferative disorders. Symptomatic measures and steroids are the main therapies, with requirement of immune-suppressive agents in only 2 patients. In these patients, oral prednisone

is given at a dose of 1 or 1.5 mg/kg/day. This fact may be in relation with the frailty status of the patients.

Deaths are reported in 2 patients in relation with the underlying disease (chronic lymphoid leukemia and lymphoma) [4].

Treatment of Cold Antibody AIHA

Avoiding cold exposure is an obvious but necessary measure in the treatment of cold antibody AIHAs [1,3,5]. By using this measure alone, acute hemolytic crises can be prevented in moderate cases of AIHA, thus reducing the need for transfusions.

In severe cases, cold avoidance is necessary but not sufficient. In this instance, corticosteroids are rarely effective, or may even be ineffective, and splenectomy is of little use as erythrocytes are destroyed in the liver and not in the spleen [1,5,10].

Rituximab has been used in the treatment of AIHAs, resulting in responses ranging from 40% to 100% [1,11,22]. It appears to be less effective in warm antibody AIHAs than in cold agglutinin disease - for which it is considered to be a first-line treatment [1,5,10].

Plasmapheresis, which shows good efficacy as a "rescue solution", is rarely used as first-line treatment [19].

In most cases, post-infectious hemolysis resolves spontaneously, and treatment is essentially symptomatic [1].

As see in Table 2, in a frailty population of patients older than 75 years with severe AIHA related to col antibody, therapy should be primarily symptomatic, with safe operation and with good results for avoidance of cold [4].

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