International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2017): 7.296

Autoimmune Hemolytic Anemia (AIHA) in HIV-Infected Patient's: Case Report and Literature Review

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Abstract: ***A 52 years old man with Human Immunodeficiency virus (HIV) infection who presented with Autoimmune Hemolytic Anemia (AIHA) which was diagnosed from clinically and serologically finding. An abnormal serology direct and indirect antiglobulin (Coomb's) test with a positive result has been observed in these patients. Corticosteroids and washed red cell tranfusion were given and have been shown a significant respons.***

Keywords: AIHA, Coomb's Test, HIV

1. Introduction

Autoimmune Hemolytic anemia (AIHA) is caused by autoimmune mediated destruction of red blood cells by autoantibodies against antigens on the erythrocyte membrane with various properties and target spesificities.[1-3] The insidens of AIHA is 0.8 per 100,000 / year and the prevalens is 17 per 100,000 / year, and a mortality rate of 11%.[2,4] Autoimmune haemolyticanaemia (AIHA) is rare in persons infected with HIV. However, a few case reports have described patients with both AIHA and HIV infection, predominantly involving patients with advanced HIV/AIDS.[5]Increasing numbers of AIHA are being seen in the Human Immunonodeficiency virus (HIV) infection.Currently, the association AIHA and subsequent development mechanism of HIV remains unclear. It has been associated with a poor prognosis when treated with red cell transfusion.[1-3]

2. Case Report

A 52-year-old man was referred to our hospital presenting fatigue and loss of apatite for 2 weeks. The patient also complained shortness of breath and headache(particulary with exercise), fever, nausea, vomitus, pale, leg cramps and insomnia. The physical examination revealed a body temperature 38^0Celsius, pallor, slight icterus, oral thrush and no lymphadenopathy. He was positive for HIV and daily treated with 1 tablet of Lamivudin 150 mg, and 1 tablet combination of Zidovudine 300mg+Nevirapin 200mg for a few years.

In laboratory investigation, the tests revealedHaemoglobin 3,4 g/dL, Hematocrite 10.1%, WBC 0.44 x 10^3/uL, Trombocyte 152 x 10^3/uL, MCV 126,3fL, MCH 42,5pg, MCHC 33,7 g/dL, RDW 18%, WBC, N 72.7%, L 13.6%, M 11.4%, B 2.3%, ALT 33 U/L AST 53 U/L, BUN 14 mg/dL and SC 0,2 mg/dL. The reticulocyte level isn't perform in this patient because of modalities issues. HBsAg and anti-HCV negative, Direct Bilirubin 0.4 mg/dL, Indirect Bilirubin 1.4 mg/dL, and Total Bilirubin 1.8 mg/dL.Result of Direct and Indirect Coombs Test was postive, absollute CD4 count was 100 cells/nL

The result of peripheral blood smear was found anisocytosis, normo hypochromom, microsite, ovalocytes, macrosite, Burr cells, tear drops cell, target cell, fragmentosit, cigar cell, pencil cell, poycilocytes, rouleaux in erythrocytes; in leukocytes obtained decreased amount of impression, relative monocytosis, there is no abnormalities platelets cells.

The patient was diagnosed AIHA and HIV/AIDS on HAART based on anamnesis, clinical presentation, laboratories investigation. With these considerations, AIHA medication was given to this patient, and was treated with transfusion 5 packed of Wash Red Cells transfusion with premedication treatment (furosemidinjection 40 mg)if systole blood plessure more than 100 mmHg, metilprednisoloninjection 62,5 mg twice daily. Previous ART medication (Lamivudin 150 mg, Zidovudine 300mg+ Nevirapin 200mg) stopped and ART subtitutions drugs therapy was given with oral fixed drugs combination (Tenofovir 300 mg, Lamivudine 300 mg, Efavirenz 600 mg) once daily. Folic acid 2 mg twice daily, and Paracetamol 500 mg three times daily for supportive therapy. He was follow up for 1 weeks and found to have Hb concentration was markedly increased to 12.6 g/dL and Metilprednisolone was gradually tapered off.

3. Discussion

Anemia is prevalent among HIV/AIDS patients, it is present in 10%-20% of patients at initial presentation and in over 70% over the course of the disease.[6]Anemia in HIV/AIDS may involve 3 basic the mechanisms anemia in HIV infection or AIDS are decreased RBC production (ex: Lymphoma), increased RBC destruction (ex: DIC, Hemolysis, or Thrombotic thrombocytopenic purpura) and ineffective RBC production (ex: vitamin B12 or folic acid deficiency).[6,7] The therapy with Zidovudine is also known can suppress erythropoiesis.It is certain that the presence of anemia in people living with HIV worsens the prognosis since it is associated with progression to AIDSand shorter survival times for HIV infected patients,it has been shown that anemia is a predictor of poorer prognosis for HIV infected patients independent of the CD4 count.[1,6-8]

Autoimmune hemolytic anemias (AIHA) refer to a spectrum of disorders in which autoantibodies against antigens on the erythrocyte membrane cause shortened survival of native as well as transfused red blood cells (RBCs).The etiology of most RBC autoantibodies is not well understood. Several mechanisms have been postulated to explain AIHA develops in patients with HIV infection. Sugested-mechanism have included decreased production as a result of concurrent infections, suppresor T-cell activity and human immunodeficiency virus (HIV) infection of hemopoetic elements. The presence of erythrocyte autoantibodiesor the presence of hypergammaglobulinemia may result in non specific coating of immunoglobulin G (IgG) to autologous erytrocytes, or the presence of immune complex associated IgG, may bind to erythrocytes via C3b receptors rather than via antibodies directed against erythrocytesresults in AIHA in some patients. The anti-erythrocytes antibodies may becaused by the general defect in antibody production regulation, a characteristic of HIV infection.[7,9]

Different mechanisms have been proposed to explain this phenomenon that includes abnormal B-cell regulation by HIV-infected T cells, direct activation of B cells by HIV, or a B-cell response to coincident infection with Epstein-Barr virus or cytomegalovirus (CMV). Nonspecific immune complexes may attach to the erythrocytes and produce a positive direct antiglobulin test. Alternately, the antibody may react with specific erythrocyte antigens or this reaction may be caused by the antiphospholipid antibodies documented in patients infected with HIV. The pathophysiology of AIHA in HIV patients is unclear and further studies should be conducted. In septic patients, microbial enzymes can modify erythrocyte membrane antigen and render the erythrocytes susceptible to hemolysis by naturally occurring antibodies. In septic patients with clinical hemolysis, a minor blood crossmatch can detect this phenomenon.[7,9]

AIHA can be classified both by the type of autoantibody and by the presence of underlying disease. Pathogenic autoantibodies are divided into either cold or warm reactive, depending on the optimum temperature at which they bind RBC. The immune hemolytic anemias are classified as indicated in **Table 1.**[10,11]

Table 1: Classification of immune hemolytic anemias[10,11]

Autoimmune hemolytic anemias (AIHA)	*Optimum temperature for binding RBC*	*Predominant autoantibody class*	*Predominant site of hemolysis*	*Predominant mechanism of hemolysis*
Warm antibody AIHA Idiopathic Secondary (e.g., chronic lymphocytic leukemia, lymphomas, systemic lupus erythematosus)	37^0C	IgG	Extravascular (spleen, liver)	Phagocytosis via macrophage IgG Fc and complement receptors
Cold agglutinin syndrome Idiopathic Secondary Non-malignant disorders (e.g., mycoplasma pneumoniae infection, infectious mononucleosis, other virus infections) Malignant disorders (e.g., lymphoproliferative disorders)	4^0C	IgM (cold agglutinin syndrome) IgG (paroxysmal cold hematuria)	Intravascular	Complement lysis (membrane attack complex)
Paroxysmal cold hemoglobinuria Idiopathic Secondary Viral syndromes Syphilis				
Combined cold and warm AIHA (‘‘mixed AIHA’’)				
Drug-induced immune hemolytic anemia Drug-related antibody identifiable Drug-induced AIHA				
Alloantibody-induced immune hemolytic anemia Hemolytic transfusion reactions Hemolytic disease of the fetus and newborn				

The clinical features of AIHA may be varied and depend on the rate of hemolysis, degree of bone marrow compensation, and the presence of an underlying disorder.[1,12]

The most common symptoms are signs of anaemia, such as fatigue, dizziness and breathlessness. The onset of symptoms may be insidious, subacute or acute. In physical examination we can find there are clinical manifestation like anemia, pallor, mild jaundice, and splenomegaly. AIHA can be classifed as mild, moderate or severe.[1,12]

1) Mild hemolytic anemia. It is caracterized by positive direct antiglobulin test result only.
2) Moderate anemia. It is caracterized by anemia and splenomegaly.
3) Severe anemia. It is characterized by fulminant hemolysis with marked spherocytosis, hyperbilirubinemia, absent or decreased levels of haptoglobin, and hemoglobinuria.

There are a classification that divides the disorders into distinctive categories which have differing clinical manifestations, prognosis and therapy, as indicated in **Table 2.**[10]

Table 2: Some characteristic features of autoimmune and drug induced immune hemolytic anemias[10]

Warm antibody AIHA
Clinical manifestations: Variable, usually symptoms of anemia, occasionally Acute hemolytic syndrome
Prognosis: Fair, with significant mortality
Most effective therapies: Steroids, splenectorny, immunosuppressive drugs
Cold agglutinin syndrome
Clinical manifestations: Moderate chronic hemolytic anemia in middle-aged or elderly person, often with signs and symptoms exacerbated by cold
Prognosis: Good, usually a chronic and quite stable anemia
Most effective therapies: Avoidance of cold exposure, immunosuppressive drugs
Paroxysmal cold hemoglobinuria
Clinical manifestations: Acute hemolytic anemia, often with hemoglobinuria, particularly in a child with history of recent viral or viral-like illness
Prognosis: Excellent after initial stormy course
Therapy: Not well defined; steroids empirically and transfusions if required
Drug-induced immune hemolytic anemia
Clinical manifestations: Variable, most commonly subacute in onset, but occasionally acute hemolytic syndrome
Prognosis: Excellent
Therapy: Stop drug; occasionally a short course of steroids empirically

The diagnosis of AIHA should be established in four step:

In the first step, it has to be demonstrated that the anaemia is a haemolytic anaemia. Haemolytic anaemias are usually normocytic anaemias, or are macrocytic because of marked reticulocytosis or because of (concomitant) folate deficiency. Usually, there is marked anisocytosis (increased red cell distribution width). Spherocytes may be seen in the blood smear, as describe in **Figure 1.** Sometimes, anemia is rapidly progressing and severe or even life-threatening. Laboratory parameters indicating haemolysis include a reduced serum haptoglobin (marker of increased red cell destruction) and an increased reticulocyte count (as sign of reactive increased erythropoiesis). On the basis of these findings, the diagnosis of haemolytic anaemia can usually be established. Other typical findings are an increase in indirect bilirubin, an increased urobilinogen in the urine, and an elevated lactate dehydrogenase (LDH) level. The latter findings are non-specific, but represent valuable information confirming the diagnosis of haemolytic anaemia. The LDH level is a useful marker related to the severity of haemolysis, and thus also a useful marker for monitoring of treatment responses.[12,13]

The second step in the diagnostic algorithm is the differentiation of immune from non-immune haemolyticanemia. This is best performed by the direct antiglobulin test (DAT, Coombs test). Using this test, the presence of immunoglobulins (in particular IgG, but also IgA or IgM) and/or of degradation products of complement (C3d or C3c) on the surface of red cells can be demonstrated. These proteins are present on normal red cells in small amounts, but are elevated in patients with immune haemolysis. When the DAT is positive for immunoglobulins and/or complement fragmens in a patient with typical signs of haemolyticanaemia (step one), the diagnosis of immune haemolyticanaemia can usually be established. [12,13]

The third step is the identification of the type of antibody. Notably, four types of antibodies can be detected in AIHA patients.

The most common type are warm antibodies (75%–90%), and the AIHA is then called warm antibody autoimmune haemo- lytic anemia (WA-AIHA). Second is cold antibodies, the antibody is usually an IgM which is directed against polysaccharide antigens. Cold antibodies are frequently monoclonal antibodies (primary cold agglutinin disease, lymphomas) but may also be polyclonal antibodies (infections and possibly T-cell lymphomas). The haemolysis in cold agglutinin disease is mainly an intravascular haemolysis (in contrast to paroxysmal cold hemoglobinuria). The clearance of red cells in these patients occurs in the liver.In some case, mixed antibodies (warm and cold antibodies) are detectable These patients have severe haemolysis but show (in contrast to patients with cold agglutinins alone) a good clinical response to therapy with glucocorticosteroids. [12,13]

The last step in the diagnostic algorithm is to define whether the AIHA is an idiopathic (primary) disease or developed on the basis of an underlying disease (secondary AIHA). The spectrum of underlying diseases in warm antibody AIHA and cold antibody AIHA is similar but is not identical. [12,13]

In addition, the results from routine laboratory tests (acute phase reaction, electrophoresis) and the type of antibody (warm or cold) must be considered. A careful examination of the blood smear is essential to document or to exclude a malignant haematologic disorder, in particular a lymphoproliferative disease. A bone marrow examination is recommended in all cases of suspected lymphoma or other haematological neoplasms. An abdominal CT scan is indicated in otherwise unexplained AIHA to exclude intraabdominal lymphomas or a solid tumor. Quantitative determination of immunoglobulins and immunofixation should be performed in all cases in order to detect monoclonal gammopathy or/and immunoglobulin deficiency.Immuno- phenotyping of lymphocytes may be a sensitive method to detect smaller amounts of monoclonal peripheral or bone marrow lymphocytes. A screen test for lupus anticoagulant (APTT with a lupus sensitive reagent) should also be performed, since coexistence of AIHA with a lupus anticoagulant is not uncommon. Such patients may be at high risk of thrombosis. Anticardiolipin or antinuclear antibodies are often elevated in patients with AIHA, but such test results have no predictive value – they should thus only be determined when clinically indicated.[12]

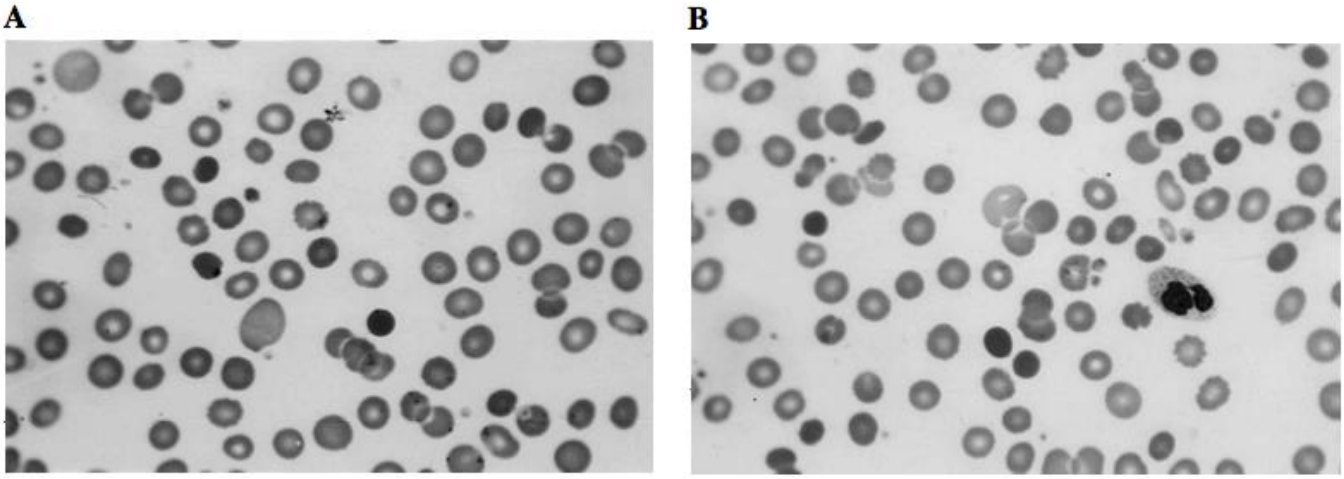

Figure 1. A and B : Peripheral blood smear that showing spherocytosis in AIHA asociated HIV infection

Treatment
The traditional treatment of AIHA includes corticosteroids, splenectomy and conventional immunosuppressive drugs.

First-line therapy
Corticosteroids
There is general agreement that corticosteroids represent the first-line treatment for patients with warm antibody type AIHA, albeit their use is based on experience rather than hard evidence. Corticosteroids, usually prednisone, are given at the initial dose of 1.0-1.5 mg/kg/day for 1-3 weeks until hemoglobin levels greater than 10 g/dL are reached. Response occurs mainly during the second week, and if none or minimal improvement is observed in the third week, this therapy is assumed to be ineffective. After stabilization of hemoglobin, prednisone should be gradually and slowly tapered off at 10-15 mg weekly to a daily dose of 20-30 mg, then by 5 mg every 1-2 weeks until a dose of 15 mg, and subsequently by 2.5 mg every two weeks**.** AIHA patients should be treated for a minimum of three or four months with low doses of prednisone (≤10 mg/day).[1,4]

Prolonged steroid therapy in AIHA patients on should be given bisphosphonates, vitamin D, calcium, and folic acid supplementation. Patients with particularly rapid hemolysis and very severe anemia, or complex cases such as Evans syndrome, may require intravenous methylprednisolone at 100-200 mg/day for 10-14 days or 250-1000 mg/day for 1-3 days, although highdose corticosteroid therapy for AIHA has been described essentially as case reports. Patients unresponsive to first-line therapy should undergo a diagnostic re-evaluation for a possible underlying disease, since AIHA associated with malignant tumors, ulcerative colitis, benign ovarian teratomas, or with IgM warm autoantibodies are often steroidrefractory. [1,4]

Second-line therapy
Once the decision for a second-line treatment has been taken, there are several options, although splenectomy and rituximab are the only second-line treatments with a short erm efficacy.[1,4]

Splenectomy
Splenectomy is commonly thought to be the most effective conventional second-line treatment of warm AIHA to be proposed to patients unresponsive or intolerant to corticosteroids, in those that require a daily maintenance dose of prednisone greater than 10 mg, and in those with multiple relapses. However, its efficacy has never been compared to that of other second-line approaches, and no convincing data on remission duration after surgery are available.[1,4]

Patients with persistent or recurrent hemolysis after splenectomy often require lower doses of corticosteroids than before surgery. A drawback of splenectomy is the lack of reliable predictors of the outcome, since its effectiveness is not related to disease duration, response to steroids nor the extent of splenic sequestration. Moreover, splenectomy may be associated with surgical complications (pulmonary embolism, intra-abdominal bleeding, abdominal abscess, abdominal wall hematoma), although laparoscopic intervention has lowered the surgical risk compared to conventional surgery. The most feared complication after splenectomy is overwhelming sepsis due to encapsulated bacteria, with a risk of 3.3-5% and a mortality rate of up to 50%, even after the introduction of pre-operative vaccination against pneumococci, meningococci, and hemophilus. The incidence of infection in children and adults is reported to be similar, the death rates among children are higher than adults.[1,4]

Rituximab
Rituximab (375 mg/m weekly for a median of 4 weeks), a monoclonal antibody directed against the CD20 antigen expressed on B cells, has been shown to be effective in AIHA. Responses to treatment were observed in monotherapy or in combination with corticosteroids, immunosuppressants and interferon-α, and regardless of prior therapy.[4]

Low-dose rituximab as first- or second-line therapy (100 mg fixed dose/weekly for 4 weeks) was reported to be effective in patients with AIHA who failed to respond to conventional treatment.[4]

Immunosuppressive drugs
Before the introduction of rituximab in the therapy of AIHA, azathioprine (100-150 mg/day) and cyclophosphamide (100 mg/day) were often used as second-line treatment. Longterm therapy with cyclosporine was reported to induce complete remission in 3 in 4 of warm AIHA patients with life-threatening hemolysis unresponsive to previous treatments.[4]

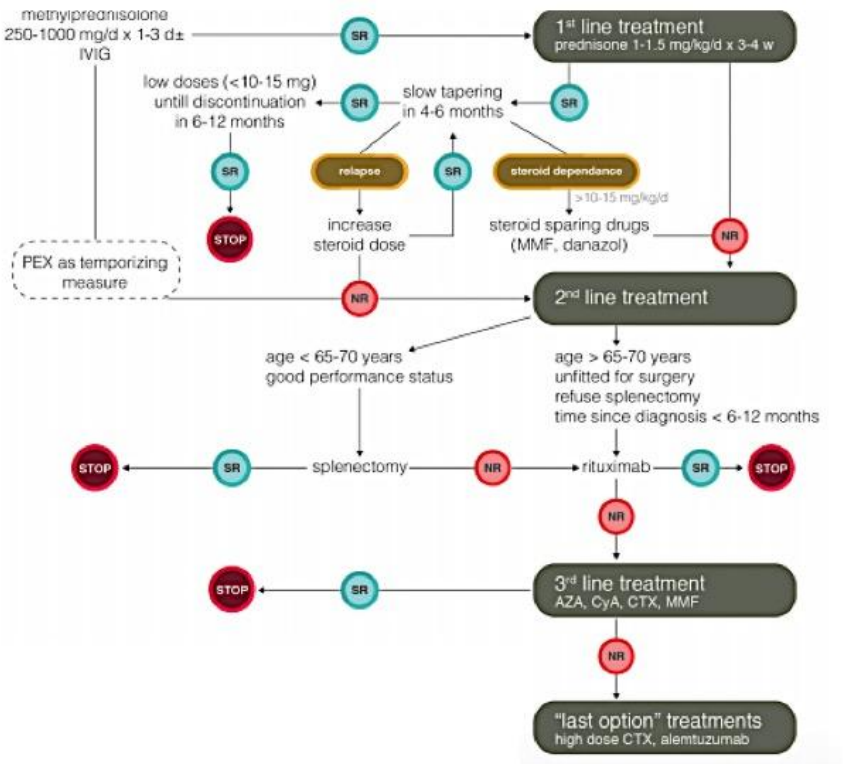

Figure 2: Treatment algorithm for warm AIHA in adults. SR: sustained response defined as maintenance of Hb values >10 g/dL over time; NR: no response; d: day; w: week; AZA: azathioprine; CyA: cyclosporine A; CTX: cyclophosphamide; MMF: mycophenolatemofetil; PEX: plasma exchange; IVIG: intravenous immunoglobulin.[4]

Hematopoietic stem cell transplantation
Information on the use of hematopoietic stem cell transplantation (HSCT) in warm AIHA is limited to single cases or small series, mostly Evans syndromes, with an overall complete remission rate of approximately 60% in allogeneic and 50% in autologous HSCT.[4]

Plasmapheresis may be useful in acute hemolytic crisis and before surgery requiring hypothermia, although its effect is transient.[1,4]

Supportive therapy
Patients with AIHA may often require red blood cell (RBC) transfusion to maintain clinically acceptable hemoglobin values, at least until specific treatments become effective. The decision to transfuse should depend not only on the hemoglobin level, but rather on the patient's clinical status and comorbidities (particularly ischemic heart or severe pulmonary disease), the acuteness of disease at onset,the rapidity of progression of the anemia, and the presence of hemoglobinuria or hemoglobinemia and other manifestations of severe hemolysis. The blood transfusion should never be denied to patients in a critical clinical situation, even in cases in which no truly compatible units can be found, since warm autoantibodies are frequently panreactive. ABO- and RhD-matched red cell concentrates can found in any case be safely administered in urgent cases if alloantibodies (known to occur in 12-40% of AIHA patients) are reasonably excluded on the basis of the previous transfusion and/or pregnancy history. In less urgent cases, an extended phenotyping is advisable and compatible red cell units may be selected for transfusion.[1,4]

4. Conclusion

A 52-years old male patient was presented in this case report, with diagnosed AIHA with HIV infections. Laboratory tests revealed severe anemias, elevated Indirect and Total Bilirubin,with positive for Direct and Indirect Coombs Test. In therapy with 5 packs of Wash Red Cell transfusion, corticosteroid and ART subtitutions drugs therapy, patients experience significant clinical and laboratory improvement. The use of antiretroviral drugs regularlyand routine control is recommended to prevent the risk of recurrence of severe anemia.

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