Autoimmune Hemolytic Anemia
in Systemic Lupus Erythematosus Patient
A Case Report
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ABSTRACT
Autoimmune hemolytic anemia (AIHA) is a relatively uncommon disorder caused by autoantibodies directed against self red blood cells. It can be idiopathic or secondary, and classified as warm, cold (cold hemagglutinin disease (CAD) and paroxysmal cold hemoglobinuria) or mixed, according to the thermal range of the autoantibody. AIHA may develop gradually, or have a fulminant onset with life-threatening anemia.

Hematologic abnormalities are common in patients with systemic lupus erythematosus (SLE); nearly all SLE patients develop some hematologic manifestation during the course of the disease. After lymphopenia, anemia is one of the most common hematologic disturbances, with almost 50% of SLE patients developing it at some point, attributed in the majority of cases to anemia of (normocytic, normochromic) chronic disease. But systemic lupus erythematosus (SLE)-associated autoimmune hemolytic anemia (AIHA) is also common in clinical practice.

We report the case of a 18 years-old female came to the Adam Malik hospital with complaints of pallor, weakness, dizziness, and dyspnoe on exertion for about 1 month. History of spontaneous bleeding was not found. Sclera icteric was noted. After several laboratory tests and other supporting investigations, patient was diagnosed with AIHA + SLE. Patient was treated with wash red cell transfusion and glucocorticoid therapy. After being hospitalized for 10 days the patient was discharged with clinical improvement.

Key Word: Autoimmune hemolytic anemia, systemic lupus erythematosus, glukokortikoid

INTRODUCTION
The incidence of AIHA is estimated to be between 0.6 and 3 cases per 100,000 persons. AIHA is mediated by antibodies directed against self RBCs, and in the majority of cases immunoglobulin (Ig) G is the mediating antibody. This type of AIHA is referred to as
"warm" AIHA because IgG antibodies bind best at body temperature. "Cold" AIHA is mediated by IgM antibodies, which bind maximally at temperatures below 37°C. ¹²

It is a common hematological abnormality in SLE that is defined as hemoglobin levels of < 12g/dL for women and <13 g/dL for men. It is categorized into the following: anemia of chronic disease (ACD), which is the most common form (60%-80%), iron deficiency anemia (IDA), autoimmune hemolytic anemia (AIHA), and anemia due to chronic renal insufficiency. In a cohort study comprising 132 anemic patients with SLE, ACD was found in 37.1% of the cases, IDA in 35.%, AIHA in 14.4% and other causes of anemia in 12.9% of the patients.³

The diagnosis of AIHA is usually made by laboratory finding: normocytic or macrocytic anemia, elevated reticulocyte counts, low haptoglobin levels, increased indirect bilirubin concentration and a positive direct Coombs' test. It has been noted in 5% up to 10% of patients with SLE. The presence of hemolytic anemia may associate with manifestations of severe disease such as renal disease, seizures and serositis. The presence of both immunoglobulin and complements on red blood cells is usually associated with some degree of hemolysis, while presence of complements alone (C3 and /or C4) is often not associated with hemolysis.¹³⁴

CASE REPORT

A Javanese female, Ms. A 18 years-old came to the Adam Malik hospital with complaints of pallor, weakness, dizziness, and dyspnoe on exertion in the one last month. History of spontaneous bleeding e.g gum bleeding, epistaxis, hematemesis, melena, hematoma on her body was not found. History regular contact with chemicals was denied. Yellow eyes have been realized by family since the one last month accompanied by dark yellow urine like tea. History of jaundice had not previously encountered. A history of using drugs was not clear. History of hair loss, atralgia, fotosensitivity, oral ulcer were not found. The patient got 2 bag of red blood cell transfusion due to her same complaints and laboratory finding Hb 5.3 gr/dL in Insani hospital and then patient was referred to the Adam Malik hospital for further diagnostic evaluation and treatment.

On admission, vital sign: sensorium: compos mentis, blood pressure: 120/70 mmHg heart rate: 96x/i regular, respiratory rate: 24 x/i, temp: 37°C. On physical examination we found pale of conjunctival palpebral inferior, sclera subikterik, cardiomegaly and no hepatospleenomegaly.
In early laboratory test was found Hb 4.9 g/dl, Leukosit: 2500 /mm3, Ht: 11%, Trombosit: 136.000/mm3 MCV: 124 fL, MCH: 57 pg, MCHC: 45 g/dl. Neutrophil 1540/uL, lymphocyte 750/uL, monocyte 170/uL, eosinophil 40/uL, basophil 0. Reticulocyte count 15.88%, Ferritin : 421, Serum Iron : 56, TIBC : 254 (22 % transferrin saturation). PT: 21,4 / 14 (1,52), INR 1,48, APTT: 31,2/33.6 (0,92), TT: 16,7/17,2 (0,97). Bil.total 2,8 mg/dl; Bil.direk 1,0 mg / dl), SGOT 29 U/L and SGPT 12 U/L. Coombs test (+); malaria peripheral blood smear (-), LDH 607 U/L. HbsAg and Anti HCV non reaktif. ANA test 135,03, Anti dsDNA 236,3. KGD adrandom 84 mg/dL. Ureum 15 mg/dL, creatinin 0,4 mg/dL. Na 137 mEq/L, K 3,1 mEq/L, Cl 104 mEq/L. ECG was sinus tachycardia. Chest X-ray showed cardiomegaly with suspect of pleural effusion. BMP investigation with summary AIHA with erythropoietic hyperactive of bone marrow. Echocardiography showed mild pericardial effusion.

From our examination, we diagnosed the patient with Autoimmune Hemolytic Anemia + Systemic Lupus Erythematosus. Patient was treated with transfusion of 350 mL washed red cells and injection Methylprednisolone 125 mg/12 hours iv. After being transfused washed red cells we did routine blood examination Hb 6.8 g/dl, Leukosit: 2550 /mm3, Ht: 19%, Trombosit: 197.000/mm3. After being hospitalized for 10 days, the patient got clinical improvement with Hb 9.0 g/dl, Leukosit: 8200 /mm3, Ht: 19%, Trombosit: 329.000/mm3, and than patient was discharged with treatment Methylprednisolone 50mg/day (4-4-4) and Cyclosporin (sandimun) 2 x 100mg and we advised the patient to have medical control routinely.

DISCUSSION

Autoimmune hemolytic anemia (AIHA) is a relatively uncommon disorder caused by autoantibodies directed against self red blood cells, with an estimated incidence in adults of 0.8-3 per 105/year, a prevalence of 17:100,000 affects women more frequently than men and a mortality rate of 11%. AIHA is very rare in infancy and childhood (0.2 per 105/year). 2,5

In this case patient is a female, 18 years-old.

Patients with AIHA present with constitutional signs and symptoms of anaemia, including fatigue and dyspnoea on exertion. AIHA can be diagnosed in a stepwise manner. First, the anaemia must be established as haemolytic, which can be ascertained by serum biochemistry of haemolytic markers (eg, low haptoglobin levels, lactate dehydrogenase, indirect bilirubin), normocytic or macrocytic anemia, presence of reticulocytosis and by
examination of the peripheral blood smear. The bone marrow typically reveals erythroid hyperplasia. Second, using direct antiglobulin test (positive Coombs' test), the clinician should determine whether autoimmunity against red blood cells is triggering haemolysis. Lastly, identification of the type of antibody responsible for haemolysis has to be defined. Warm-acting-AIHA and cold-acting-AIHA are based on the optimal temperature of antigen–antibody reactivity. This multitiered approach should lead to diagnosis or exclusion of the diagnosis of AIHA in patients with SLE. Warm” refers to the fact that the antibody binds best at body temperature (37°C).1,3,4,6 In warm AIHA, testing will show IgG molecules attached to the surface of the red cells, with 50% of patients also showing C3. Between 50% and 90% of AIHA cases are due to warm antibodies.2

Anemia is a common hematological abnormality in SLE which categorized into the following: anemia of chronic disease (ACD), which is the most common form (60%-80%), iron deficiency anemia (IDA), autoimmune hemolytic anemia (AIHA), and anemia due to chronic renal insufficiency. Autoimmune hemolytic anemia (AIHA) noted in 5% up to 10% of patients with SLE. The presence of hemolytic anemia may associate with manifestations of severe disease such as renal disease, seizures and serositis.3,4,7 The presence of hemolytic anemia may associate with manifestations of severe disease such as renal disease, seizures and serositis. The presence of both immunoglobulin and complements on red blood cells is usually associated with some degree of hemolysis, while presence of complements alone (C3 and /or C4) is often not associated with hemolysis.1,3,4,6 In SLE the anti-erythrocyte antibody is mainly IgG of warm type and usually displays non-Rhesus specificity.8

In this case patient was diagnosed as autoimmune hemolytic anemia (AIHA) based on the complaints pallor, weakness, dizziness, and dyspnoe on exertion in the one last month, history of transfusion red blood cells without increasing of Hb as expected. Laboratory finding: anemia macrocytic, reticulocytosis, indirect bilirubin increased, Coombs test (+), LDH increased, and BMP summary : AIHA with erythropoietic hyperactive of bone marrow.

Autoimmune hemolytic anemia (AIHA) can be idiopathic (50%) or secondary to lymphoproliferative syndromes (20%), autoimmune diseases (20%), infections and tumors. They can range in severity from mildly symptomatic illness to a rapidly fatal syndrome.2,5 Classification of immune hemolytic anemias can be described as in table in Table 1.1
We assume that autoimmune hemolytic anemia (AIHA) in this patient associate with systemic lupus erythematosus (SLE), and meet the ARA criteria (hematological disorder, ANA and Anti dsDNA test are positive, and serositis (mild pericardial effusion)).

Glucocorticoid therapy is first-line treatment for AIHA. A majority of patients show a clear response to therapy (Hg >10 g/dL) within the first three weeks of treatment. Once response has been achieved, glucocorticoid should be tapered. About 10% of patients do not respond to this therapy and will require a second-line treatment. Many drugs have been used as second-line agents. Patient eligibility criteria for second-line therapy have been proposed (table 2). Still there is no general consensus on the best second-line agent. Drugs reported in the treatment of refractory AIHA in SLE include IVIG, azathioprine and other immunosuppressive medications as well as danazol and rituximab (figure 1).5,6

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 with the aim of withdrawing the drug. Although one might be tempted to discontinue steroids more rapidly, AIHA patients should be treated for a minimum of three or four months with low doses of prednisone (≤10 mg/day). In fact, patients receiving low doses of corticosteroids for more than six months have a lower incidence of relapse and longer duration of remission than those discontinuing the medication within six months. Moreover, an earlier onset of steroid therapy correlates with a lower probability of relapse. 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.\(^5\)

First-line therapy with corticosteroids is expected to provide a response in 70-85% of patients; however, only 1 in 3 cases remain in longterm remission once the drug is discontinued, a further 50% require maintenance doses, and approximately 20- 30% need additional second-line therapies. It is not known how many adult patients are cured by steroids alone, but it is estimated that this occurs in less than 20% of patients. 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.\(^5\)

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 in any case be safely administered in urgent cases if alloantibodies (known to occur in 12- 40% of AIHA patients\(^1\)) are reasonably excluded on the basis of the previous transfusion and/or pregnancy history.\(^5\)

The patient was treated with transfusion of 350 mL washed red cells and injection Methylprednisolone 125 mg/12hours iv. After being hospitalized for 10 days patient got clinical improvement and than patient was discharged with treatment Methylprednisolone 50mg/day (4-4-4) and Cyclosporin (sandimun) 2 x 100mg and we advised the patient to have medical control routinely.

CONCLUSION
It has been reported a case a young adult females who came with complaints of pallor, weakness, dizziness, and dyspnoe on exertion. After several laboratory tests and other supporting investigation we diagnosed the patient with Autoimmune Hemolytic Anemia in Systemic Lupus Erythematosus patient. We treated the patient with transfusion washed red cells and glucocorticoid and immunosuppressive agent. After being hospitalized for 10 days patient got clinical improvement and than patient was discharged and we advised the patient to have medical control routinely.

REFERENCES


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