

Case Report

Autoimmune hemolytic anemia warm-antibody type (Warm AIHA) in an 8-year-old Balinese girl

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ABSTRACT A case of autoimmune hemolytic anemia warm antibody type A (warm AIHA) in an 8-year-old Balinese girl was reported. The diagnosis was established based on clinical features, laboratory findings including positive Coombs' test positive. The etiology was probably primary or idiopathic. The child was transfused with packed red cells and treated with oral prednisone. The response of the treatment was good and she experienced complete remission. The prognosis in patients with idiopathic warm AIHA are unpredictable. The girl underwent further follow-up in the child hematologic division every two weeks. [Paediatr Indones 2001;41:64-68]

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Autoimmune hemolytic anemia warm-antibody type (warm AIHA) is a disorder of the immune system in which normal erythrocytes are attacked and destroyed by antibodies.¹ It is characterized by antibody (IgG) and complement mediated lysis, with the autoantibody maximally active at body temperature of 37°C.² AIHA is a relatively uncommon disorder. The annual incidence is estimated to be 1 per 80.000 people.^{1,2} Seventy to eighty percent of these cases are due to warm AIHA, 10-20% are due to cold AIHA, and 2-5% are due to paroxysmal cold hemoglobinuria (PCH). Approximately 50% of the patients with warm AIHA have an associated disease, such as malignancy, systemic lupus erythematosus, or leukemia. Warm AIHA may occur idiopathically or may be induced by drugs such as penicillins, cephalosporins, phenacetin, quinidine, or alpha-methyl dopa.^{1,3,4}

The bases of diagnosis of warm AIHA are shortened red blood cells (RBC) survival, evidence of the

host's antibodies that are reactive to autologous RBC with autoantibody active at body temperature of 37°C, most frequently demonstrated by a positive Coombs' test. A positive direct Coombs' test indicates autoantibody mediated hemolysis, while a positive indirect Coombs' test points to the presence of alloantibody.^{1,3,5} The purpose of this paper is to report a case of autoimmune hemolytic anemia warm antibody type (warm AIHA) in an 8-year-old Balinese girl.

Report of the Case

An 8-year-old Balinese girl was admitted to the Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Denpasar, on March 1, 1999 with the chief complaints of pallor and fatigue since a few weeks. Initially the symptoms were mild which then became worse. She also had dizziness, light headache, weakness, jaundice, and dark-colored urine since three days before treated. There was no history of fever, dyspnea, malaria, petechiae, or bleeding, nor evidence of blood loss, transfusion, snake bites, or use of drugs.

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On physical examination she looked fatigued with the blood pressure of the superior extremity of 110/80 mmHg, the pulses were equal and regular at 98/minute, respiratory rate 26/minute, axillary temperature 37°C, body weight 20 kg, height 122 cm and was well-nourished. The conjunctiva was anemic and the sclera was jaundiced. The neck was normal. Chest examination revealed no abnormalities; both sides were symmetrical, breath sound was normal and cardiac murmur was negative. It was found that she had hepatomegaly (palpable 1/3-1/3, soufflé and sharp margin), and moderate splenomegaly.

Results of blood analysis revealed hemoglobin 4.9 g/dl, hematocrit 9.7%, red blood cells 900,000/ μ L, MCV 108 fl, MCH 54.3 pg, MCHC 50.3 g/dl, WBC (white blood cells) count 6800/ μ L, differential neutrophil 3200/ μ L (46.5%), lymphocyte 2900/ μ L (43.0%), monocyte 500/ μ L (7.7%), eosinophil 100/ μ L (2.1%E), basophil 100/ μ L (0.8%), and platelet 368,000/ μ L. Blood smear showed normochromic, normocytic erythrocytes, spherocytes, anisocytosis, polychromasia, normal leukocytes and thrombocytes.

The working diagnosis was severe anemia (suspected hemolytic anemia). It was planned to do investigation of liver function test (LFT), reticulocyte count, G6PD, Coombs' test, serum iron/IBC/TIBC, malaria, HbsAg, urine and feces. She was treated with multivitamin, 1 teaspoon two times daily. On March 2, 1999 she was still pallor, jaundiced, and excreted dark urine. Results of the liver function test showed total bilirubin 4.97 mg/dl (normal value: 0-1.00), direct bilirubin 0.25 mg/dl, SGOT 60 U/L, SGPT 10 U/L, alkaline phosphatase 153 mg/dl, cholesterol 170 mg/dl, albumin 4.89 g/dl and globulin 4.58 g/dl. Reticulocyte count was 26.0% (N 0.5-1.5%). The iron analysis revealed serum iron 42 mg/dl (N: 49-151), iron binding capacity 143 mg/dl (N: 180-260), and total iron binding capacity 185 mg/dl (N: 380-400). Blood examination for malaria was negative, stool examination gave normal results. Urine profile: leukocyte 15/ μ L, negative nitrite, pH 6, negative protein, normal glucose, negative ketone, urobilinogen: 46 mg/L (+ +), bilirubin >5 mg, erythrocyte 10/ μ L. HBsAg was negative. To find out the cause of hemolytic anemia we did hemoglobin electrophoresis, G6PD erythrocyte, bone marrow and Coombs' test. She was treated with PRC (packed red cells) transfusion 560 ml (200 ml one time daily for three days) and multivitamin.

On March 5, 1999, the jaundice and pallor were minimal. Result of Hb electrophoresis: Hb A1 96%, Hb A2 5% and Hb C, Hb F, and Hb S 0% (in normal limits), G6PD erythrocyte: 125 mU/109 (N: 118-144 mU/109 erythrocytes). Direct Coombs' test was positive. Bone marrow profile was hypercellular with increased activity of erythrocyte system, myeloid and megakaryocyte systems were normal. These meant that the hemolytic process occurred in the bone marrow. Results of blood analysis showed Hb 10 g/dl, HCT 22.6%, WBC 5800/ μ L and platelets 202,000/ μ L.

The definitive diagnosis was autoimmune hemolytic anemia warm-antibody type (warm AIHA). Subsequently the patient was treated with oral dose of 1.5 mg/kg BW/day prednisone (body weight 20 kg), which made dose of 30 mg/day divided into three doses given three times daily and multivitamin. On March 12, 1999 the patient showed close to normal clinical features. The urine was clear and had yellow color. Liver and spleen were not palpable. Results of blood analysis: Hb 10.7 g/dl, HCT 27.7%, WBC 4300/ μ L, platelets 300,000/ μ L. Urine bilirubin was negative. Liver function test: total bilirubin 1.88 mg/dl and direct bilirubin 0.25 mg/dl. She was then treated with prednisone, 1 mg/kg BW/day, divided into two doses.

On March 17, 1999, the patient was discharged from the hospital, with blood analysis: Hb 11.8 g/dl, HCT 32.1%, RBC 3,580,000/ μ L, WBC 5000/ μ L, platelets 217,000/ μ L, total bilirubin 0.99 mg/dl and direct bilirubin 0.20 mg/dl. She was referred to the outpatient clinic of the Hematologic Division.

On March 24, 1999, the patient was in good condition with the result of blood analysis: Hb 12 g/dl, HCT 36%, WBC 6500/ μ L, platelets 300,000/ μ L, reticulocyte count 12%, total bilirubin 0.99 mg/dl and direct bilirubin 0.20 mg/dl. She was treated with oral dose of 0.5 mg/kg BW/day prednisone, and was continued follow-up every two weeks in the Pediatric Hematology Outpatient Clinic.

Discussion

The diagnostic approach to hemolytic anemia is based on the understanding of the physiology of hematopoiesis. In the case of hemolysis, bone marrow can compensate for shortened red blood cell survival. This in turn can be clinically detected by an increase in the reticulocyte count. Hemolysis itself can be

caused by immune mediated processes (e.g., autoimmune hemolytic anemia), defects in red blood cells (RBC) membrane (e.g., hereditary spherocytosis), derangements in RBC enzyme machinery (e.g., G6PD deficiency), failure in the synthesis of hemoglobin molecules (e.g., thalassemia or sickle cell disease), or a mechanical disruption of erythrocytes (e.g., microangiopathic hemolytic anemia).^{6,9,10}

Autoimmune hemolytic anemia (AIHA) is characterized by the presence of autoantibodies, which in turn causes short red blood cell survival.² AIHA is divided into three classes on basis of serologic autoimmune process; warm AIHA which is characterized by antibody (IgG) and complement mediated lysis, autoantibody maximally active at body temperature of 37°C, cold AIHA which is characterized by antibody (IgM) and complement mediated lysis, autoantibody active at temperatures below 37°C, and mixed cold and warm autoantibodies. It is also useful to classify AIHA based on the presence or absence of underlying diseases. When no recognizable underlying disease is present, the AIHA is termed primary or idiopathic. When AIHA appears to be a manifestation or complication of an underlying disorder, the term secondary AIHA is applied.^{3,7,9}

In our case, the diagnosis of warm AIHA was based on clinical manifestations and laboratory findings, including positive Coombs' test.

The anemia of warm AIHA is frequently severe with an initial hemoglobin level of 7 g/dl or less. Progression of the anemia frequently occurs before therapy

becomes effective. The reticulocyte count is usually elevated. Evaluation of the blood film can reveal several features related to AIHA. Polychromasia indicates reticulocytosis, reflecting an increased rate of reticulocyte process from the marrow. Spherocytes are seen in patients with moderate to severe hemolytic anemia. Hyperbilirubinemia is highly suggestive of hemolytic anemia, although its absence does not exclude the diagnosis. Total bilirubin is only modestly increased, up to 5 mg/dl with rare exceptions, the conjugated (direct) fraction constitutes less than 15 percent of the total bilirubin. Urinary urobilinogen is increased regularly, but bile is not detected in the urine unless serum conjugated bilirubin is increased.²⁻⁴

A polyspecific Coombs' antiserum or Coombs' test that contains antibodies to human immunoglobulin and complement components is added to a washed suspension of the patient's red cells. The appearance of agglutination indicates membrane-bound immunoprotein and is a presumptive evidence of an immune hemolytic disorder. In warm AIHA, the patient's red cells are almost always coated with either IgG, C3d, or both. Coombs' test detects the presence of immunoproteins (immunoglobulin of fragment of activated complement) that have adhered to the red cells.^{5,6} The cardinal feature of immune hemolytic anemia is a positive direct Coombs' test or direct antiglobulin test (DAT). In more than 95% of the patients with immune hemolysis, the direct Coombs' test is positive. In less than 5% the test is negative.

TABLE 1. MOST COMMON PRESENT SIGNS AND SYMPTOMS IN PATIENTS WITH AIHA OF THE WARM-REACTIVE ANTIBODY TYPE*

Symptom	Freq. (%)	our case	Sign	Freq. (%)	our case
Weakness	88	+	Splenomegaly	82	+
Dizziness	50	+	Hepatomegaly	45	+
Fever	37	-	Lymphadenopathy	34	-
Jaundice	21	+	Jaundice	21	+
Bleeding	10	-	Thyromegaly	10	-
Dyspnea	9	+	Edema	6	-
Cough	6	-	Cardiac failure	5	-
Weight loss	5	-	Pallor	4	+
Gastrointestinal disturbance	5	-			
Anorexia	4	+			
Dark urine	3	+			
Angina	2	-			
Confusion	2	-			

In general, most AIHA is secondary while the frequency of idiopathic AIHA is probably close to 50% of all cases. In idiopathic AIHA, splenomegaly occurs in 50-60% of the patients, hepatomegaly in 30%, and lymphadenopathy in about 25%. Only about 25% of the patients have no enlargement of the spleen, liver, or lymph nodes. Based on serologic findings, 70-80 percent of these cases are due to warm AIHA, 10-20% are due to cold AIHA, and 2-5% are due to paroxysmal cold hemoglobinuria (PCH).^{4,5,6}

In our case the clinical manifestations were pallor, fatigue, weakness, dizziness, light-headache, anemia, jaundice, hepatosplenomegaly, and dark urine. The laboratory results were low hemoglobin level (4.9 g/dl), low hematocrit (9.7%), increased reticulocyte count (26.0%), and RBC characteristics showed hypochromic, macrocytic erythrocyte, spherocyte, anisocytosis and polychromasia. It meant that severe hemolytic anemia with an increase of hemopoiesis process occurred in the bone marrow. The liver function test showed total bilirubin of 4.97 mg/dl, direct bilirubin 0.25 mg/dl, and urine urobilinogen 46 mg/L (+ +). These indicated intravascular hemolysis process. The result of direct Coombs' test was positive, indicating that autoantibody (IgG), complement, or both were detected.

The etiology of AIHA is unknown. It has been diagnosed in people of all ages, from infants to the elderly. Warm AIHA with specificity for red cell antigens have been described in association with many diseases, including viral infections, malignancies, immune deficiency states, and autoimmune disorders, such as lupus erythematosus. The ultimate cause of the autoimmune phenomena has yet to be identified; however, several contributing factors have been discovered, including an appropriate genetic predisposition and a fundamental disorder of immunologic regulation in affected individuals.^{3,4,6}

In our case, the differential diagnoses are hereditary hemolytic anemias and hereditary spherocytosis (HS). Family studies of patients with HS, however, usually can identify other affected individuals. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy of the pentose phosphate pathway. It can manifest in three forms; neonatal jaundice, the most severe form, where exchange transfusion may be life-saving; a mild form of this deficiency, G6PD A-variant, the most common

type present in American blacks; the severe form of the deficiency, G6PD Mediterranean. Most importantly, the RBC of the patients with congenital hemolytic anemia generally do not have a positive direct Coombs' test reaction. Cold AIHA are characterized by autoantibody (IgM) and complement mediated lysis, with autoantibody active at temperatures below 37°C. Paroxysmal cold hemoglobinuria (PCH) has specificity for found Donath-Landsteiner antibody. We didn't find any secondary cause or other diseases, including thalassemia, hereditary spherocytosis (HS), G6PD deficiency, PCH and Cold AIHA, or history of AIHA inducing drug use. Accordingly we assume that our case might be of idiopathic type.

Corticosteroids are the initial therapy for patients with warm AIHA. An appropriate regimen is prednisone, 1-1.5 mg/kg BW/day orally. A large majority of patients show a clinical response within 2 weeks of treatment, and a complete lack of response at day 21 should be considered as steroid failure. For those who respond to corticosteroids, a normal or stable hematocrit and reticulocyte count are found in 30-90 days. At this time the dose of prednisone should be reduced weekly by 0.5 mg/kg BW/day or by 10 to 20 mg/day. Alternate-day therapy may be used with the dose of less than 30 mg/day. Some patients may be maintained on acceptably low doses of prednisone, but if more than 10-15 mg/day is required to keep the hematocrit at an acceptable level, the response should be considered inadequate and other treatment should be strongly considered. The decision regarding the use of other therapies should be made within several months after diagnosis to prevent the adverse effects of long-term corticosteroid administration. Treatment with danazol has usually been used in conjunction with prednisone either as initial therapy or after inadequate response to corticosteroids alone. Danazol may be used in a dose of 600-800 mg/day. Once remission is sustained the dose of danazol may be reduced to 200-400 mg/day.^{2,4,5}

Transfusion therapy must never be considered as an contraindication, even though the crossmatch test may be strongly incompatible. When life-threatening manifestation of anemia is present, transfusion is mandatory, even at hemoglobin level of 5-8 mg/dl.^{2,1}

Our patient was treated with packed red cells (PRC) of low hemoglobin, 200 ml per day for three days, because of transfusion hemoglobin level. Subsequently the pa-

tient was treated with oral dose of 1.5 mg/kg BW/day prednisone. The dose of prednisone was reduced 0.5 mg/kg BW/day every two weeks, and this patient was maintained on low dose of prednisone. The treatment response was good.

Splenectomy, if the response of corticosteroids is inadequate, should be performed unless surgery is strongly contraindicated. Approximately 50-75% of the patients showed marked improvement or had complete hematologic remission after splenectomy. Remission are not always permanent, however, and relapse may occur months or years later. If an incomplete remission or a relapse occurs following splenectomy, much lower corticosteroid doses may prove effective in controlling the disease activity.^{2,4,5}

Immunosuppressive drugs may be given to patients whose hemolysis are inadequately controlled by steroid and splenectomy. Oral azathioprine (Imuran), 50-200 mg/day or cyclophosphamide (cytoxan), 50-150 mg/day, is commonly used. If the drug is tolerated by the patient, it is reasonable to continue treatment for up to 6 months while waiting for a response. When response occurs the patient may be slowly weaned from the drug. If there is no response, the alternative drug may be given.^{2,3}

The prognosis in patients with idiopathic warm AIHA have unpredictable clinical courses characterized by relapses and remissions. No particular feature of the illness has been a consistent predictor of outcome. A minority of patients have complete resolution of their disease and others have a chronic but manageable course. The estimated mortality of patients followed up for 5-10 years is 15-25%.^{1,6} In our case; the patient had complete resolution of her disease.

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