EVANS SYNDROME IN A 10 YEAR OLD GIRL

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ABSTRACT

Evans syndrome is a coexistence of simultaneous or sequential positive direct Coombs test in conjunction with immune-mediated thrombocytopenia with no known underlying etiology. The clinical course is chronic and relapsing, and the therapy is generally progressive. Recurrences of thrombocytopenia, anemia and neutropenia are common, as well as episodes of hemorrhage and serious infections. Noncrossreacting autoantibodies are directed against red cells, platelets, and neutrophils antigens. Evans syndrome is a rare condition, no predilection is known and its exact prevalent is unknown. We report a case of Evans syndrome in 10 years old girl with severe anemia and thrombocytopenia. Patient came with clinical symptoms of severe anemia. The laboratory evaluation showed severe anemia, increased reticulocyte count, anisopoikilocytosis erythrocyte, increased unconjugated bilirubin, positive direct Coombs test and thrombocytopenia. Patient was then managed with high doses of corticosteroids and showed good response from both clinical and laboratory evaluations. **[MEDICINA 2015;46:61-66].**

Keywords: *Evans syndrome, anemia, thrombocytopenia*

ANAK PEREMPUAN USIA 10 TAHUN DENGAN SINDROM EVANS

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ABSTRAK

Sindrom Evans adalah suatu penyakit yang ditandai dengan adanya hasil positif pada *direct Coombs test* dan trombositopenia yang diperantarai imun secara simultan atau sekuensial tanpa penyebab yang jelas. Perjalanan klinis umumnya bersifat kronis, sering mengalami relaps dan memerlukan terapi yang progresif. Kejadian trombositopenia, anemia, neutropenia, perdarahan dan episode infeksi berat berulang umum terjadi. Pada sindrom ini, terjadi reaksi autoantibodi spesifik terhadap antigen sel darah merah, trombosit dan juga neutrofil. Sindrom Evans merupakan kasus yang jarang ditemukan dan dengan predileksi serta prevalensi yang belum banyak diketahui. Kami melaporkan satu kasus Sindrom Evans pada anak perempuan usia 10 tahun. Pasien dengan gejala klinis anemia berat dan pada pemeriksaan laboratorium menunjukkan suatu anemia berat, peningkatan hitung retikulosit, gambaran eritrosit anisopoikilositosis, peningkatan kadar bilirubin yang tidak terkonjugasi, *direct Coombs test* yang positif dan trombositopenia. Pasien kemudian diterapi dengan kortikosteroid dosis tinggi dan didapatkan respon yang baik pada evaluasi klinis dan laboratorium. **[MEDICINA 2015;46:61-66].**

Kata kunci: *sindrom Evans, anemia, trombositopenia*

INTRODUCTION

Evans syndrome is an coexistence of simultaneous or sequential positive direct Coombs test in conjunction with immune-mediated thrombocytopenia, with no known underlying etiology.[1] Evans has been observed that there is a risk of developing other autoimmune problems with recent research finding that 58% of children with Evans syndrome have decreased CD_4/CD_8 T cells ratio which is a strong predictor for having autoimmune lymphoproliferative syndrome. Noncrossreacting autoantibodies are directed against antigens specific to red cells, platelets, or neutrophils.[2,3]

Evans syndrome is a rare condition and its exact frequency is unknown. Familial occurrence is rare and no predilection is known. Evans syndrome has a mortality rate of 23.5%.[4] The typical clinical course is chronic and relapsing, and therapy is generally progressive.[1] Initial treatment is corticosteroids and/or intravenous immunoglobulin,[5] which is in children, good response to a short steroid course is achieved in approximately 80 percent of cases.[6] Although the majority of cases initially respond well to treatment, relapses are common and immunosuppressive drugs (e.g. ciclosporin, mycophenolate mofetil, vincristine and danazol) are subsequently used, or

combinations of these.[6] We report a case of Evans syndrome in 10 years old girl with signs of severe anemia and thrombocytopenia who respond well to the initial corticosteroid therapy.

CASE ILLUSTRATION

On November 20th 2012, a 10 years old girl referred from Klungkung Hospital came to Sanglah Hospital with suspected diagnosis of Thalassemia. Her major complaint was weakness. She had been weak for 15 days and getting worst in every each day. Pale and yellowish skin was found from 3 days before. Since 15 days, she was unable to go to school, lose her appetite and preferred to lie down and sleep. She had also complaint of fever for around 20 days before admitted into Sanglah Hospital.

Earlier in June 2012, the patient was admitted to Klungkung Hospital with complaints of fever and weakness. She treated about 7 days and received 2 kolf of packed red cells (PRC) transfusion. Later on November 11th, 2012 she was came again to Klungkung Hospital for the same problems; fever and weakness. Complete blood count showed severe anemia with Hgb 2.2 g/dL, MCV 119 fL, MCH 43.6 pg, Hct 6.1%, WBC 10.4 x 10^3/iL, neutrophil 6.8 x 10^3/iL, lymphocyte 2.3 x 10^3/iL, and Plt 141 x 10^3/iL. From the examination of peripheral blood film showed anisopoikilocytosis normochromic erythrocytes (macrocyte, microcyte, microspherocyte, ovalocyte) and normoblast. Leukocytes was still in the normal amount, the dominance of segmented neutrophils and morphology was also normal with no blast cells were found. As for the thrombocyte, decreasing number and giant platelets was impressed. Peripheral blood film test concluded anemia with erythrocyte deformity and thrombocytopenia. Patient was diagnosed for suspected thalassemia differential diagnosed with iron deficiency anemia and given a blood transfusion with 7 kolf of PRC. Post-transfusion laboratory then re-evaluated and defined WBC 5.0 x 10^3/iL, neutrophil 3.6 x 10^3/iL, lymphocyte 1.1 x 10^3/iL, Hgb 7.9 g/dL, MCV 91.5 fL, MCH 33.2 pg, MCHC 36.3 g/dL, Hct 21.8% and Plt 109 x 10^3/ìL. Patient then referred to Sanglah Hospital on November 20th 2012.

She was born full term with normal delivery. Birth weight was 3500 gram and 50 cm length. Neonatal period was uneventful with normal growth and development milestones. Neither of the parents and other family member have the same symptoms like her.

Physical examination revealed an alert girl and her general appearance looked moderate ill. Her conjunctiva was pale and the sclera was icteric. There were abnormalities of heart sounds which systolic ejection murmur grade 2 was heard in the entire heart. Liver palpated at 4cm/4cm, sharp border, plain surface, soft consistency and without pain. Spleen enlargement palpated at Schuffner line 3. Her complete blood count examination showed WBC 5.54 x 10^3/iL, neutrophil 2.87 x 10^3/iL, lymphocyte 2.23 x 10^3/iL, Hgb 2.9 g/dL, MCV 87.8 fL, MCH 31.4 pg, MCHC 35.7 g/dL, Hct 8.1% and Plt 58 x 10^3/iL with B blood type. Laboratory tests of liver function and total bilirubin was conducted and obtained results was total bilirubin 4.34 mg/dL, unconjugated bilirubin 3.36 mg/dL, AST 28 U/L, ALT 13.6 U/L, Gamma GT 23 U/L, total protein 6.85 g/dL, albumin 3.46 g/dL and CRP 2.5 mg/L. From further examination, reticulocytes count was increased to 11.32% with the absolute number of 182 x 10^9 cells/L. In peripheral blood film, erythrocytes was anisopoikilocytosis, polichromasia and found spherocytes. Leukocytes was normal, so was the differentiation and none of blast cells obtained. However, platelets were obtained decreasing but still did not found any giant platelets **(Figure 1)**.

The patient was diagnosed with observation of bicytopenia et causa hemolytic anemia differential diagnosed with anemia hemolytics autoimune (AIHA) and hereditary spherocytosis. She

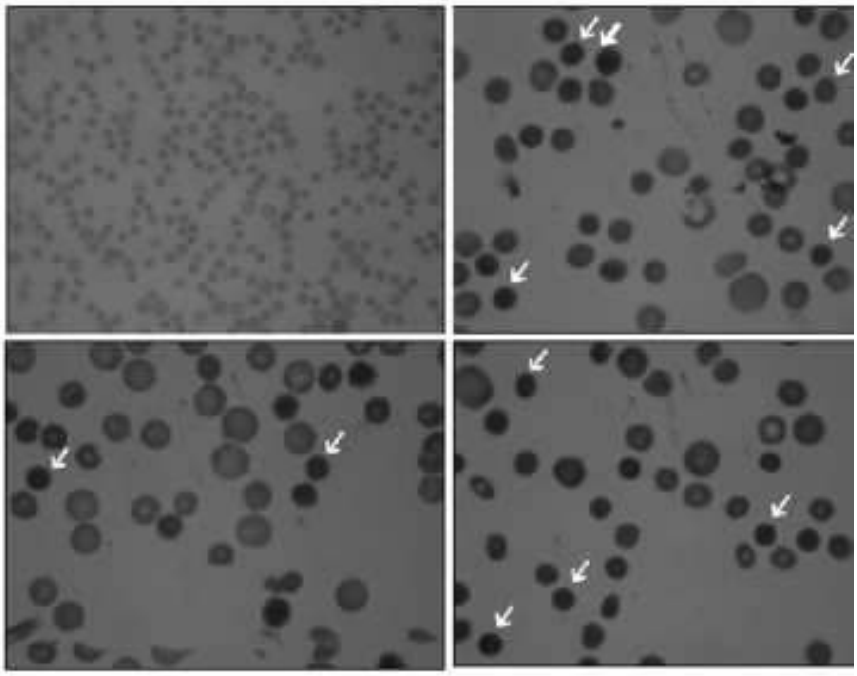

Figure. 1. Peripheral blood film found an anisopoikilocytosis and polichromasia erythrocytes with spherocytes* (*white arrow mark).

scheduled for laboratory Coomb test and given PRC transfusion based on Rutski techniques which targeted Hgb 10 g/dL which is PRCs given in 4 times of each 90 mL, 150 mL, 150 mL and 210 mL.

Coombs test result indicated presence of autoimmune antibody (direct coombs test/DCT positive), red blood cells were covered with C3 and IgG and the presence of free irregular alloantibody in the patients serum (indirect Coombs test/ICT positive), which reactive within temperatures of 20°C and 37°C with the impression toward mixed-type AIHA (warm and cold). Evans syndrome was diagnosed later for the patient. PRC transfusion was discontinued and she then planned to get a high dose corticosteroid therapy using intravenous methylprednisolone administered for 7 days with a total dose of 30 mg/kg body weight/dose for 3 days then followed by a dose 20 mg/kg body weight/dose for another 4 days.

After the administered of methylprednisolone intravenous 30 mg/kg body weight/dose, from complete blood count examination found WBC 0.84 x 10^3/ìL, neutrophil 0.31 x 10^3/ìL, lymphocyte 0.38 x 10^3/ìL, Hgb 7.1 g/dL, MCV 91.2 fL, MCH 30.8 pg, MCHC 33.7 g/dL, Hct 21.1%, Plt 93 x 10^3/ìL, with 5.87% reticulocyte count. Methylprednisolone therapy was continued at 20mg/kg kg body weight/dose for 4 days followed by another complete blood count, with result obtained WBC 3.43 x 10^3/ìL, neutrophil 2.7 x 10^3/ìL, lymphocyte 0.45 x 10^3/ìL, Hgb 9.3 g/dL, MCV 95.6 fL, MCH 30.6 pg, MCHC 32.0 g/dL, Hct 28.9% and Plt 112 x 10^3/ìL. The evaluation of liver function obtained total bilirubin 1.36 mg/dL, unconjugated bilirubin 1.05 mg/dL, AST 21 U/L, ALT 20.0 U/L, gamma GT 17 U/L, total protein 6.3 g/dL and albumin 3.5 g/dL. In general, she appeared to be improving. Weakness began to decrease and appetite improved. Pale conjunctiva and icteric sclera was decreased, no murmur on cardiac examination, enlarged liver and spleen were reduced in size, which liver was palpable at 2cm/2cm and lien at Schuffner line 2. Due to the result, patient then allowed to an ambulatory care with a therapeutic oral dose of 10mg methylprednisolone per-day for a week.

DISCUSSION

Evans syndrome is an uncommon condition defined by the combination (either simultaneously or sequentially) of AIHA with a positive direct Coombs test and immune-mediated thrombocytopenia, sometimes together with immune neutropenia, in the absence of known underlying etiology.[5-7] In this case, the spectrum of Evans syndrome included AIHA and thrombocytopenia without neutropenia. Signs of anemia found with enlarged liver and spleen without any signs of bleeding. From the complete blood count, we obtained a normochromic normocyter anemia and thrombocytopenia, with a progressive decrease in hemoglobin levels in a relatively short time without bleeding. Peripheral blood film obtained a anisopoikilocytosis and polichromasia erythrocytes which suggests there has been a process of hemolysis. The existence of significant increase in reticulocyte count up to 3 times and increased levels of unconjugated bilirubin was also a sign process of hemolysis.

Evans syndrome is a condition with unknown etiology that results from an alteration of the immune system that produces multiple autoantibodies targeting red blood cells and platelets.[1,8] The time of onset, course, duration and severity of anemia and thrombocytopenia are variable among patients.[1,6] In this case, the etiology of Evans syndrome was also unknown. Before the complaints first appeared, there were no history of severe illness. She was able to live well and interact in a social environment. She had not also been hospitalized for severe illness. Other family members were also have no blood disorder disease or immune diseases.

Exact frequency of Evans syndrome is unknown. Familial occurrence is rare. No predilection is known in Evans syndrome; it affects boys more frequently than girls at a ratio of 1.4:1. Evans syndrome is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). This means that Evans syndrome affects less than 200,000 people in the US population.[1] This case was the first case of Evans syndrome treated in Sanglah Hospital and her age at presentation of this disease is about 10 years old.

The hallmark of AIHA in Evans syndrome is a positive direct Coombs test (DCT) by which immunoglobulin G (IgG) and/or complement are found on the red blood cells (RBCs) surface.[7,9] In this case, we found a positive mixed type Coombs test, including both direct and indirect Coombs test. Hemolysis occurred at both warm and cold temperatures, which will give a severe manifestations of hemolysis such as those found in this patient.

Immune-mediated trombocytopenia occurs due to autoantibodies binding to platelet surface proteins. These antibodycoated platelets then bind to macrophages and removed from circulation. Presentation can range from asymptomatic patient with low platelets found on a routine blood count to a massive and life-threatening bleeding. The platelet count cut-off for considering immune-mediated trombocytopenia is 100 x 10^3/iL. In general, therapy should be guided by the patient's signs of bleeding and not by unquestioning adherence to measuring platelet counts, as patients tolerate their thrombocytopenia well. It is

unusual to have life-threatening bleeding with platelet counts over 5 x 10^3/iL in the absence of mechanical lesions.[10,11] In this case, 58 x $10e^3$/μL was the lowest platelet rate found in her case, without any bleeding.

The most likely differential diagnosis of Evans syndrome is a hereditary spherocytosis. Hereditary spherocytosis and Evans syndrome have a different mechanisms of pathophysiology one another. Hereditary spherocytosis is caused by a variety of molecular defects of erythrocyte membrane proteins where the disorder is inborn and hereditary. These proteins are necessary to maintain the normal shape of erythrocytes. Normal red blood cells are donut shaped which enables them to change their shape to pass through small blood vessels. In hereditary spherocytosis, the red cells are spherical and thus lack flexibility and are more prone to break. If a child has hereditary spherocytosis, either parent or sibling may also have the disease. In hereditary spherocytosis, the child will experience anemia, jaundice, enlarged spleen and even poor growth.[7] In Evans syndrome, there is an autoimmune process in which antibodies attack RBCs and also platelets so will cause anemia and thrombocytopenia.[2,6,7] In this case, the clinical symptoms of anemia appeared at the age of 7 years which she had not previously been found to experience the history of similar complaints. Both parents and siblings of patients also never have complaints related to previous blood disorders. Patients also had the status of body growth is within normal limits. On examination of peripheral blood film found spherocytes morphology on red blood cells where it can be found both in hereditary spherocytosis and anemia due to hemolysis process in Evans syndrome. Presence of throm-bocytopenia in patient give the impression that there has been a process of blood disorders other than red blood cells.

The most commonly used first-line therapy is corticosteroids and/or intravenous immunoglobulin (IVIG). In the acute setting, blood and/or platelet transfusions may also be required to alleviate symptoms although their use should be minimized. Despite the lack of controlled trials demonstrating their effectiveness, corticosteroids remain the mainstay of treatment for control of the acute, symptomatic cytopenias with good initial results.[6,12,13] Corticosteroids often result in improvement, but relapses are common and maintenance steroid therapy seems necessary in the majority of effected children.[6,12,13] Methylprednisolone and prednisone therapy, the most commonly used first-line therapy, often effectively controls acute episodes.[6,7] Initial dose of methylprednisolone intravenous is 30 mg/kg body weight/dose for 3 day then 20 mg/kg body weight/ dose for 4 day, subsequently 10,5,2,1 mg/ kg body weight/day, 1 week each.[6] Patients with Evans syndrome are known to respond well to corticosteroid therapy, present however, frequent relapses, once corticosteroids are tapered or stopped.[6-8] In this case, initial therapy with methylprednisolone give a good response in clinically and laboratory evaluation.

Evans syndrome usually has a chronic, relapsing course with episodes of thrombocytopenia and hemolysis that are refractory to multiple modes of treatments.[1] The typical clinical course is chronic, frequent exacerbations and relapsing, and therapy is generally progressive and poor.[1,6] In children, good response to a short steroid course is achieved in approximately 80 percent of cases.[6] Although the majority of cases initially respond well to treatment, relapses are common.[1,4,5] Risks which may occur in these patients are bleeding with severe thrombocytopenia and risk of serious infections.[1] In this case, after 3 months since the methylprednisolone oral therapy was stopped, she had a relapse with severe anemia and thrombocytopenia. She came to Sanglah Hospital with intracranial bleeding and unfortunately, she died during treatment.

SUMMARY

A 10 year old girl with weakness and fever for around 20 days before admitted into Sanglah Hospital. The physical examination found a pale child, pale conjunctiva, icteric sclera, liver enlargement palpated at 4cm/4cm, sharp border, plain surface, soft consistency, without pain, and splenomegaly palpated at Schuffner line 3. Innocents murmur was heard on heart auscultation, grade II/6. Laboratory evaluation showed a severe anemia, increased reticulocyte count, anisopoikilocytosis and polychromasia erytrocyte in peripheral blood film, increased unconjugated bilirubin, positive direct Coombs test, and thrombocytopenia. She diagnosed with Evans syndrome and treated with high doses of methylprednisolone. She showed good response from both clinical and laboratory evaluations. After 3 months since the methylprednisolone therapy was stopped, she had a relapse with severe anemia and thrombocytopenia. She came to Sanglah Hospital with intracranial bleeding and unfortunately, she died during treatment.

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