ANTIFOSPHOLIPID SYNDROME WITH AUTOIMUN HEMOLITIC ANEMIA

Muhammad Huki Zukhrufan[1], Irza Wahid[2]

[1]Internal Medicine Specialist Program, Faculty of Medicine, Andalas University, Indonesia.
[2]Division of Hematooncology, Internal Medicine Department, Faculty of Medicine, Andalas University, Indonesia

Correspondence email: hukizukhrufan@gmail.com

Abstract: Antiphospholipid syndrome is a part of systemic autoimmune disease (nonspecific organ), characterized by vascular thrombosis (arterial or venous) with a high antibody titter against a plasma protein that binds to phospholipid anions (antiphospholipid-aPL antibodies). *Autoimmune haemolytic anaemia (AIHA) is rare in patients with antiphospholipid antibody syndrome. A sixteen years old female patient has been reported with the main complaint of swelling in the right leg. The patient also complained of increased fatigue. On physical examination found anaemic conjunctiva, swelling in the right limb with a diameter of the right leg greater than the left leg. Homan's sign positive on the right leg. This patient belongs to the high probability criteria of DVT. Doppler Ultrasonography (USG) examination suggests thrombus in the iliac vein, femoral vein, and right leg popliteal vein, and thrombus in the left leg popliteal vein. In the antibody anticardiolipin (ACA) IgG examination an increase was found. The comb test was positive, and haemolytic anaemia antibody screening was the warm type. Heparinisation and immunosuppressant administration were performed in patients. The incidence of antiphospholipid syndrome with AIHA cannot be ascertained whether there is a direct relationship.*

Keywords: *antiphospholipid syndrome, DVT, AIHA*

INTRODUCTION

Antiphospholipid syndrome belongs to a group of autoimmune diseases that are systemic (non-specific organs), with the characteristics of vascular thrombosis (arterial or venous) and / or pregnancy morbidity associated with high antibody titers to a plasma protein that binds to the phospholipid anion (antiphospholipid-antibody) aPL). Anti-phospholipid syndrome usually occurs in the fourth decade of life and is classified as a primary or secondary disease in other underlying autoimmune diseases, solid tumors or haematological disorders. 10-40% of patients with Systemic Lupus Erythematosus (SLE) and nearly 20% of rheumatoid arthritis patients have a positive APL.[1,2]

Lupus anticoagulants and anticardiolipin antibodies (ACA) can be found 1-5% in healthy young adults. SLR patients who have positive anticoagulant lupus have a 50% chance of developing arterial or venous thrombosis on observation over a 20-years period. Antiphospholipid syndrome can affect various organs of the body, and patients with antiphospholipid syndrome have a greater risk of becoming thrombosis, increased incidence of atherosclerosis, myocardial infarction, and stroke.[2]

Antiphospholipid antibodies (aPLA) are defined as immunoglobulins that react with the outer cell walls whose main component is phospholipids. These antiphospholipid antibodies have procoagulant activity against protein C, annexin V, platelets, and inhibit fibrinolysis. Anticoagulant phospholipids are also referred to as antiphospholipids (aPL), which are structurally almost similar to complement. Naturally / physiologically, the aPL formed by the body is β2-glycoprotein I (β2GPI). β2GPI binds to phospholipids that are negatively charged and inhibits the contact activity of the coagulation cascade and prothrombin-thrombin conversion. β2GPI functions as a natural plasma anticoagulant, so that the presence of antibodies to this protein can stimulate thrombosis, because it functions as a controller of the activity of procoagulant phospholipids (PL) containing the enzyme phospholipase A2 (PLA2). β2GPI is an enzyme that is bound by apolipoprotein-H (apo-H) as an enzyme inhibitor PLA2.[1,3]

Apart from β2GPI, the human body naturally forms annexin V or placental anticoagulant protein I, also known as placental aPL, which is very ntense4 in inhibiting the PLA2 enzyme, especially in pregnancy and cell death (apoptosis). Pathologically formed PLA2 inhibitors known as Lupus inhibitors are Lupus Anticoagulants (LA) which consist of 2 subgroups: LA sensitive thromboplastine that blocks VIIa, Ill, PL, and Ca2 + complexes, resulting in prolongation of prothrombin (PT), and LA thromboplastine non-sensitive which inhibits complexes VIIIa, IXa, PL, Ca^{2+}. Activation of the complement through attachment of the aPL to the endothelial surface can cause endothelial damage and stimulate thrombosis which plays a role in fetal death.[1]

Clinical manifestations based on the type of blood vessel affected are: (1) Thrombosis in large veins: convulsions, amaurosis fugax. blue toe syndrome, myocardial infarction, pulmonary embolism, aortic thrombosis, acute renal failure, ascites, adrenal infarction or crisis, thrombosis of the extremities, intrauterine growth retardation, hemolytic anemia, thrombocytopenia, avascular necrosis of the bone, etc .; (2) Arterial thrombosis: clinical manifestations related to the size of the diameter of blood vessels and the location of the affected arteries; (3) Microvascular thrombosis: Eye abnormalities: superficial gangrene retinitis, myocardial infarction, acute respiratory distress syndrome, acute renal failure, infarction or hepatic gangren, and spleen,

disseminated intravascular coagulation / DIC.[1]

Clinical manifestations based on the type of organ or tissue affected can be: skin disorders (livedo reticularis, necrotizing vasculitis, livedoid vasculitis, ulceration and skin necrosis, macular erythematosus, purpura, ecchymosis, discoid lupus erythematosus); lung disorders (pulmonary embolism, pulmonary hypertension); gastrointestinal disorders (hepatic thrombosis, mesentric thrombosis, etc); renal disorders (aPL-associated nephropathy, renal artery stenosis, etc); retina disorders; adrenal haemorrhage; bone marrow necrosis; sudden hearing lost; and haematology disorders (DIC, hemolotic anemia, etc).[1]

Criteria for diagnosis of antiphospholipid syndrome (2006 The International Consensus Statement on an update of the Classification criteria for Definite Antiphospholipid Syndrome), that is if at least 1 clinical criterion and 1 laboratory criterion are obtained.[3,4] Clinical criteria is having 1 or more episodes of venous, arterial or small blood vessels in the tissues or organs of the body, and / or pregnancy morbidity. Laboratory criteria include having a high antiphospholipid antibodies (aPLA) titer permanently on 2 or more different tests in a minimum period of 12 weeks but no more than 5 years before clinical manifestations occured, detected according to Guidelines of the International Society on Thrombosis and Hemostasis.[3,4]

CASE ILLUSTRATION

A 16-year-old female patient came to the ER of Dr. M. Djamil Padang General Hospital with the main complaint of swelling in the right leg since 5 days ago. Swelling is felt from the feet to the calves, gradually getting bigger, feels heavy, painful and difficult to carry on walking, pain is felt continuously, not reduced by rest. Skin color turns reddish. Weak tired since 1 month ago, especially felt while moderate activity. The patient is not married, the patient is a first year high school student. The patient lives in a sparsely populated environment, a permanent house with 4 rooms shared with 2 other family members, adequate windows and ventilation, a cement floor and good lighting. The patient does not smoke and does not consume alcohol.

On arrival at the ER, the patient was fully conscious, with blood pressure of 110/70 mmHg, breathing frequency 18 x / min, pulse frequency 98 x / min and body temperature 37 ° C. An eye conjunctiva is obtained from the eye examination. On physical examination of the lower resulted extremities edema (+/-), rubor (+/-), heat (+/-), dolor (+/-), homans sign (+/-); while external inferior extremities with a calf circumference of 39 cm while a left calf circumference of 35 cm. additional examinations showed 8.6 g / dl Hb, leukocytes 6,470 / mm3, platelets 98,000 / mm3, hematocrit 27%, DC 0/0/2/87/10/1, MCV / MCH / MCHC 87 fl / 29 fl / 31 pg, reticulocytes 2.2%, D Dimer 5584 ng / ml. In the peripheral blood picture, normochromic erythrocytes are obtained by polychromation.

Figure 1. DVT bilateral in pantient

The patient had some test: a comb test, with the result was DCT (+3); antibody screening tests with the impression of a warm type AIHA; ACA IgG, ANA IF, ANA Profile dan Anti DsDNA test; and also Doppler Ultrasonografi (USG) test. Doppler USG test showed deep vein thrombosis (DVT) in total in the iliac vein, femoral vein, and popliteal veins in the right leg, and total DVT in the left leg popliteal vein.

Treatment of this patient with non-pharmacological therapy was carried out by installing elastic circular verband dressing and leg elevation at 30^{o}. Pharmacological therapy given was low molecule weight heparin (LMWH): injection of enoxaparin 2x60 mg subcutaneously for 5 days. Doppler USG test was repeated after 5 days of enoxaparin administration, but there was no improvement in this patient's DVT. The theraphy continued with administration of 10,000 units of heparin drip for 7 days, and continued with warfarin tablets 1 x 2 mg orally, aspilet 1 x 80 mg orally. Auto-immune hemolytic anemia in the patient was treated with oral methylprednisolone 16 mg - 16 mg - 16 mg, lansoprazole 1 x 30 mg, and osteocal 1 x 1000 mg.

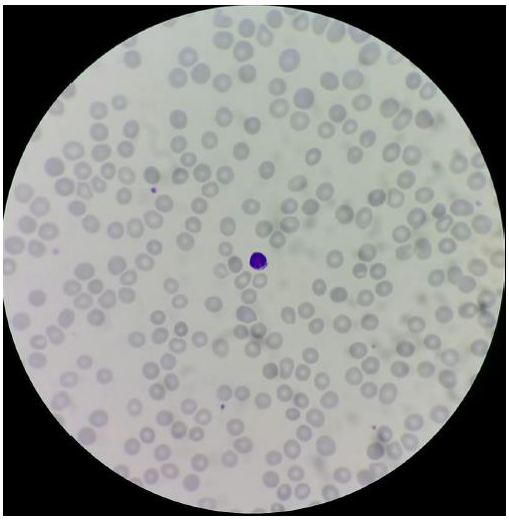

Figure 2. Peripheral blood features indicate polychromacy

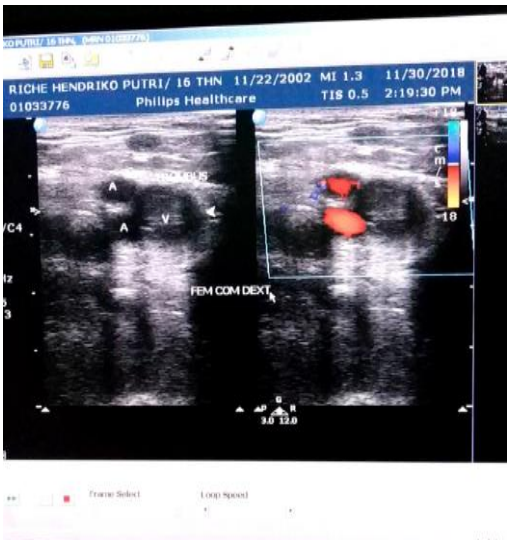

Figure 3. Doppler USG test result at lower extremities

DISCUSSION

A 16-year-old female patient was treated in the internal medicine ward of Dr. M. Djamil General Hospital with a final diagnosis of antiphospholipid syndrome and warm type of autoimmune hemolytic anemia. The diagnosis of DVT in this patient was made based on the main complaint of swelling in the right leg accompanied by pain since 5 days ago. On physical examination found swelling in the right limb with a diameter of the right leg greater than the left leg. The right leg diameter was 39 cm, compared to the right leg 35 cm and the positive Homan sign on the right leg. In this patient, a wells score of 3 was obtained. This patient was included in the high probability criteria of DVT.[5]

Doppler Ultrasound (USG) examination in this patient found thrombus in iliac vein, femoral vein, and right leg popliteal vein, and thrombus in left leg popliteal vein. There was an increase in D Dimer in this patient which was 5584 ng / ml (<500ng / ml). Increased D Dimers are an indicator of active thrombosis. This examination is sensitive but not specific and has more role in getting rid of thrombosis if the results are negative. Radiological examination is an important examination to

diagnose thrombosis. The accuracy of doppler ultrasound examination in patients with DVT can reach 94%.[6,7]

Kesieme (2011) states the incidence of DVT is very rare in young people. The annual incidence is 0.07 to 0.14 per 10,000 patients. Kearon (2014) states DVT is uncommon at a young age and very rarely occurs at <20 years of age. Predisposing the occurrence of DVT in young women can be caused by several things. Yilmaz (2015) states that antiphospholipid syndrome is a common cause of venous thrombosis. More than 20% of DVT cases with or without pulmonary embolism are related to APL antibodies. Dewi (2014) states that DVT is the most clinical presentation of antiphospholipid syndrome in 29-55% of patients.[8-11]

There are clinical manifestations of DVT at a young age in the patient, so the cause of DVT was traced. Kreidy (2012) found that of 66 patients aged less than 50 years who suffered from DVT, 46.9% were caused by thrombophilia, 18,2% due to pregnancy, and 9,1% due to a malignancy. Other investigations to rule out the cause of DVT are abdominal ultrasound, with results within normal limits, and examination of levels of protein C, protein S, Anti-thrombin III, ANA IF, and ANA profile. In the ACA IgG examination, 57 GPL U / mL results were obtained, while the qualitative anti DsDNA examination was negative.[12]

This patient was stated having antiphosphoslipid syndrome because it fulfilled the diagnostic criteria: at least 1 clinical criteria and 1 laboratory criteria of antiphospholipid syndrome. Clinical criteria are bilateral limb DVT manifestations while laboratory criteria are increased levels of ACA IgG anticardiolipin antibodies with 57 GPL U / mL of titer. Corban (2017) states the diagnosis of antiphospholipid syndrome is made when a minimum of 1 clinical criteria and 1 laboratory criteria are obtained. The clinical criteria in question is the presence of thrombosis. Laboratory criteria are an increase in titer at 1 of 3 antiphospholipid antibodies: anticardiolipin antibodies, lupus anticoagulants and β2-glycoprotein I (β2-GPI) antibodies.[2]

The treatment of antiphospholipid syndromes with DVT manifestations in this patient aims to stop the increase of thrombus, limit progressive swelling of the limbs, lyse and remove blood clots and prevent venous dysfunction or post-thrombotic syndrome, and to prevent emboli. Non-pharmacological therapy was carried out by installing elastic circular bandage with foot elevation 30°. The given pharmacological therapy was LMWH: injection of enoxaparin 2x60 mg subcutaneously for 5 days.[2]

Kesieme (2011) states LMWH is a more recommended therapy for DVT because it has several advantages, such as having better bioavability, lower risk of bleeding, and lower the incidence of heparin induced thrombocytopenia. However clinically, laboratory and imaging evaluation after giving LMWH therapy for 5 days in this patient did not get improvement so continued with intravenous heparin for 7 days. PT / APTT checks must be conducted periodically every 6 hours / day while maintaining an APTT value of 1.5-2.5 controls. The duration of administration of heparin was for 7 days, then continued with the administration of oral anticoagulants.[1] Oral anti-coagulant (warfarin) is given if the patient is ready to be mobilized starting at a dose of 2 mg. The treatment should be continued for at least 6 months in patient without other risk factors. In this patient the treatment was continued with the administration of warfarin 1x2 mg and aspirin 1x80 mg planned for 6 months.[8,9]

Non-pharmacological treatment in this patient was intended to reduce the risk of morbidity in acute attacks and reduce the incidence of post thrombosis syndrome which is usually characterized by pain, stiffness, edema, paresthesias and erythema.

To reduce these symptoms, patient was advised to rest in bed elevate the position of the legs and put on compression stockings.

This patient was also diagnosed with warm type of autoimmune hemolytic anemia. Patient treated with immunosuppressants. Zanella (2014) states that the first-line therapy for warm AIHA is corticosteroid administration at a dose of 1-1.5 mg / kg / day. Within 2 weeks most will show good clinical response. If a positive response to steroids, the dose is lowered every week until reaching a dose of 10-20 mg / day.[13]

The condition of antiphospholipid antibody syndrome accompanied by the presence of warm type of autoimmune hemolytic anemia in this patients is a rare case. Rottern (2006) obtained 32 cases of AIHA from 308 patients with antiphospholipid antibody syndrome. The presence of AIHA in patients with antiphospholipid antibody syndrome increases the risk for developing systemic lupus erythematosus.[14]

CONCLUSSION

Antiphospholipid syndrome can occur in young patients, with manifestations of DVT. Autoimmune hemolytic anemia rarely accompanies antiphospholipid syndrome. The presence of AIHA in antiphospholipid syndrome can increase the risk for developing systemic lupus erythematosus.

REFFERENCES

1. Arachchillage DRJ, Mike L. Pathogenesis and management of antiphospholipid syndrome. BJH. 2017;178:181 – 95
2. Corban MT, Garcia AD, McBane RD, Matteson EL Lerman LO, Lerman A. Antiphospholipid Syndrome Role of Vascular Endhotelial Cells and Implications for Risk Stratification and Targeted Therapeutics. JACC. 2017; 69 (18):2317-30
3. Gardiner C, Hills J, Machin SJ, and Cohen H. Diagnosis of antiphospholipid syndrome in routine clinical practice. Lupus.2013;22.18-25
4. Gomez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. Journal of Autoimmunity. 2014;48(49);20-25
5. Modi S, Deisler R, Gozel K, Reicks P, et al. Wells criteria for DVT is a reliable clinical tool to assess the risk of deep venous thrombosis in trauma patients. World Journal of Emergency Surgery. 2016;11(24).
6. Zitek JA, Jamie B, Jeremy B. Tools for the Clinician: The Essentials of Bedside (ED or ICU). Springer. 2013;1:65 – 70
7. Puliyarthi S, Murali KG. Effectiveness of D-Dimer as a screening test for venous thromboembolism: an update. PMC. 2014;6(1): 491 – 9
8. Kesieme E, Kesieme C, Jebbin N, Irekpita E, et al. Deep Vein Thrombosis : a clinical review. Journal of Blood Medicine. 2011:2; 59-69.
9. Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood. 2014 Mar 20; 123(12)1794-801.
10. Yilmaz S, Fusun T, Hadice SS, Yasar Y, Zulfukar Y, Ali VK *et al.* Primary antiphospholipid syndrome associated with pneumonia: a case report of a 16-year-old male patient. Hindawi. 2015:1- 4
11. Dewi S. Sindrom Antifosfolipid Antibodi : Buku Ajar Ilmu Penyakit Dalam Jilid II Edisi VI. Jakarta : Interna Publishing 2014.
12. Kreidy R, Waked M, Stephan E, Irani J, et al. Acquired and genetic risk factors for deep vein thrombosis of lower extremities among Lebanese patiens. J Med Liban. 2012 Jan-Mar;60(1)24-9.
13. Zanella A, Barcellini W. Treatment of Autoimmune Hemolytic Anemia. Haematologica. 2014. 99(10).
14. Rottem M, Krause I, Fraser A, Stojanovich L, Rovensky J and Shoenfeld Y. Autoimmune hemolytic anaemia in the antiphospholipid syndrome.Lupus.2006:15;473 – 77