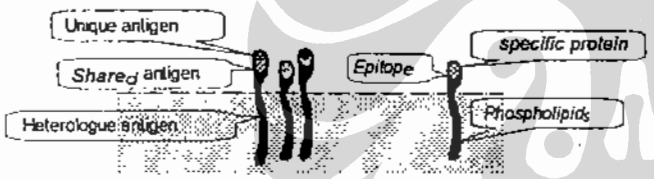
Anti-phospholipid Antibody and Anti-phospholipid Antibody Syndrome

Shufrie Effendy, Karmel L. Tambunan

INTRODUCTION

Phospholipid is a lipoprotein particle that contains a specific protein called apolipoprotein. Apolipoprotein is the outer, exposed portion of negatively charged phospholipids (anionic phospholipids), which functions as enzyme or specific protein binding agents. The cell wall is formed by phospholipids, while apolipoproteins in the outer portion of the cell wall function as uptake receptors.



Unique antigen: specific antigen
Shared antigen: anionic (epitope) phospholipids
Heterologue antigen: phospholipids

During hemostasis, free apolipoproteins that binds with A2 phospholipase are known as procoagulant phospholipids (PL). PL is a coagulation activator when kininogen (Fitzgerald), prealikrein (Fletcher), arachidonic acid metabolism, factors Vc, VIIc, Xc, and IIc (prothrombine) are activated. The natural (physiologic) control mechanisms for PL is the formation of anti-phospholipid apolipoproteins (aPLs), which structurally resemble complement, known as the beta2-glycoprotein I (beta 2 – GPI). A type of aPL that is crucial during pregnancy is placental anticoagulant protein I, which is also known as annexin V, which is very potent in inhibiting phospholipase A2. There are two known clinically important pathologic anti-phospholipid apolipoprotein: (1) the anti-phospholipid traditionally known as Lupus Inhibitor or Lupus Anticoagulant (LA), and (b) anti-cardiolipin (aCL), an apolipoprotein dependent on beta2-GPI, as well as anti-phosphatidil etanolamine (aPE), which still lacks clinical information.

The body naturally forms humoral and cellular immune responses to eliminate abnormal proteins bound to the phospholipid apolipoprotein. Anti-phospholipid (AAP), a result of the humoral immune response, is defined as the immunoglobulin that reacts to glicoproteins with phospholipids as its chief component. AAP belongs to a family of autoantibodies, including Anticoagulant Lupus Antibody (LA), and anticardiolipin antibody (ACA). AAP is strongly associated with the morbidity and mortality in cardiovascular diseases, where AAP is a promotor for acquisitive thrombophillia. Venous thrombosis is more commonly found than arterial thrombosis, but nevertheless, arterial thrombosis is the main cause of morbidity and mortality in cardiovascular diseases. The LDL cholesterol oxide antibody is more commonly found in the serum of ACA positive patients compared to ACA negative patients.

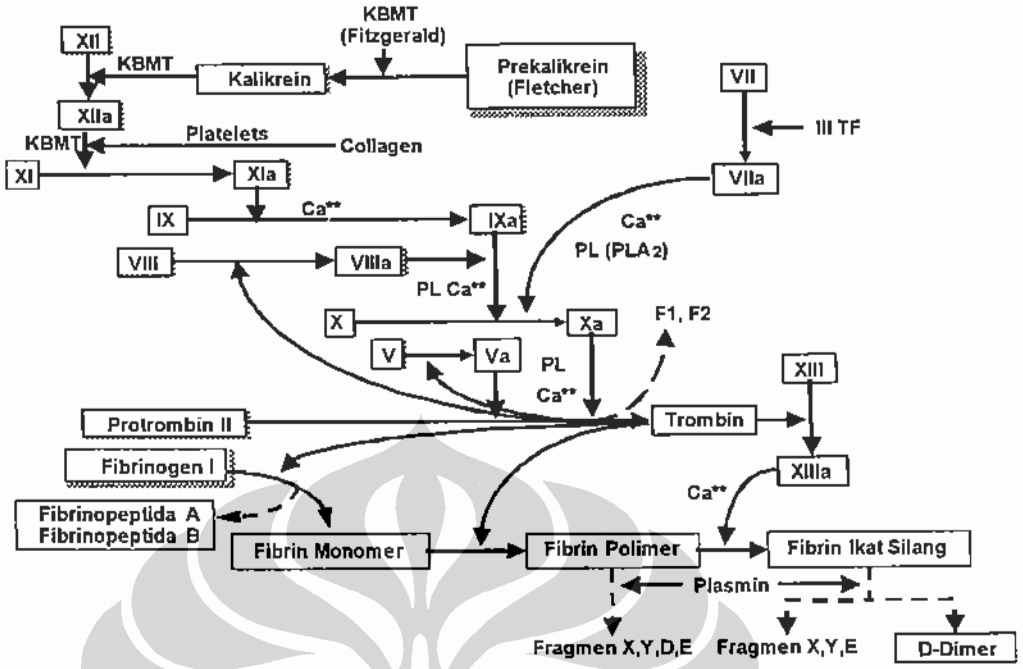
AAP is formed due to the attachment of abnormal protein on phospholipid apolipoprotein, as an antigen classified as follows:

Class 1:
Unique/specific/antigenic autolog or specific protein antigen boud to specific apolipoproteins on the phospholipid.

Class 2:
Shared/antigenic allogenic/antigenic homolog. Some of these antigens are formed by specific apolipoproteins on phospholipids that bind to specific protein antigens.

Class 3:
Heterolog antigen, formed by phospholipids that contain specific apolipoproteins on phospholipids that bind to specific protein antigens.

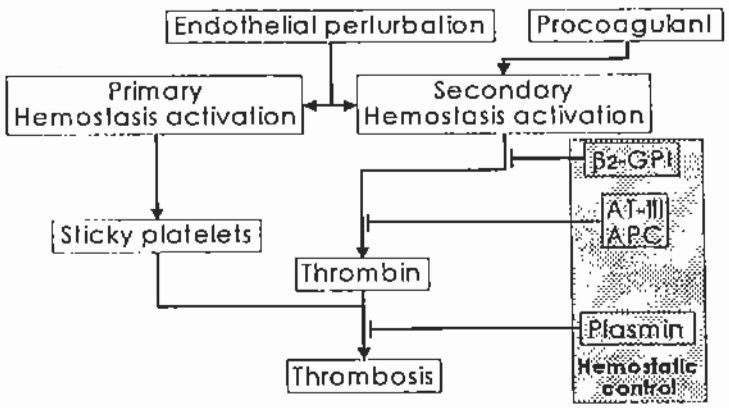
* *Division of Hematology, Department of Internal Medicine, Faculty of Medicine of The University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia*



The presence of these anti-phospholipid antibodies (AAP) causes the natural control mechanism for PL to malfunction, resulting in hypercoagulation, deficiency of thrombomodulin, C and S proteins, and finally thrombosis. Other accompanying symptoms are due to the presence of antigen-antibody complex that activate the complement system, causing an increase in effector immune cells with the receptor Fc gamma RII, and thus thrombocytopenia, hemolysis, leukopenia, and destruction of cells with beta2GPI binding uptake receptors on their outer walls, such as endothelial cells, or trophoblast cells (placenta), with annexin V binding uptake receptors.

Table 1. Antigenic (protein binding phospholipid) Target of Anti-Phospholipid Antibodies.

Protein	Cell
Neutral PL (?)	Endothelial cell
Anionic PL	Trophoblasts
Beta-2-glycoprotein-I	Platelet
Annexin V	Erythrocytes
Thrombomodulin	Leukocytes
Protein C	
Protein S	
Prothrombin	
Factor XI	



THE EFFECT OF ANTI-PHOSPHOLIPID ANTIBODIES ON THE HEMOSTASIS SYSTEM

Under tolerated conditions, such as in geriatric or pregnant patients, where there is a low titer of persistent ACA IgG, approximately 30% of cases demonstrate no signs or symptoms. The main signs and symptoms are as follows:

a. Ischemia, caused by the surface of venous or artherial endothelial cells (uptake receptors)
b. Hemorrhage, due to inefficient VIIa + III + PL + Ca2++ complex Ixa + VIIIa + PL + Ca++ and complex Xa + Va + PL + Ca++, due to LA action as dependent antifactor coagulant phospholipids (PL).

Destruction/potential destruction of endothelial cells would activate both primary and secondary hemostasis process.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Antiphospholipid Antibody Syndrome (APS) is a collection of the following symptoms:

- Arterial and/or venous thrombosis
  a. Catastrophic APS: sudden and widespread arterious/venous thrombosis (multiple vascular occlusions) on the central nervous system, heart, lungs, kidneys, and intraabdominal organs (liver, spleen, adrenal, pancreas, gastrointestinal system/mesentery),
  b. Avascular osteonecrosis,
  c. Marantic endocarditis: small nodular thrombosis on heart valves,
  d. Ischemia or cardiac infarct, intracardiac thrombotic mass,
  e. Peripheral vascular disease (DVT, thromboangitis),
  f. Acrocyanosis (distal cutaneous ischemia, ulceration, gangrene,
  g. Acute cerebral ischemia (transient ischemic attact – TIA, hemorrhagic/non-hemorrhagic stroke, encephalopathy),
  h. Severe migraine,
  i. Multiple infarct cerebral dementia, Guillan Barre syndrome, multiplex mononeuritis,
  j. Sudden blindness/deafness without symptoms of increased intracranial pressure,
  k. Myasthenia gravis,
  l. Fetal wastage syndrome, intrauterine growth retardation, chorea gravidarum, preeclampsia,
- Thrombocytopenia
- LA and/or ACA positive (IgM and/or IgG and/or IgA)

Antiphospholipid antibody syndrome (APS) is defined

Diagnostic for hypercoagulation	Diagnostic for thrombosis
F1 & 2 > 2 x control	Compression color doppler or angiography
Alternative:	Clinical probability
PT < 80% of control	D-dimer
Prothrombin level > 130%	Active: D-dimer 500-1000 ug/mL without significant hemorrhage/pregnancy, or D dimmer => 1000 ug/ml
INR < 0.9	Inactive: D-dimer <= 500 ug/ml
APTT < 80% of control	

Table 2. Clinical Diagnosis Associated with Antiphospholipid Protein Antibody

Phopholipid
Priamary APS, autoimmune disorder without obvious cause
Immune Thrombocytopenic Purpura (ITP), AIHA
Secondary autoimmune disorder:
Systemic Lupus Erythematosus (SLE), autoimmune diseases, and other collagen diseases (RA and Behcet's)
Drug induced: Procainamide, Hydralazine, Quinidin, Fenotiazin, Penicillin
Cancer: leukemia, lymphoproliferative, and plasma cells, solid tumors
Chronic hepatitis/ liver cirrhosis:
Alcoholism, hepatitis C
Maternal-feral incompatibility (ABO, Rh, HLA)
Infection:
viral (CMV, hepatitis C, HIV, HTLV-1, etc.)
bacterial (Streptococcus hemolyticus, Helicobacter pylori, Rickettsia sp., etc.)
parasitic (malaria, etc.)

by the presence of persistent antiphospholipid antibodies (ACA and/or LA) and recurrent clinical events such as arterial or venous thromboses, thrombocytopenia, or fetal loss. Refer to diagnostic criteria for antiphospholipid syndrome by International Consensus on Antiphospholipid syndrome in October 1998, based on a fixed cutoff IgG and/or IgM ACA titer of minimum 20 GPL/MPL.

TREATMENT

Symptomatic, as long as the primary cause cannot be corrected.

- DIC: heparinization (Target APTT 45"-75")
- Hypercoagulation and thrombosis: heparin, low dose aspirin, oral anticoagulant
  Target APTT 45"-75", INR 1.5-2.5 (hypercoagulation)
  Target APTT 45"-75", INR 3.5-4.8 (thrombosis)
- Thrombocytopenia, hemolysis, vasculitis: low dose corticosteroid
- Obstetric case positive for ACA IgG:

a. Antepartum (Grade 1A recommendation)
- Aspirin 80 mg/day + Heparin 100-200/kg bodyweight iu/day, in divided doses or LMWH
- Prednisone 15-30 mg/day (controversial, except in cases of thrombocytopenia), or
- IVIg 400 mg/kg bodyweight/day for 5 consecutive days if ACA IgG/IgM level is persistently high.

b. Persistently positive postpartum ACA (Grade 1C recommendation)
- Aspirin 80 mg/day + Heparin 100-200/kg bodyweight iu/day, in divided doses or LMWH
- Aspirin 80 mg/day + oral anticoagulant (if not breastfeeding)

REFERENCES

References : available with the author.