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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Antiphospholipid Syndrome

Role of Vascular Endothelial Cells and Implications for Risk Stratification and Targeted Therapeutics

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ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by venous thromboembolism, arterial thrombosis, and obstetric morbidities in the setting of persistently positive levels of antiphospholipid antibodies measured on 2 different occasions 12 weeks apart. Patients with APS are at increased risk for accelerated atherosclerosis, myocardial infarction, stroke, and valvular heart disease. Vascular endothelial cell dysfunction mediated by antiphospholipid antibodies and subsequent complement system activation play a cardinal role in APS pathogenesis. Improved understanding of their pathogenic function could help in the risk stratification of patients with APS and provide new molecular therapeutic targets.
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The term *antiphospholipid syndrome* (APS) was coined in the 1980s to describe a condition of autoantibody-induced thrombophilia (1). This autoimmune prothrombotic condition is characterized by venous thromboembolism, arterial thrombosis, and pregnancy morbidity in the setting of laboratory evidence of elevated levels of antiphospholipid antibodies (aPLs). aPLs can be identified by 1 of 3 assay platforms, namely, clot-based assays to identify lupus anticoagulant, or enzyme-linked immunosorbent assays to identify anticardiolipin (aCL) or anti-β_2-glycoprotein 1 (β_2-GP1) antibodies (immunoglobulin G or immunoglobulin M). Regardless of the assay, this class of antibodies targets antiphospholipid-bound proteins. The prevalence of aPLs in a random sample of 552 healthy blood donors was found to be 6.5% and 9.4% for aCL immunoglobulin G and immunoglobulin M antibodies, respectively. None of those normal subjects with positive aPLs developed thrombotic events at 1-year follow-up (2).

A definite diagnosis of APS requires the presence of at least 1 clinical and 1 laboratory criterion. Clinical criteria may include objectively confirmed venous, arterial, or small-vessel thrombosis or pregnancy morbidity attributable to placental insufficiency, including pregnancy loss or premature birth. Laboratory criteria encompass persistently positive test results for at least 1 of these 3 aPLs measures on 2 or more occasions 12 weeks apart. The 12-week testing interval is particularly important, given that some infections and medications can cause transient aPL-positive testing (3,4).

APS typically presents in the fourth decade of life and is classified as either a primary disease or secondary to another underlying autoimmune disease, solid tumor, or hematologic disorder. Approximately 10% to 40% of patients with systemic lupus

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ABBREVIATIONS AND ACRONYMS

aCL = anticardiolipin antibody

aPL = antiphospholipid antibody

apoER2 = apolipoprotein E receptor 2

APS = antiphospholipid syndrome

β_2-GP1 = β_2-glycoprotein 1

CAPS = catastrophic antiphospholipid syndrome

eNOS = endothelial nitric oxide synthase

HCQ = hydroxychloroquine

INR = international normalized ratio

mTORC = mammalian target of rapamycin complex

NO = nitric oxide

NOAC = new oral anticoagulant agents

SLE = systemic lupus erythematosus

erythematosus (SLE) (5) and up to 20% of patients with rheumatoid arthritis (6) have positive aPL serologies. Moreover, patients with SLE who have positive lupus anticoagulant have a 50% chance of developing venous or arterial thrombotic events within a 20-year follow-up period (5). APS can affect any body organ, and patients with APS have increased risk for thrombosis, accelerated atherosclerosis, myocardial infarction, and stroke (7,8). In a large prospective cohort study of 1,000 patients with APS followed over a 10-year period, deep vein thrombosis was the most common presenting clinical manifestation (39%), followed by thrombocytopenia (30%), livedo reticularis (24%), stroke (20%), pulmonary embolism (14%), and myocardial infarction (6%). In that study, thrombotic events occurred in 16.6% of patients during the first 5-year period and in 14.4% during the second 5-year period; 90.7% of patients were still alive at 10 years (9). Despite high survival rates, these data reflect a substantial disease burden and morbidity in patients with APS on current treatment.

Obstetric morbidities in APS are thought to be secondary to placental vascular insufficiencies, with early (<10 weeks) and late (≥10 weeks) miscarriages being the most common obstetric manifestations (35% vs. 17%, respectively) of APS, followed by premature labor (11%), pre-eclampsia and/or eclampsia (5%), and intrauterine growth restriction (2%) (9).

A recent meta-analysis demonstrated that APS is associated not only with clinical adverse cardiovascular events but also with subclinical cardiovascular risk factors associated with endothelial cell dysfunction, such as increased carotid artery intima-media thickness and lower flow-mediated dilation, higher frequency of carotid plaques, and increased prevalence of pathological ankle-brachial indexes (10). The renal vasculature may also be affected in APS, leading to nephropathy, renal vein thrombosis, renal artery stenosis, thrombotic microangiopathy, hypertension, kidney infarction, and ultimately end-stage kidney disease (11,12). The most severe, yet fortunately infrequent form of APS is catastrophic APS (CAPS). CAPS, with an incidence of 0.9% (9) and mortality >50% (9,13), is defined as small-vessel thrombosis involving ≥3 organs, organ systems, and/or tissues, occurring simultaneously or in <1 week, along with positive laboratory evidence of aPLs and no alternative diagnosis (13).

PATHOGENESIS

THE CARDINAL ROLE OF ENDOTHELIAL CELLS. The fact that normal healthy subjects with circulating aCL antibodies remained free of thrombotic events at 1-year follow-up on one hand and the important direct role of aPLs in the pathogenesis of APS on the other hand imply that additional underlying host susceptibility characteristics are necessary for the development of the disease. More than a decade ago, it was suggested that endothelial cells play a central role in APS pathogenesis and may represent the common pathway through which autoimmunity and inflammation participate in APS (14). Although circulating aPLs and underlying endothelial dysfunction are a necessary "first hit" for thrombosis in APS, an inflammatory "second hit" is needed to precipitate a thrombotic event (15–17). Although elevated levels of aPLs have been associated with both vascular thrombosis and pregnancy morbidity in patients with APS (18,19), human aPLs injected into mice did not promote thrombosis in the absence of endothelial injury (20,21). Growing evidence demonstrates that endothelial cell dysfunction, mediated by aPLs binding to endothelial cell β_2-GP1 receptors, results in increased risk for thrombosis, accelerated atherosclerosis, myocardial infarction, and stroke in patients with APS (7). Similarly, a recent in vitro study associated obstetric morbidity in APS to placental inflammatory response mediated by binding of aPLs to β_2-GP1 receptors on the surface of placental trophoblasts (22). Moreover, an inflammatory insult secondary to surgery, trauma, or infection has been demonstrated to up-regulate expression of β_2-GP1 receptors on the endothelial cell surface (**Figure 1A**) (15,17).

Endothelial nitric oxide synthase inhibition and thrombosis. Endothelium-derived nitric oxide (NO), produced by endothelial NO synthase (eNOS), is important for normal endothelial function and vascular health (23–25). Patients with APS have lower plasma nitrite levels and an impaired endothelium-dependent vascular response, suggestive of impaired eNOS activity and reduced NO production and endothelial function (26,27). The antithrombotic effects of eNOS and NO secreted from endothelial cells and platelets have been demonstrated in multiple animal and human studies. Indeed, eNOS-knockout mice demonstrated enhanced platelet aggregation (28) and increased predisposition to thrombosis, stroke, and atherosclerosis (29–32), and decreased endogenous NO production in humans has also been associated with increased risk for thrombosis (33–35).