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Antiphospholipid syndrome

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A B S T R A C T

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by the occurrence of thrombosis (arterial and/or venous), often multiple, and/or pregnancy morbidity.

Thrombosis is one of the major disease mechanisms, mainly caused by activating endothelial cells, monocytes, and platelets. At present, the management of APS patients with a history of thrombosis is based on long-term antithrombotic therapy, due to the high rate of recurrent thrombosis (29% per year without treatment). Obstetrical APS includes heterogeneous pregnancy complications whose pathogenesis has been increasingly elucidated in the past years. This is due to the current management and treatment, as 80% of APS patients achieve a live birth. The standard approach of APS is not supported by extensive evidence and the best options for refractory and incomplete cases need to be clarified. New and promising molecules are under investigation.

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Introduction

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by the occurrence of thrombosis (arterial and/or venous), often multiple, and/or morbidity in pregnancy (recurrent miscarriages, fetal deaths (FDs), and late pregnancy complications such as preeclampsia (PreE) and intrauterine growth restriction (IUGR)), in the presence of antiphospholipid antibodies (aPLs), typically the antibodies included in the classification criteria for APS, lupus anticoagulant (LA), anticardiolipin (aCL), or anti-β2 glycoprotein-I (anti-β2GPI) antibodies (Table 1), although other "non-criteria" antibodies may also play a role. APS may be associated with other autoimmune diseases, mainly systemic lupus erythematosus (SLE), but it can also be seen in patients having no other definable rheumatologic condition (primary APS). Occasionally, it can accompany other conditions, such as infections, drugs, or malignancies [1].

In this review, we discuss recent advances in the diagnosis of APS including new insights into the pathogenesis and the implications for the identification of new biomarkers. In addition, the importance of recent longitudinal observational studies in understanding the natural history of the syndrome and for embedding research in clinical practice will be elucidated.

Thrombotic APS

Pathogenesis

Although the full pathogenesis of APS is not yet clear, the key mechanisms have been described recently. Thrombosis is one of the major disease features, driven by multiple mechanisms including activation of endothelial cells, monocytes, platelets, coagulation, and complement pathways in addition to inhibition of fibrinolytic and anticoagulation pathways [2]. Recent evidence indicates that vasculopathy, enhanced mainly by severe intimal hyperplasia, can also play a role in arterial vascular occlusion (due to stenotic lesions) and pregnancy morbidity [3]. In support of this hypothesis, Canaud et al. [3] recently demonstrated that the vascular endothelium of proliferating intrarenal vessels from patients with APS nephropathy showed indications of activation of the mammalian target of rapamycin (mTOR) pathway. In cultured vascular endothelial cells, IgG antibodies in patients with APS stimulated mTOR through the phosphatidylinositol 3-kinase (PI3K)-AKT pathway. Patients with APS nephropathy who required renal transplantation and were treated with sirolimus (also known as rapamycin, which can inhibit mTOR) showed no recurrence of vascular lesions and decreased vascular proliferation on biopsy compared with patients with aPLs who were not treated with sirolimus. Of 10 patients treated with sirolimus, seven (70%) had a functioning renal allograft 144 months after transplantation versus three of 27 untreated patients (11%). This study conducted in patients with primary and secondary APS nephropathy, which is mainly mediated by vasculopathy rather than thrombosis, revealed that the activation of the mTOR enzyme stimulates intimal hyperplasia, leading to the formation of the chronic

Table 1
Revised classification criteria for antiphospholipid syndrome.

Vascular thrombosis	≥1 clinical episode of arterial, venous, or small vessel thrombosis. Thrombosis must be objectively confirmed. For histopathological confirmation, thrombosis must be present without inflammation of the vessel wall
Pregnancy morbidity	1 ≥1 unexplained death of a morphologically normal fetus ≥10 weeks of gestation 2 ≥1 premature delivery of a morphologically normal fetus <34 weeks of gestation because of: • severe preeclampsia or eclampsia defined according to standard definition; • recognized features of placental insufficiency 3 ≥ 3 unexplained consecutive miscarriages <10 weeks of gestation, with maternal and paternal factors (anatomic, hormonal, or chromosomal abnormalities) excluded
Laboratory criteria	Presence of antiphospholipid antibodies (aPL), on two or more occasions at least 12 weeks apart and no more than 5 years prior to clinical manifestations, as demonstrated by ≥1 of the following: a Lupus anticoagulant; b Medium to high-titer (>40 GPL or MPL, or >99th percentile) anticardiolipin IgG or IgM; c Anti-β2 glycoprotein-I (anti-β2GPI) IgG or IgM >99th percentile