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Opinion Article

Antiphospholipid Syndrome and Arterial Thrombosis: Diagnostic Challenges and Therapeutic Strategies

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DESCRIPTION

Antiphospholipid Syndrome (APS) is a systemic autoimmune disorder characterized by the presence of Antiphospholipid Antibodies (aPLs) and a predisposition to arterial and venous thrombosis. While venous thromboembolism is the most frequently recognized manifestation, arterial thromboses including stroke, myocardial infarction, and limb ischemia are equally significant and often more debilitating. The diagnosis and management of arterial events in APS pose unique challenges due to the variable clinical presentation, heterogeneity of antibody profiles, and need for long-term anticoagulation.

The primary aPLs associated with APS include Lupus Anticoagulant (LA), Anticardiolipin (aCL) and Anti-β2 Glycoprotein I (anti-β2GPI) antibodies. These antibodies target phospholipid-binding proteins on endothelial cells, platelets and monocytes, inducing cellular activation and promoting a hypercoagulable state. The pathogenesis of arterial thrombosis in APS involves multiple mechanisms, including endothelial dysfunction, platelet activation, complement activation and upregulation of tissue factor expression. This prothrombotic environment is exacerbated by oxidative stress and inflammatory cytokines, particularly in patients with underlying Systemic Lupus Erythematosus (SLE).

Arterial thrombosis in APS typically presents as ischemic stroke in younger individuals without conventional cardiovascular risk factors. Transient ischemic attacks, retinal artery occlusion and acute coronary syndromes have also been reported. Recurrent events are common and traditional stroke workups often fail to identify atherosclerotic or embolic sources, delaying the diagnosis. Screening for aPLs should be considered in young patients with cryptogenic stroke, especially in the presence of autoimmune features or recurrent pregnancy loss.

Laboratory diagnosis of APS requires persistent positivity for at least one aPL on two occasions 12 weeks apart. The variability in assay sensitivity, antibody titers and clinical significance of isolated low-titer results complicates diagnosis. Furthermore, a subset of patients may present with "seronegative" APS, exhibiting thrombotic phenomena and characteristic clinical features despite negative standard aPL tests. These cases challenge existing criteria and emphasize the need for more inclusive diagnostic markers, such as anti-phosphatidylserine/prothrombin antibodies or anti-annexin V.

Treatment of arterial thrombosis in APS is centered on long-term anticoagulation. Vitamin K antagonists (VKAs) such as warfarin remain the gold standard, aiming for an international normalized ratio (INR) of 2.0–3.0 for first events and 3.0–4.0 for recurrent events or arterial involvement. The use of Direct Oral Anticoagulants (DOACs) in APS, particularly in high-risk patients with triple positivity, has been associated with increased thrombotic recurrence and is currently not recommended. Studies such as the TRAPS trial have confirmed the inferiority of rivaroxaban in preventing thrombosis in this population.

Adjunctive antiplatelet therapy may be considered in arterial events, especially in stroke or myocardial infarction. Combination therapy with aspirin and warfarin is sometimes used, though evidence for its superiority remains limited and must be weighed against bleeding risk. Hydroxychloroquine, widely used in SLE, may exert antithrombotic effects through inhibition of platelet aggregation and aPL binding and is increasingly recommended in APS patients with coexisting autoimmune disease.

The management of refractory APS, characterized by recurrent thrombosis despite therapeutic anticoagulation, includes escalation of warfarin intensity, addition of low-dose aspirin, or transition to low molecular weight heparin. Experimental therapies targeting B cells, complement pathways and cytokines are under investigation, particularly in Catastrophic APS (CAPS), a rare and life-threatening form involving multiorgan thrombosis.

Risk stratification in APS requires a comprehensive assessment of antibody profile, thrombotic history, comorbidities and

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lifestyle factors. Triple positivity (positivity for all three major aPLs) is associated with the highest risk, whereas isolated low-titer aCL or anti-β2GPI may have limited clinical relevance. Modifiable risk factors such as smoking, hypertension, hyperlipidemia and estrogen use should be aggressively managed. Regular monitoring of anticoagulation, patient education and interdisciplinary care are essential to optimize long-term outcomes.

In conclusion, arterial thrombosis in antiphospholipid syndrome represents a complex clinical entity requiring nuanced diagnosis and vigilant management. While anticoagulation remains the mainstay of therapy, emerging insights into the immunopathogenesis of APS may lead to novel targeted treatments. Enhanced awareness and early detection can significantly improve prognosis and reduce the burden of thrombotic complications in this high-risk population.