Antiphospholipid Syndrome and the Kidney

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Summary: The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis, pregnancy morbidity, and the persistent presence of circulating antiphospholipid antibodies (aPL). APS has been described as *primary* APS when it occurs in the absence of any features of other autoimmune disease, and as *secondary* in the presence of other autoimmune diseases, mainly systemic lupus erythematosus (SLE). There is a well-known link between SLE and APS; 40% of SLE patients have aPL, and, in turn, some, but only a minority of patients with APS, eventually will develop features of SLE. Because SLE and APS can target the kidneys independently or at the same time, discriminating between inflammatory or thrombotic lesions is crucial in planning therapy. We provide an overview of the renal manifestations associated with the presence of aPL in patients with SLE, and discuss the impact of aPL in selected scenarios such as lupus nephritis, end-stage renal disease, and pregnancy.
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The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis and the persistent presence of circulating antiphospholipid antibodies (aPL).[1] APS has been described as *primary* APS when it occurs in the absence of any features of other autoimmune disease, and as *secondary* in the presence of other autoimmune diseases, mainly systemic lupus erythematosus (SLE).

Because SLE and APS can target the kidneys independently or at the same time, discriminating between inflammatory and thrombotic lesions is crucial in planning an adequate therapeutic strategy.

The incidence of kidney involvement in SLE ranges from 30% to 50%, depending on the definition of abnormal renal function, and represents a severe organ manifestation that is associated with significant patient morbidity and mortality.[2,3] Although all renal compartments (glomerular, tubulointerstitial, and vascular) can be injured in SLE, the term *lupus nephritis* refers specifically to immune-complex mediated glomerulonephritis. Lupus nephritis (LN) presents with diverse clinical and histologic manifestations. However, the main driver of LN remains the immune system and therefore the main therapeutic approach is immunosuppression.[4]

Among SLE patients, the prevalence of aPL ranges from 30% to 40%.[5] Approximately 50% of patients with both SLE and aPL will develop APS during long-term (10-20 y) follow-up evaluation.[5] The presence of aPL in patients with SLE and LN has been shown to be associated with increased mortality and a poorer prognosis, and renal APS requires treatment beyond immunosuppression.[6]

In this review we describe the role of aPL/APS in kidney injury in SLE, and focuses on state-of-the art treatment and future therapies of APS.

aPL SPECIFICITIES AND THROMBOSIS

APS has been known for over three decades and advances in research have identified the coagulation system and the immune system as key players underlying the clinical manifestations of the syndrome.[5]

The persistent presence of aPL is crucial for the classification of APS. aPL are recognized as a heterogeneous group of antibodies directed against anionic phospholipids or protein-phospholipid complexes. Laboratory tests aimed to identify aPL include solid-phase immunoassays (enzyme-linked immunosorbent assay) to detect anticardiolipin (aCL) and anti-β2 glycoprotein 1 (aβ2GPI) antibodies, and functional assays to detect lupus anticoagulant (LAC). LAC has the ability to interfere with phospholipid-dependent coagulation reactions.

The first international consensus statement on classification criteria for APS was developed in 1998 in Sapporo, Japan. Eight years later the consensus criteria were updated.[1] According to the current classification criteria of APS (Table 1), at least one clinical manifestation is needed. This may include any vascular thrombosis and/or

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Table 1. Criteria for the Classification of Antiphospholipid Syndrome

Vascular thrombosis	Clinical criteria
One or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology); for histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall	
Pregnancy morbidity	
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (1) eclampsia or severe preeclampsia defined according to standard definitions or (2) recognized features of placental failure or Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded In studies of populations of patients who have more than one type of pregnancy morbidity, stratification of subjects according to this list is strongly encouraged	
Lupus anticoagulant present in plasma on 2 or more occasions at least 12 weeks apart and detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LA/phospholipid-dependent antibodies)	Laboratory criteria
Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titers (ie, >40 GPL or MPL, or >99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA	
aβ2GPI antibody of IgG and/or IgM isotype in serum or plasma (in titers >99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA	

Definite antiphospholipid syndrome may be diagnosed if at least one of the clinical criteria and at least one of the laboratory criteria are met.
Abbreviation: ELISA, enzyme-linked immunosorbent assay; GPL, IIgG phospholipid units; MPL, IgM phospholipid units.

pregnancy morbidity in combination with a positive laboratory test, including LAC, aCL, or aβ2GPI, detected at least twice 12 weeks apart.

The syndrome can present with a variety of clinical manifestations caused by thrombosis of any vessel. Deep vein thrombosis and pulmonary embolism are the most frequent features in the venous vasculature.[6] The most common arterial manifestations are neurologic, such as transient ischemic attacks or strokes, or dermatologic manifestations, such as livedo reticularis, seen in 20% of APS patients. aPL-mediated placental dysfunction, which partially, but not entirely, can be explained by thrombosis, may cause intrauterine growth restriction, preeclampsia, intrauterine fetal death, or placental abruption.[7]

Thromboses are the main cause of renal involvement in APS and can occur at any level within the renal vasculature. These thrombotic events can lead to various manifestations that reflect the site and size of the involved vessel. A substantial body of evidence supports the inclusion of aPL-related nephropathy in the classification criteria for definitive APS.[8]

aPL ANTIBODIES AND THROMBOSIS IN VIVO

A two-hit hypothesis for the pathogenesis of APS has been suggested. This is based on the fact that the presence of aPL in the circulation sometimes, but not always, leads to thrombotic events. Therefore, the presence of aPL is necessary but not sufficient for thrombi formation in vivo. This hypothesis implies that the presence of aPL (the first hit) does not itself cause a thrombus, but increses the risk of any thrombotic events when another prothrombotic factor is added (the second hit).[9,10] Thus, according to this model, the presence of aPL creates a prothrombotic state, while the second hit leads to thrombus formation. In this regard, it is useful to speculate on the reported association between an acute thrombotic event and a recent or concomitant infectious process in APS patients, or with a traumatic or inflammatory stimulus in experimental models.[11] Furthermore, a genetically determined thrombophilic diathesis, or ability to mount a prompt inflammatory response, may enhance the thrombotic risk of subjects with aPL further.

The proposed pathophysiological mechanisms underlying aPL-mediated thrombosis in APS have been divided into two main types.[10,12] First, aPL may act in vivo by disrupting the normal balance between procoagulants and anticoagulants. Second, aPL may interact with specific cell surface receptors (proteins and/or lipids), inducing downstream signals that up-regulate procoagulant cell surface proteins.[13]