Antiphospholipid syndrome and kidney disease

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The antiphospholipid syndrome is a common autoimmune disease caused by pathogenic antiphospholipid antibodies, leading to recurrent thrombosis and/or obstetrical complications. Importantly for nephrologists, antiphospholipid antibodies are associated with various renal manifestations including large renal vessel thrombosis, renal artery stenosis, and a constellation of intrarenal lesions that has been termed antiphospholipid nephropathy. This last condition associates various degrees of acute thrombotic microangiopathy, proliferative and fibrotic lesions of the intrarenal vessels, and ischemic modifications of the renal parenchyma. The course of the disease can range from indolent nephropathy to devastating acute renal failure. The pejorative impact of antiphospholipid antibody–related renal complication is well established in the context of systemic lupus erythematous or after renal transplantation. In contrast, the exact significance of isolated antiphospholipid nephropathy remains uncertain. The evidence to guide management of the renal complications of antiphospholipid syndrome is limited. However, the recent recognition of the heterogeneous molecular mechanisms underlying the progression of intrarenal vascular lesions in antiphospholipid syndrome have opened promising tracks for patient monitoring and targeted therapeutic intervention.

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The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of circulating antiphospholipid antibodies (aPLs), vascular thrombosis, and pregnancy complications.[1,2] Since the postconference workshop led in Sapporo in 1998, classification criteria have been used to homogenize case criteria, which lead to the definition of "definite APS." The criteria were updated in 2006[3] and include the following: (i) clinical manifestations consisting of either thrombosis in arterial, venous, or small vessels, or obstetrical manifestations; and (ii) the sustained detection of at least 1 of the 3 main types of aPLs, namely lupus anticoagulant (LA), anti-cardiolipin (aCL), or anti–β2 glycoprotein I antibodies.

The APS is classified further as primitive when APS occurs in the absence of other autoimmune diseases, or as secondary when it occurs in association with a number of autoimmune disorders, mostly systemic lupus erythematosus (SLE).

The clinical spectrum of aPL-related manifestation extends beyond these classification criteria. These so-called "noncriteria APS manifestation" include thrombocytopenia, heart valve disease, and cutaneous, renal, and neurologic manifestations that can result in dramatic presentations. Among the different clinical manifestations associated with the presence of aPLs, modification of renal parenchyma has a prominent and particular place. Apart from large renal vessel thrombosis, which is classified as APS criteria, other lesions affecting the renal microarchitecture were recognized in the 1990s.[4–7] The important place taken by kidney biopsies in the diagnosis of renal disease has allowed pioneer pathologists to finely describe the spectrum of the renal lesions associated with the presence of aPLs.[8–11] These lesions are associated with deleterious consequences on renal function. This condition, known as APS nephropathy (APSN), currently is considered as a "non-criteria" APS manifestation[12] (Figure 1). It is worth noting that the lesions observed in APSN are not found in other thrombophilia disorders such as mutations in genes implicated in the regulation of coagulation or fibrinolysis. This suggests that large-vessel thrombosis and microvascular disease are caused by distinct, yet potentially overlapping, mechanisms. Recently, molecular analysis of APSN occurrence or recurrence on the renal allograft and reports of eculizumab efficacy on the thrombotic microangiopathy (TMA) associated with aPLs have provided evidence for a pathophysiologic heterogeneity in the development of renal lesions associated with aPLs.[13–15] Although the identification of the mechanistic target of rapamycin complex (mTORC) pathway as a potential

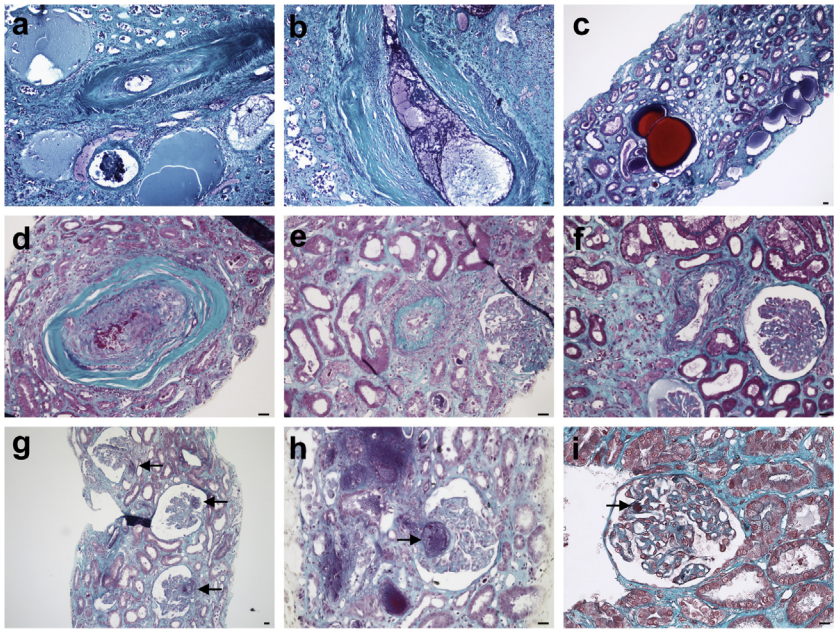

Figure 1 | Antiphospholipid syndrome nephropathy. (**a**) Severe fibrous intimal hyperplasia lesion with ischemic tubular dilation in a kidney transplant recipient with antiphospholipid syndrome (APS). The kidney presented here was removed 4 months after transplantation owing to renal failure. A preimplantation biopsy showed no vascular modification. (**b**) Severe fibrous intimal hyperplasia lesion in a native kidney in a patient with APS. (**c**) Pseudo aspect of tubular thyroidization. (**d**) Severe vascular rearrangement leading to the obstruction of the lumen in a patient with APS. (**e,f**) Typical aspects of intimal proliferation observed in patients with APSN. (**g,h,i**) Thrombotic microangiopathy lesions observed in patients with APS (arrows). Bar = 10 μm.

mediator of the chronic vascular lesions associated with APSN represents an exciting breakthrough, it should be emphasized that the evidence supporting a role for mTORC in APSN currently remains limited. Future studies will have to determine if mTORC activation represents a significant biomarker and/or a valid therapeutic target in APSN.

RENAL LARGE-VESSEL THROMBOSIS

Epidemiology and clinical presentation

Large-vessel thrombosis represents a well-defined manifestation of APS and is used to classify patients. Although certain vessels, such as cerebral arteries, tend to be affected more frequently, virtually all of the vascular beds may be sites of thrombosis. Indeed, thrombosis in both arterial[16–23] and venous[19,24–28] renal vessels has been described in APS patients. Most of the renal arterial and vein thromboses were reported in case reports and the overall incidence of these events in APS appeared relatively low compared with deep-vein thrombosis affecting the legs, pulmonary embolisms, or strokes.[29] The clinical spectrum of arterial thrombosis encompasses worsening hypertension, renal infarction with loin pain, and acute or chronic renal failure, whereas venous thrombosis may be associated with proteinuria, decreasing renal function, loin pain, hematuria, or a secondary pulmonary embolism. Although the presentation is nonspecific, precipitating factors such as infection, surgery, pregnancy, delivery, anticoagulation withdrawal, as well as hydroxychloroquine withdrawal may trigger thrombotic events, and particularly renal vessel thrombosis in APS patients.[30] In addition to local formed thrombosis, arterial embolisms from an upstream lesion have been reported in APS patients.[23]

In the setting of renal transplantation, a definite APS, or the presence of LA, seems to be associated with a high risk of large renal vessel thrombosis, leading to early graft loss.[31–34]

Pathophysiology

The pathophysiology of thrombosis in APS has been investigated extensively. The obvious observation that patients with aPLs do not develop thrombosis systematically directly points to the fact that aPLs do not cause thrombosis directly, but rather induce a clotting-prone context (also called a "first hit") in which thrombotic events are triggered by additional insults (also called a "second hit")[35] (Figure 2). Stemming from the clinical observation that thrombotic events in APS frequently are precipitated by a specific event, this "two-hit" hypothesis now is supported by concordant experimental evidence. Indeed, passive transfer of human aPL to mice does not cause thrombosis directly, but increases thrombus size when thrombosis is induced experimentally by endothelial injury or when animals are "primed" through the administration of lipopolysaccharide.[36–39] Multiple molecular mechanisms have been proposed to explain the second hit in thrombosis induction but the precise mechanism is unknown. Among them, a threshold of lipopolysaccharide has been suggested to favor the interaction between antiphospholipid antibodies and endothelial cells.[40] By contrast, experimental and epidemiologic evidence has partially shed light on the multiple mechanisms by which aPLs induce a