Kidney International, Vol. 62 (2002), pp. 733–744

PERSPECTIVES IN RENAL MEDICINE

"Black swan in the kidney": Renal involvement in the antiphospholipid antibody syndrome

Chike M. Nzerue, Karlene Hewan-Lowe, Silvia Pierangeli, and E. Nigel Harris

Department of Medicine, Renal Section Morehouse School of Medicine, Pathology Department, Emory University School of Medicine, Atlanta, Georgia; The Antiphospholipid Antibody Standardization Laboratory at Morehouse School of Medicine

"Black swan in the kidney": Renal involvement in the antiphospholipid antibody syndrome. The antiphosphospholipid antibody syndrome (APS) describes a clinical entity with recurrent thrombosis, fetal loss, thrombocytopenia in the presence of lupus anticoagulant and/or antibodies to cardiolipin. These antibodies may be associated with connective tissue diseases such as systemic lupus erythematosus (secondary APS) or be found in isolation (primary APS). Renal syndromes increasingly being reported in association with these antibodies include thrombotic microangiopathy, renal vein thrombosis, renal infarction, renal artery stenosis and/or malignant hypertension, increased allograft vascular thrombosis, and reduced survival of renal allografts. Although much has been understood concerning the biology of these antibodies and the pathogenesis of thrombosis, the optimal therapy remains to be elucidated. This article presents a historical review of the renal involvement in the antiphospholipid syndrome and discusses therapeutic options. Further research is needed.

It has been more than 15 years since Harris, Hughes and others described the clinical features of the antiphospholipid antibody syndrome (APS) [1–3]. Since then, the syndrome originally scorned as a "black swan" or a laboratory error has evolved as a distinct clinical entity [4] that is associated with protean clinical manifestations such as arterial and venous thrombosis, recurrent abortions, and thrombocytopenia. Renal manifestations of this syndrome have recently received more attention as the kidney appears to be a major target organ in both primary and secondary APS. Although more prevalent in patients with systemic lupus erythematosus (SLE), antiphospolipid antibodies (APAs) occur in patients without other manifestations of autoimmune disease, the so-called "primary" APS. The preliminary classification and criteria for diagnosis of APS were published in 1999 [5] and were recently validated [6]. In this review, we provide an overview of the mechanism of thrombosis in APS, the spectrum of renal abnormalities encountered with this syndrome, and the available treatment options.

Key words: Antibodies; antiphospholipid; thrombosis; renal failure; hypertension; lupus anticoagulant; anticardiolipin; graft non-function; SLE.

Received for publication October 9, 2001
and in revised form February 7, 2002
Accepted for publication March 15, 2002

BIOLOGY OF ANTIPHOSPHOSPHOLIPID ANTIBODIES

Antiphospholipid antibodies are a heterogeneous group of immunoglobulins directed against negatively charged phospholipids (such as phosphatidyl serine, or cardiolipin), protein-phospholipid complexes, or plasma proteins such as beta 2-glycoprotein I (β2-GPI). Phospholipids play a critical role in the normal control of the coagulation as depicted in Figure 1. For example, activated protein C inactivates factors Va and factor VIIIa in the presence of phospholipids and factor S, thus inhibiting the generation of thrombin [7]. APA include lupus anticoagulant and anticardiolipin antibodies. The lupus anticoagulant is detected in coagulation assays as it slows the rate of thrombin generation by perturbing interactions that require phospholipid, thus acting as an anticoagulant. The clue to the presence of a lupus anticoagulant is often an increased partial thromboplastin time (PTT) that fails to correct on mixing studies with normal plasma. The anticardiolipin antibodies, in contrast, are recognized by the ability to bind anionic phospholipids in solid-phase immunoassays. Thus, anticardiolipin and lupus anticoagulant are distinct but complementary tests for APAs. The genesis of APAs may involve both autoimmune and alloimmune reactions. Alloimmune APAs may be observed following an infection such as hepatitis C, Lyme disease [8–10], human immunodeficiency virus infection (HIV), or in association with lymphoproliferative disease, and appear to have a weaker association with thrombotic complications [8, 9]. Autoimmune APAs bind phospholipid epitopes in the presence of a cofactor and have more consistently been associated with hypercoagulability. Vascular thrombosis represents the clinical hallmark of APS and both arteries and veins may be

affected. Thrombosis may affect deep leg veins, as well as those of the skin, lungs, kidney, central nervous system, and placenta. Thrombocytopenia is quite common. While the association between these APAs and thrombosis is now well established, the unresolved central issue in both primary and secondary APS is how antibodies against phospholipids lead to increased tendency to thrombosis. In the case of lupus anticoagulant, this effect appears paradoxical since an anticoagulant would be expected to cause bleeding, not thrombosis. Phospholipid-dependent coagulation reactions include the following reactions: (*1*) tissue factor-factor VII (VIIa) mediated activation of factors X and IX; (*2*) factor IXa and factor VIIIa activation of factor X to factor Xa; and (*3*) factor Xa and factor Va activation of prothrombin to thrombin (see Fig. 1). The lupus anticoagulant appears to act by limiting the amount of phospholipid available to support these reactions, and thus prolonging the coagulation times. A major advance in the understanding the thrombophilic effect of these antibodies occurred when two groups led by McNeil et al [11] and Galli et al [12] independently observed that the major antigen (cofactor) for APA is a plasma protein, apolipoprotein H, or β2-GP1. This protein, a glycosylated single-chain plasma protein composed of 326 amino acids with a molecular weight of 50 kD, is a weak anticoagulant that binds to anionic phospholipids and inhibits the contact phase of coagulation and the activity of platelet prothrombinase. The exact nature of these epitope(s) remains uncertain. Data from this laboratory however, show that though β2-GPI increases antibody binding to phospholipid, it is not an absolute prerequisite for binding [13]. Other data suggest that monoclonal antibodies with lupus anticoagulant activity can increase the binding of β2-GPI to phospholipid [14]. This process then interferes with essential phospholipid-dependent steps in coagulation, especially the assembly of the tenase and prothrombinase complexes on anionic phospholipids. Consistent with these observations, thrombosis has been induced experimentally by immunoglobulins (Ig) IgG, IgM, and IgA from patients with APS [15]. Proteins besides β2-GPI have also been implicated in antiphospholipid antibody activity. Patients with positive serology for antibodies to β2-GPI often have positive anticardiolipin assays, while serum samples positive for lupus anticoagulant but negative for anticardiolipin appear not to exhibit binding to β2-GPI [16, 17]. Substantial heterogeneity exists among APAs as they react with other hemostatic plasma proteins, with platelets and vascular endothelial cells. Alterations of tissue factor activity [18], as well as the inhibition of activated protein C and protein S by plasma containing APAs, represent potentially thrombophilic changes that have been shown by other investigators. While binding of APAs to platelets appear to be dependent on β2-GPI, other autoantibodies react with the major platelet membrane glycoproteins [19, 20]. The anti-platelet effects of APAs have been suggested to be analogous to that observed in heparin-induced thrombocytopenia [20], as β2-GPI binds to exposed anionic phospholipids on the surface of activated platelets. Platelets circulate in an increased state of activation in APS, but it is unclear if this is a cause or effect of thrombosis. APAs also show substantial reactivity against endothelial cells. [21] In vitro data suggest that this reactivity of APAs against endothelial cells involves both β2-GPI-dependent and independent mechanisms. Since virtually any of the biologic processes that involve or require phospholipids may be affected by the presence of antibodies that bind to the phospholipids (either directly or via cofactors), any proposed APA-mediated effect based on in vitro studies must be evaluated for in vivo relevance. Some of these effects are discussed below and summarized in Table 1.

PATHOGENESIS OF THROMBOSIS IN APS

The precise mechanism by which the presence of APAs induces thrombosis is not completely understood. Experimental and human data suggest that thrombosis induced by APAs may involve changes at the following sites: (*1*) dysregulation of coagulation; (*2*) platelet activation; or (*3*) endothelial injury, disordered transmembrane signaling, and microvasculopathy. These putative pathophysiologic changes are summarized in Table 1. Thus, these antibodies induce a hypercoagulable state, which meets Virchow's triad for thrombosis (that is, abnormal rheology, tissue injury and abnormal blood constituent(s) for thrombogenesis) [22]. Data from our institution have shown that the thrombogenic effects of these antibodies are not confined to human APA, but have also been shown for antibodies induced in mice [23]. There is substantial evidence that endothelial cell injury/activation plays a role in both in vitro an in vivo models of APS [23–25]. Nakamura et al showed that lupus anticoagulant can induce apoptosis in human umbilical endothelial cells [21]. In their study, annexin V was necessary for induction of apoptosis. Recent data suggest that endothelial cell activation in APS may involve enhanced expression of adhesion molecules such as intercellular cell adhesion molecule-1 [1CAM-1], vascular cell adhesion molecule [VCAM-1], and E selectin [26, 27]. The fact that arteries, veins, and capillaries are potential thrombotic sites in patients with APA reflects the complexity of the underlying pathophysiologic mechanisms. However, thrombotic episodes are generally either venous or arterial in a given patient, but not both. While venous thrombotic events with APAs likely result from perturbations of the protein C/protein S regulatory system [17, 24, 28], platelet activation appears to play a central role in arterial thrombosis in APS. Other poten-

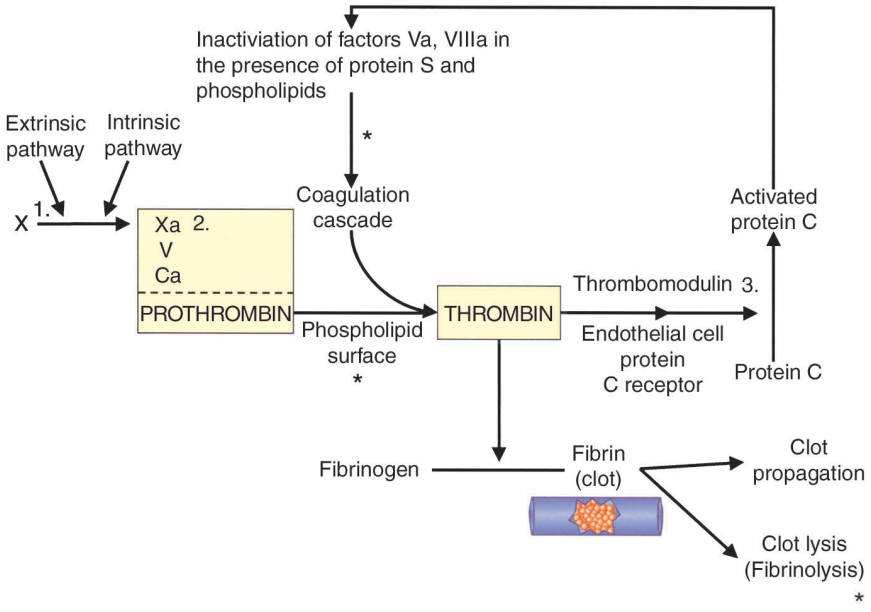
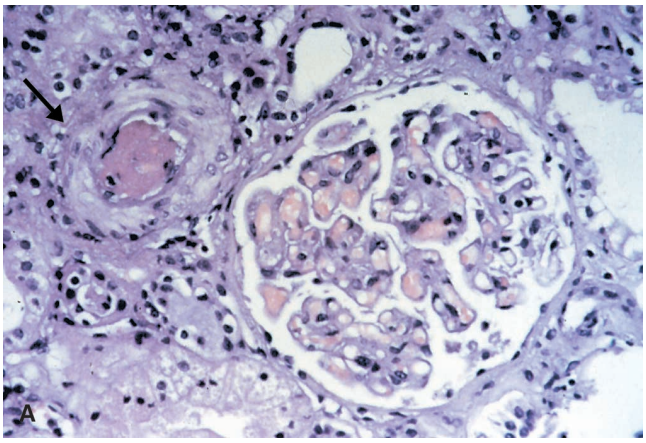
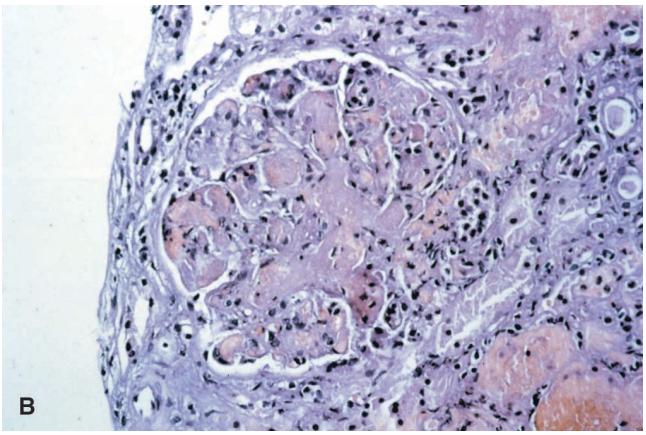


Fig. 1. Control of coagulation showing the role of phospholipids and sites of potential antiphospholipid antibody (APA) action. Three critical steps of the cascade are catalyzed by phospholipids: (1) the tenase complex; (2) the prothrombinase complex; and (3) the protein C activation complexes. Activation of the extrinsic or intrinsic pathway leads to conversion of factor X to Xa. Factor Xa forms a complex with factor Va and prothrombin on a phospholipid template (prothrombinase complex) and this results in thrombin generation from prothrombin. Activated protein C inactivates factor Va and factor VIIIa in the presence of protein S and phospholipids. APAs may affect all the pathways indicated with an asterisk, resulting in a procoagulant effect or in a "lupus anticoagulant effect" (by inhibition of conversion of prothrombin into thrombin).





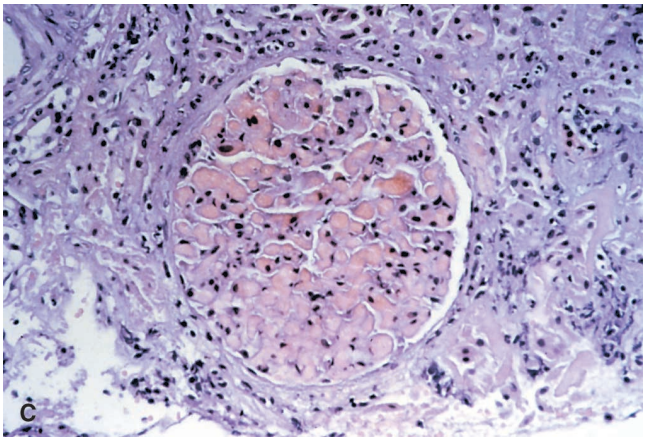


Fig. 2. Kidney biopsy findings in 35-year-old woman with antiphospholipid antibody syndrome (APS) nephropathy and systemic lupus erythematosus (SLE) who developed rapidly progressive renal failure. The biopsy findings of glomerular and arteriolar thrombosis, clearly suggest that APS nephropathy caused the renal failure, rather than lupus nephritis. (*A*) Arteriole with recent thrombus (arrows) (hematoxylin and eosin stain; magnification ×400). Reprinted from reference [46] with permission. (*B*) Glomerular capillaries in same patient are filled with fibrin thrombi (hematoxylin and eosin stain; magnification ×200). (*C*) Glomerular capillaries occluded by agglutinated red blood cells.

Table 1. Pathophysiologic changes contributing to thrombosis in APS

Abnormality	Comments	References
Persistent activation of coagulation	Increased markers of thrombin generation have been observed; increased levels of plasminogen activator inhibitor-1 (PAI-1)	[8, 13]
Interference with the anticoagulant effect of β2-GPI	Poor association of levels of β2-GPI with thrombosis; affinity of APA from patients for β2-GPI may be low	[8–10]
Inhibition of fibrinolysis, activated protein C resistance	Increased clot thickness observed in animal model of APS	[15]
Increased plasma concentration of tissue factor	APAs enhance endothelial release of tissue factor	[16]
Endothelial cell injury	Lupus anticoagulants induce apoptosis in human umbilical vein endothelial cells	[21]
Cellular activation involving platelets, monocytes, endothelial cells	APAs up-regulate expression of adhesion factors ICAM, VCAM	[23–25]
Inflammation, accelerated atherosclerosis	APAs increase production of arachidonic and metabolites	[26]

Abbreviations are: APS, antiphospholipid antibody syndrome; β2-GPI, beta 2-glycoprotein I; ICAM, intercellular adhesion molecule; VCAM, vascular cellular adhesion molecule.

Table 2. Renal syndromes associated with APAs

Abnormality	Comments	References
SLE	Glomerular thrombosis (TMA)	[31, 32, 34]
	? worsens outcome	[40]
	Renal infarct and vein thrombosis	[47]
Acute renal failure	May be reversible or irreversible	
	Renal vein thrombosis	[55, 56]
Renal artery thrombosis/infarction		[64]
Pregnancy-related renal failure		[36]
Glomerulonephritis	With IgA deposits	[53]
TMA	TTP/HUS	[37, 42, 43]
Renovascular/malignant hypertension	Renal artery stenosis may be unilateral or bilateral	[68–74]
Proteinuria	Variable from mild to nephrotic	[60]
Chronic renal disease	Vascular access thrombosis	[89–92]
	High prevalence in hemodialysis	
Renal transplantation	Graft thrombosis and allograft failure	[93–96, 97, 100, 101]
	APAs may be acquired post-transplant	
	Increased morbidity	

Abbreviations are: SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; APA, antiphospholipid antibodies; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic pupura.

tially thrombogenic effects involve inflammation and atherosclerosis [29]. Taken together, these experimental data suggest that thrombosis in association with APAs involves interference with endogenous anticoagulant systems (such as protein C, annexin V, or vascular anticoagulant alpha), cellular activation (involving platelets, endothelial cells, and leukocytes), persistent activation of coagulation system due to tissue factor activation and inhibition of the antithrombin III pathway, as well as inhibition of fibrinolysis (see Table 1).

RENAL SYNDROMES IN APS

The kidney manifestations of APS may result from thrombosis occurring at any location within the renal vasculature, that is, in the renal artery trunk or branches, intra-parenchymal arteries and arterioles, glomerular capillaries, and the renal veins. The resulting clinical syndromes consists of variable degrees of proteinuria; exacerbation of SLE nephropathy; acute renal failure; systemic hypertension, ranging from mild to accelerated hypertension; renal cortical necrosis; thrombotic microangiopathy; progressive chronic renal failure; as well as thrombosis in patients with renal allografts (Table 2).

ANTIPHOSPHOLIPID ANTIBODIES IN SLE-ASSOCIATED NEPHRITIS

Conley and Hartman initially described the presence of lupus anticoagulant in SLE patients in 1952 [30]. Subsequently, Bowie et al described thrombosis occurring in patients with circulating anticoagulants in a seminal paper in 1963. [31] These observations of the association of APA with glomerular and arterial thrombosis in SLE were extended over the next two decades by Kant et al, who reported a strong association between the presence of lupus anticoagulant and the presence of glomerular thrombi in renal biopsy specimens systematically performed in SLE patients seropositive for lupus anticoagulant [32]. While the precise origin of APAs in SLE is unclear, their presence appears to consistently correlate with the occurrence of renal thrombotic microangiopa-

thy (TMA). It is possible that these antibodies are generated by autoimmune responses akin to that which generates anti-nuclear antibodies (ANA). In a meta-analysis of 21 studies by Love and Santoro, an average prevalence of 44% for anticardiolipin antibodies and 34% for lupus anticoagulant, respectively, was documented in patients with SLE [33]. The proportion of SLE patients with both lupus anticoagulant and anticardiolipin antibodies varies from as high as 61 to 91% [32, 33–35] to about 15 to 30% in other series, although not all of them have APS. This wide variation in incidence reflects differences in assay methods and case-mix of patients. The morbidity associated with APAs in SLE has been a subject of considerable controversy [36–39]. While some data show that TMA occurring in SLE patients with APAs was associated with worse prognosis, Naiker et al recently confirmed a high prevalence of APAs in South African patients with lupus nephritis (45%), but found that the presence of these antibodies per se appeared not to change outcome [38], except for an increased incidence of thrombocytopenia and renal vascular thrombosis. These thrombotic events involved large arteries and veins as well as the glomerular and intrarenal arteries and arterioles. However, the study is limited by the fact that these observations were based on a study of only 18 patients. Previously, Kincaid-Smith et al had reported the occurrence of pregnancy-related acute renal failure in 12 women (only two of whom had lupus nephritis) caused by TMA in relation to lupus anticoagulant [36]. It is unclear at present if APA are initiators or accelerators of arterial lesions in TMA, but both roles may be involved. It should be emphasized that the frequent absence of immunoglobulin deposits in vessels involved in TMA suggests that thrombosis may be due to mechanisms other than immune-complex disease. In most series [38–40], more glomerular thrombi are found in those SLE patients with APAs than those without APAs, suggesting an increased morbidity, mostly related to TMA, although these APAs do not affect the World Health Organization's (WHO) histologic classification. In the same area, it is unclear at this time if these antibodies affect the response to chemotherapy in lupus nephritis; although microvasular lesions of SLE, in general, are considered to be independent risk factors for the progression to end-stage renal disease (ESRD) [41]. An area of on-going controversy relates to the association between the APS-associated lesions (such as glomerular thrombi) and those of lupus nephritis. Miranda et al found no association between the presence of these glomerular thrombi and severity/activity of lupus nephritis [40]. However, only nine of their patients were positive for APAs. These findings support earlier observations by Farrugia et al, who equally found no association between APAs and the type of lupus nephritis lesion [42]. In contrast, Bandari et al suggest from their study of 51 patients, that the presence of anticardiolipin antibody and/or glomerular thrombi portends a worse renal outcome, as patients with APA-positivity had significantly more crescents, more sclerosis, and more glomerular necrosis [43]. This finding does not, however, prove a causal relationship between inflammatory lupus renal lessions and APA positivity. Moreover, Perez-Vaquez et al have suggested that the prevalence of APS in SLE increases with duration of follow-up and on the number of samples tested for APAs [44]. This finding further confounds the interpretation of the relationship between APAs and lesions of lupus nephritis. It is interesting that loss of renal function in SLE patients with APAs can also occur without evidence of lupus nephritis due to APS [45]. In this situation, distinguishing between renal failure in SLE due to nephritis (immune-complex disease) from that die to APS (glomerular thrombosis) can only be accomplished by kidney biopsy [46] (see Figure 2). This distinction is critical as the treatment for each syndrome is different. Aggressive lupus nephritis requires cytotoxic therapy, whereas APS nephropathy benefits from anticoagulation. The nephropathy of APS occurring in the course of SLE is the most common form of secondary APS. In one study of a cohort of 100 patients with SLE, APS nephropathy was observed in 63% of patients with APS (abstract; Daugas E et al, *J Am Soc Nephrol* 10:A99, 1999). In a recent systematic review of renal biopsies in another 114 patients with SLE, the same investigators studied the lesions of secondary APS nephropathy co-existing with those of lupus nephritis. They found secondary APS nephropathy in 36% of this cohort of SLE patients, even though only 22% of their patients had APS [47]. This higher proportion of APS nephropathy raises the possibility that renal-limited microvascular disease may occur in the course of SLE in some patients. The strengths of this study include a fairly large sample size (114 patients), as well as a strict definition criterion for APA. This study also found greater correlation between lupus anticoagulant positivity and intrarenal thrombosis than was found in patients seropositive for anticardiolipin antibodies. In addition to the TMA lesions seen acutely in APS nephropathy associated with SLE, other lesions such as fibrous intimal hyperplasia, and focal cortical atrophy have also been observed in the affected kidneys [47]. An aggressive vasculopathic state with widespread thrombosis called catastrophic antiphospholipid syndrome (CAPS) may also occur in SLE [46, 48]. This syndrome is described in greater detail in the discussion of primary APS below. Hughson et al reported on the outcome of treatment in three SLE patients with renal TMA and APS [37]. Renal failure and thrombocytopenia resolved in each case following therapy with plasmapheresis, prednisone, and anticoagulation [37]. The association between the presence of APAs in SLE and renal transplant outcomes, as well as other renal complications

such as renal vein thrombosis and renal infarction, is discussed below. In some cases, chronic lesions of APS nephropathy (such as fibrous intimal hyperplasia and focal cortical atrophy) may co-exist with lesions of lupus glomerulopathy [47]. The balance of the evidence at this time favors the possibility that the occurrence of APS nephropathy in patients with lupus nephropathy may increase the risk of progression to ESRD, even though the WHO classification is unaffected. In the largest series published to date [47], these patients had higher creatinine at time of diagnosis, increased interstitial fibrosis, and a higher prevalence of hypertension, as discussed later. No study, to our knowledge, has addressed the relative prevalence of both TMA and large-vessel occlusive disease in SLE patients with or without APS.

RENAL DISEASE IN PRIMARY APS

In contrast to the well-described nephropathy associated with SLE and APS, it was not widely appreciated that the primary APS could lead to nephropathy until recently. The studies of the renal lesions in primary APS have enabled investigators to observe the lesions due to APS in pure form [47, 49–54], without the confounding effect of co-existing inflammatory changes. Several patients in these reports presented with acute renal failure (ARF). The precise pathogenesis of ARF in the primary APS has not been clearly delineated, but is likely to be multifactorial. It may result from TMA, renal cortical necrosis, renal infarction, renal vein thrombosis [55, 56], or in the unique aggressive vasculopathy, CAPS [57–63]. This is associated with multi-organ failure and widespread thrombotic diathesis. The renal lesions of the primary APS nephropathy are identical to those seen in other TMAs, including postpartum renal failure and sclerodermal renal crisis, with severe narrowing of the interlobular arteries and afferent arterioles. Predictably, renal ischemia follows these diffuse thromboses. In a few cases, mesangial IgA deposition has been described [53, 54]. Occasionally, thromboses occur in the large renal arteries leading to renal infarcts [64]. The urine sediment typically contains few cells or casts, and the level of proteinuria varies from mild to nephrotic. The histologic lesions associated with primary APS-related nephropathy have been well characterized and include arteriosclerosis (75%); fibrous intimal hyperplasia (75%); tubular thyroidization (75%); arteriolar occlusions (68%); TMA (31%), and organizing thrombosis (37%) [49]. Some novel glomerular ultrastructural changes have recently been proposed to be pathognomonic for APS nephropathy [62]. On light microscopy, the silver stains show a combination of glomerular basement membrane wrinkling and reduplication. By electron microscopy, redundant wrinkled segments of basement membrane are accompanied by a "new," straighter thin basement membrane adjacent to the endothelium. However, this suggestion was based on a biopsy series of eight patients and must await confirmation in larger biopsy series. In CAPS, renal pathologic findings included TMA [51, 52, 60], although crescentic glomerulonephritis was observed in one case [63]. Renal involvement in the form of ARF and/or hematuria has been observed in 14% of a large series of patients with CAPS [59]. TMA may be the initial clinical manifestation of both primary APS and secondary APS. Thus, APS should be considered in the differential diagnosis of hemolytic uremic syndrome (HUS), including pospartum cases [65, 66]. It has been suggested by some that APAs may be generated in response to thrombosis, rather than being the cause of thrombosis, but the evidence appears to favor a causal role for APAs in the genesis of TMA in this syndrome.

APA IN SYSTEMIC HYPERTENSION

Hypertension is a common feature of the primary and secondary APS [47, 49]. In the series of primary APS reported by Nochy et al, hypertension was present in 93% of their patients and was sometimes the only clinical sign suggestive of nephropathy [49]. In the secondary APS series reported by Kleinknecht et al, all patients with SLE and APS had severe hypertension with renal insufficiency [67]. Thus, hypertension appears to be a marker of nephropathy in both primary and secondary APS. No study to our knowledge has addressed the prevalence of APAs in an unselected population of patients with essential hypertension. Hypertension in APS may often be severe, with some patients presenting with hypertensive emergencies. Rarely, hypertension associated with APS may be associated with microangiopathic hemolytic anemia. It needs to be emphasized that both microvasculopathy and/or occlusion of the main trunk of the renal artery can contribute to malignant hypertension in the APS. Caccoub et al described five patients with APS complicated by hypertensive crises who all had normal magnetic resonance angiograms of the renal vessels [68]. Three of their patients underwent contrast angiography, which showed distal microangiopathy, but no stenosis nor thrombosis of the main renal arteries. High-dose steroids (prednisone, 1.5 mg/kg/day) and anticoagulation led to rapid resolution of hypertensive crises in three of their patients. Five other reports have documented occlusion of main renal arteries leading to renovascular hypertension [68–74]. Most of the patients reported with main renal artery stenosis had had very high titers of APAs, but in one case the titers were moderate [64]. The outcome of renovascular hypertension with APS appears to be good with treatments like anticoagulation, with or without percutaneous balloon angioplasty, leading to recovery of renal function and return to normal blood pressure [68–74]. The contribution of undiag-

nosed APS in cases of ESRD assumed to be due to essential hypertension is unknown. That the renin-angiotensin system appears to be activated in malignant hypertension due to APS is supported by data showing a positive catopril test in those with large vessel renal artery stenosis, as well as positive staining for renin containing cells in some biopsied subjects [49].

APA IN END-STAGE RENAL DISEASE

Data are few and conflicting concerning the prevalence and risk factors for APAs in ESRD. These differences probably depend on the patient mix and assays used for diagnosis. Patients with ESRD have higher frequency of positivity for APAs compared to the general population [75–78].

Moreover, the prevalence of lupus anticoagulant was higher among patients treated by hemodialysis (30%), compared to those treated by conservative (non-dialytic) approach. Subsequently, Sitter, Spannal, and Schiffl reported that the prevalence of APAs were higher in hemodialysis patients compared to those on continous ambulatory peritoneal dialysis (CAPD) [77]. This higher prevalence in hemodialysis has been confirmed by others [78]. Quereda et al in a prospective study of 138 patients with nephropathy, found that the prevalence of APAs was higher in patients with SLE (34%) than in those with chronic primary glomerulonephritis (9%) and lowest in patients with non-immunologically mediated renal diseases (2.6%) [79]. The origin of APAs in ESRD patients is unclear. It has been postulated that uremia is a form of immunodeficiency in which autoimmunity may develop as a result of altered immune function [80]. Some have suggested that dialysis membranes generate APAs due to incompatibility. In the study by Garcia Morton et al [78], patients dialyzed with cuprophane membranes had a greater incidence of APAs than those dialyzed against more biocompatible membranes. However, in a larger study by Brunet et al, there was no relationship between the APAs and the type of dialyzer used [80]. Other suggested reasons for generation of APAs in ESRD patients include trauma to blood passing through the hemodialysis circuit, as observed in recipients of left ventricular assist devices [81] and induction by microbial agents [82] or their products, such as endotoxins present in dialysate. If this were true, one would expect a correlation between prevalence/titers of APAs and length of time on dialysis. Such a relationship has not been shown at this time. Moreover, not all patients exposed to same dialysate develop APAs. Although the precise mechanisms involved in the genesis of APAs in ESRD are unknown, they appear to mostly β2-GPI-independent [83]· Substantial controversy surrounds the precise risks associated with the presence of APAs in ESRD patients. While some studies suggest that these antibodies are not pathogenic [84–87], other studies have suggested that APAs are associated with hemodialysis vascular access thrombosis [88–91]. Whether both anticardiolipin antibodies and lupus anticoagulants are equipotent in causing recurrent access thrombosis is unclear at this time. Some studies suggest that both lupus anticoagulants and anticardiolipin antibodies are associated with an increased risk of vascular access thrombosis [88, 89], while other studies have verified this relationship only with lupus anticoagulation [86, 90]. Other unresolved issues at this time concerning vascular access thrombosis with APAs include whether rates of occlusion of native arteriovenous fistula thrombosis are identical to those of polytetrafluoroethylene (PTFTE) grafts, or whether APAs cause in-dwelling catheter thrombosis, and if prophylactic anticoagulation would prevent these events. However, on the strength of the epidemiologic and clinical association of these antibodies, it would appear prudent to incorporate APA testing into the diagnostic evaluation of recurrent thrombotic episodes on patients receiving hemodialysis [88–91].

APAs IN RENAL TRANSPLANTATION

In renal transplant patients, the incidence of APAs may also be increased, even in those without SLE [92]. In this study of patients without SLE, a prevalence of 28.1% was documented. Patients with and without APAs did not differ in age, gender, underlying disease, immunosuppressive regimen, serum creatinine concentration, and platelet count. Of these APAs, 65.4% were acquired in the pre-transplant period, while 15.7% acquired APAs during the post-transplant period. Interestingly, 19 pre-transplant APAs disappeared in 52.7% of patients in that series after transplant. The genesis of APAs after renal transplant is unclear. Both pre-transplant and post-transplant APAs were associated with thrombosis affecting the dural, femoral, and transplant veins.

In the case of SLE patients with APAs in renal transplantation, their survival is worse than those of SLE renal transplant patients without APAs [93]. Because of this, Joseph, Radhakrishn, and Appel have suggested that patients with SLE who have APAs require attention in the post-transplant period to detect possible thrombotic events and/or consider prophylactic anticoagulation [94]. Stone, Amend, and Criswell studied the clinical events in 96 consecutive patients with SLE after renal transplantation [95]. They observed positivity for APAs in 29.1%. Among these, 60% had clinical events related to APAs, including deaths related to APS (10%); deep venous thrombosis and pulmonary embolism (24%); strokes (16%); renal artery or renal vein thrombosis (16%); and fetal loss (12%) [95].

Although APAs in hepatitis C-positive ESRD patients appear to be non-pathogenic, preliminary data suggest

this may not be the case in post-renal transplantation, as these patients may be at increased risk for allograft TMA [96]. Anecdotal case reports also suggest that patients with primary APS who undergo renal transplantation may also have increased risk for graft failure [97]. How APAs may be acquired after transplantation is curious, but is as yet unexplained. None of these patients were on drugs such as chlorpromazine, hydralazine, or procainamide that can induce these antibodies. It has been suggested that these APAs may be related to post-transplant infection or autoimmune reactions to infections. Consistent with these observations, high levels of APAs are associated with cytomegalovirus infection in unrelated bone marrow and cord blood allogeneic stem cell transplantation [98].

Other studies have addressed the impact of APAs on renal allograft failure [99–101]. In one study Wagen Knecht et al reported significantly more APAs in patients with early renal allograft failure than in patients with functioning grafts. In that study, 57% final cross-matched sera from patients with early nonfunction were positive for 1gG, 1gM, and 1gA APAs [99]. Thus, it is possible that testing for APA may identify certain patients at risk for allograft failure. Biopsies of these failed allograft kidneys from APA-positive patients showed thrombi in nine patients and infarction in five. However, these patients also received OK T3 induction therapy, which may have induced renal allograft thrombosis [102], even though the same OK T3 indication therapy was used in patients with functional allografts. Thus, the impact of immunosuppression in renal allograft thrombosis must be excluded to better quantify the impact of APAs in early allograft failure. However, a role for coagulation anomalies, such as factor V Leiden mutation, deficiencies of protein C and S, as well as lupus anticoagulant in early renal transplant failure, has been suggested by some investigators [99]. Fischereder et al found that thrombophilia represented a 3.5-fold increase in risk for 1-year renal allograft loss [103]. Although the mechanism for early graft failure in APA-positive patients is unclear, perturbations of hemostasis appear plausible. In an immunocytochemical study of failed renal allografts, significantly more depletion of vascular antithrombin and increased fibrin deposition were observed by Tory et al in transplants that failed in the first month than those that failed 2 to 12 months or later after renal transplantation [104]. No differences in cellular infiltrates were observed, thus excluding cellular rejection. This pattern of allograft loss with fibrin deposition in the absence of cellular infiltrates has also been observed in failed cardiac allografts where depletion of vascular tissue plasminogen activator and endothelial cell activation have been implicated [105, 106]. Wagen Knecht et al provide further proof of the role of APA in early renal allograft loss in their report of a case in which they isolated APA from a thrombosed renal allograft [107]. This patient lost two renal allografts in the first month after renal transplantation. The risk of early renal allograft loss in patients with ESRD with APAs who received renal transplants without hemodialysis was 100% in the study of Wagen Knecht et al, suggesting a possible protective role for renal allograft thrombosis by a period of hemodialysis. The reason for the possibly protective effect of a hemodialysis history is unclear, but it is likely that prolonged exposure to heparin with hemodialysis may be responsible. Consistent with these observations, in vitro studies show that heparin can inhibit or neutralize APA binding [108]. Other possible mechanisms of renal allograft dysfunction in APA-positive patients include allograft glomerulonephritis, renal vein thrombosis, and post-transplant ARF [109].

Unresolved questions include whether patients with APAs with normal renal function should serve as kidney donors, in light of possible future renal complications. Recently, a case was reported of a patient who developed ARF requiring hemodialysis due to renal artery occlusion 6 years after donating a kidney to his mother [110]. ARF in this patient was irreversible, and the patient became dialysis-dependent.

Table 3. Testing for antiphospholipid antibodies

Tests for lupus anticoagulants
Criteria
Prolongation of phospholipid-dependent coagulation test
Evidence of an inhibitor shown by mixing studies
Confirmation of the phospholipid-dependent nature of the inhibitor
Screening
APTT
Dilute Russel viper venom time (DRVVT)
Kaolin cephalin clotting time (KCT)
TTI
Tests for anticardiolipin antibodies
Solid-phase ELISA immunoassay for IgM, 1gG, 1gA
β-2-glycoprotein I (β2-GPI)
ELISA for detection of other negatively charged phospholipids

ELISA is enzyme-linked immunosorbent assay.

MANAGEMENT OF THROMBOSIS IN APS

Diagnostic difficulties

It is clear that APS shows substantial heterogeneity in clinical features, as well as the range of autoantibodies. Accurate diagnosis is critical because of the high risk of recurrent thrombosis. This heterogeneity mandates a comprehensive approach to laboratory testing [111–114], as shown in Table 3. Thus, it is recommended that when APS is suspected, a panel of tests, including lupus anticoagulant, and anticardiolipin antibody, assays be performed.

Lupus anticoagulant assays

The common denominator of all lupus anticoagulant tests is that they detect the inhibition of phospholipid-

dependent coagulation reactions, thus prolonging coagulation times [9]. The term "lupus anticoagulant" is a misnomer, since this phenomenon is not seen exclusively in SLE patients. A number of methods have been used to detect the presence of lupus anticoagulant, including modifications of the activated partial thromboplastin times (aPTT), the kaolin cephalin clotting time (KCT), the dilute Russell viper venom time (dRVVT), and the thromboplastin inhibition test (TTI). The dRVVT is considered to be one of the most sensitive tests for lupus anticoagulant.

Tests for anticardiolipin antibodies

Most patients with APS are identified with elevated anticardiolipin antibodies. The precursor for this assay, the biologic false positive test for syphilis developed at the Venereal Disease Research Laboratory, is itself an anticardiolipin test in which cardiolipin is the antigen. High levels of anticardiolipin antibodies are predictive of an increased risk of thrombosis [8]. It should be emphasized that positive anticardiolipin antibodies assays may be found in the asymptomatic "normal" population with a prevalence that varies from 3 to 10% [8]. It should also be appreciated that in some cases of APA positivity in patients with renal disease, such as in acute poststreptococcal glomerulonephritis, the presence of APAs may be a marginal immunological phenomenon triggered by streptococcal infection, unrelated to the glomerular disease [115]. Other anticardiolipin tests include antibodies against β2-GP1, the major protein cofactor for APAs, and antibodies against phosphatidyl ethanolamine. Enzyme-linked immunosorbent assays (ELISAs) for β2-GP1 antibodies are considered to be more specific, but less sensitive for APS than anticardiolipin assays [111]. Clinical correlation is therefore necessary to decide the significance of a positive APA test. This comprehensive diagnostic approach (Table 3) often includes using a combination of coagulation-based tests for lupus anticoagulant and solid-phase ELISAs for anticardiolipin antibodies. Such an approach would help resolve the "equivocal" cases of APS [116, 117].

Treatment

Initiation of anticoagulation is indicated in thrombosis associated with APS [118–120]. This should be considered the mainstay of therapy in this syndrome. The goal is to maintain an international normalized ratio (INR) of 3.0 or higher. Anticoagulation therapy is sometimes supplemented with aspirin, although aspirin alone is less effective. The duration of anticoagulation is unknown, but lifelong anticoagulation is favored, as the risk recurrence is very high. Premature cessation of anticoagulation may also precipitate CAPS [61]. Preliminary data from Ruiz-Irastorza et al in a cohort of patients meeting the strict criteria for APS [5] shows that a target INR of 3.5 offers good protection against recurrences without a major increase in hemorrhages. (abstract; Ruiz-Irastorza G et al, *Arthritis Rheum* 43:S313, 2000). The factors that trigger recurrent thrombosis are poorly understood [120]. While steroids may decrease APA titers, they do not reduce the risk of thrombosis. Recently, it has been shown that steroids may also potentiate the anticoagulant effect of warfarin [121]. Scattered case reports suggest that plasmapheresis is beneficial in APS patients presenting with TMA [122, 123]. It should also definitely be considered in the patients presenting with CAPS, as it removes the pathogenic APAs, inducing the widespread thrombotic diathesis. The role of thrombolytics is unclear at this time, although thrombolytic therapy improved outcome in one patient with acute large-vessel occlusive disease [124]. The role of hydroxycholoroquine and/or chloroquine in preventing thrombosis in APS is controversial. Some data suggest that these drugs have antithrombotic actions. Platelet aggregation induced by adenosine diphosphate (ADP), collagen, and ristocetin can be inhibited by chloroquine in a dose-dependent manner [125–127]. Consistent with these observations, hydroxychloroquine significantly diminished both thrombus size and total time of thrombus formation in mice with APS [128]. However, the effect of chloroquine in APS in humans is unclear. Experience with intravenous immunoglobulins in treating APS is limited and uncontrolled. Some data suggest that it is effective for the prevention of recurrent pregnancy loss when therapies such as heparin and low-dose aspirin have failed [128-131]. Its role in treating renal disease in APS is unknown at this time, although intravenous immunoglobulin in combination with steroids and heparin improves survival in CAPS. Recently, we showed that immunoglobulin decreases in vivo thrombosis and endothelial cell activation in animal models of APS [131, 132]. Newer therapeutic modalities that deserve further investigation include prostacyclin, fibronolytic agents such as tissue plasminogen activator (TPA) and defibrotid. Some investigators have shown that tolerance can be induced to experimental APS by syngeneic stem cell transplantation [132].

Correspondence to: Chike M. Nzerue, M.D., Associate Professor, Renal Section, Department of Medicine, University of Rochester School of Medicine, 601 Elmwood Avenue, Box 675, Rochester, NY 14642, USA. E-mail: Chike_Nzerue@URMC.Rochester.edu

ACKNOWLEDGMENTS

We thank Sylvia Wadley for secretarial assistance. Dr Pierangeli is supported by an NIH grant # NIGMS GM082248. We thank Donald Wesson, M.D., for critical manuscript review and Pat Abramson of the division of Information Graphics at Morehouse for his help with Figure 1.

REFERENCES

1. Hughes GR: Thrombosis, abortion, cerebral disease and lupus anticoagulant. *BMJ* 287:1088–1089, 1983

2. Hughes GR, Harris EN, Gharavi AE: The anticardiolipin syndrome. *J Rheumatol* 13:486–489, 1986
3. Harris EN, Phil M, Chan JK, *et al*: Thrombosis, recurrent fetal loss and thrombocytopenia: Predictive value of anticardiolipin antibody test. *Arch Intern Med* 146:2153–2156, 1986
4. Harris EN: Syndrome of the black swan. *Br J Rheumatol* 265:324–326, 1987
5. Wilson WA, Gharavi AE, Koike T, *et al*: International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum* 42:1309–1311, 1999
6. Lockshin MD, Sammaritano LR, Schwartzman S: Validation of the Sapporo criteria for antiphospholipid syndrome. *Arthritis Rheum* 43:440–443, 2000
7. Seligsohn U, Lubetsky A: Genetic susceptibility to venous thrombosis. *N Engl J Med* 344:1222–1231, 2001
8. Rand JH: Lupus anticoagulant and related disorders, in *Hematology*, edited by Beutler E, Lichtman MA, Coller BS, *et al,* Williams Hematology, 6th ed., New York, McGraw-Hill, 2001, pp 1715–1733
9. Macworth-Young CG, Harris EN, Steere AC, *et al*: Anticardiolipin antibodies in lyme disease. *Arthritis Rheum* 31: 1052–1057, 1988
10. Al-Saeed A, Makris M, Malia RG, *et al*: The development of antiphospholipid antibodies in hemophilia is liked to infection with hepatitis C. *Br J Hematol* 58:18–23, 1994
11. McNeil HP, Simpson J, Chesterman CN, Krilis SA: Antiphospholipid antibodies are directed against a complex antigen that includes lipid binding inhibitor of coagulation: Beta 2-glycoprotein I (apolipoprotein H). *Proc Natl Acad Sci USA* 87:4120–4124, 1990
12. Galli M, Comfurius P, Massen C, *et al*: Anticardiolipin antibodies directed not to cardiolipin but to a plasma protein cofactor. *Lancet* 355:1544–1547, 1990
13. Pierangeli SS, Harris EN, Davis SA, DeLorenzo G: Beta 2 glycoprotein I (beta 2-GPI) enhances cardiolipin binding activity but is not the antigen for antiphospholipid antibodies. *Br J Immunol* 82:565–570, 1992
14. Greaves M: Antiphospholipid antibodies and thrombosis. *Lancet* 353:1348–1353, 1999
15. Pierangeli SS, Harris EN: Experimental thrombosis and antiphospholipid antibodies. *New Insights J Autoimmun* 15:241–247, 2000
16. Takeya H, Mor T, Gabbeza EC: Anti-beta 2-glycoprotein I (beta 2-GPI) monoclonal antibodies with lupus anticoagulant activity enhance the beta 2-GPI binding to phospholipids. *J Clin Invest* 99:2260–2268, 1977
17. Oosting JD, Derksen RH: Bobbin K IW, *et al*: Antiphospholipid antibodies directed against a combination of phospholipids with Protein C or Protein S: An explanation for their pathogenic mechanism. *Blood* 81:2618–2625, 1993
18. Amengual O, Atsumi T, Khamashta MA, Hughes GR: The role of tissue factor pathway in the hypercoagutable state in patients with antiphospholipid antibody syndrome. *Thromb Haemost* 79:276–281, 1998
19. Ford I, Urbamak S, Greaves M: 1gG from patients with antiphospholipid syndrome binds to platelets without induction of platelet activation. *Br J Haematol* 102:841–849, 1998
20. Arnout J: The pathogenesis of the antiphospholipid antibody syndrome: A hypothesis based on parallelisms with heparin-induced thrombocytopenia. *Thromb Haemost* 75:36–41, 1996
21. Branch DW, Rogers GM: Induction of endothelial cell tissue factor activity by sera from patients with antiphospholipid syndrome. A possible mechanism of thrombosis. *Am J Obstet Gynecol* 168:206–210, 1993
22. Rogers GM: Thrombosis and antithrombotic therapy, in *Winthrobes Clinical Hematology*, edited by Lee RG, Foerster J, Lukens J, *et al,* Baltimore, Williams and Wilkins, 1999, pp 1782–1784
23. Pierangeli SS, Colden-Stanfield M, Line X, *et al*: Antiphospholipid antibodies from antiphospholipid syndrome patients activate endothelial cells in vitro and invivo. *Circulation* 99:1997–2000, 1999
24. Nakamura N, Shidara Y, Karwagudu N, *et al*: Lupus anticoagulant autoantibody induced apoptosis in umbilical vein endothelial cells: Involvement of annexin V. *Biochem Biophys Res Commun* 205:1488–1493, 1994
25. Simantov E, LaSala J, Lo SK, *et al*: Activation of cultured vascular endothelial cells by antiphospholipid antibodies. *J Clin Invest* 13:179–185, 1995
26. Pierangeli SS, Espinola RG, Liu XW, Harris EN. Thombogenic effects of antiphospholipid antibodies are mediated by intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and P-selectin. *Circ Res* 88:245–250,2001
27. Wang CR, Liu MF, Tsai RT, *et al*: Circulating intercellular adhesion molecules-1 and autoantibodies in including antiendothelial cells anticardiolipin and antineutrophil cytoplasmic antibodies in patients with vasculitis. *Clin Rheumatol* 12:375–380, 1993
28. Carion R, Tobelem G, Soria C, Caen J: Inhibition of protein C activation by endothelial cells in the presence of lupus anticoagulant. *N Engl J Med* 314:1193–1194, 1986
29. Vaarcola O: Antiphospholipid antibodies and myocardial infarction. *Lupus* 7(Suppl 2):S132–134, 1998
30. Conley CL, Hartman RC: A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. *J Clin Invest* 31:621–622, 1952
31. Bowie EJ, Thompson JH, Pascuzzi CA, *et al*: Thrombosis in systemic lupus erythematosus: Despite a circulating anticoagulant. *J Lab Clin Med* 62:416–430, 1963
32. Kant KS, Pollack VE, Weis MA, *et al*: Glomerular thrombosis in systemic lupus erythematosus: Prevalence and significance. *Medicine (Baltimore)* 60:71–86, 1981
33. Love PE, Santoro SA: Antiphospholipid antibodies, anticardiolipin and the lupus (SLE) and non SLE disorders. *Ann Intern Med* 112:682–689, 1990
34. Triplett DA, Brandt JT, Musgrave KA, Orr CA: The relationship between lupus anticoagulants and antibodies to phospholipids. *JAMA* 259:550–554, 1988
35. Alving BM, Barr CF, Tang DB: Correlation between lupus anticoagulants and anticardiolipin antibodies in patients with prolonged activator partial thromboplastin hives. *Am J Med* 85:112–116, 1990
36. Kincaid-Smith P, Fairley KF, Kloss M: Lupus anticoagulant associated with renal thrombotic microangiopathy and pregnancy-related renal failure. *Q J Med* 69:795–815, 1988
37. Hughson MD, Nadasdy T, McCarty GA, *et al*: Renal thrombotic microangiopathy in patients with systemic lupus erythematosus and the antiphospholipid syndrome. *Am J Kid Dis* 20:150–158, 1992
38. Naiker IP, Rughubar NK, Dursma J, *et al*: Anticardiolipin antibodies in South African patients with lupus nephritis. *Am J Nephrol* 20:351–357, 2000
39. Frampton G, Hicks J, Cameron JS. Significance of antiphospholipid antibodies in patients with lupus nephritis. *Kidney Int* 39:1225–1231, 1991
41. Banfi G, Bertain T, Boeri V, *et al*: Renal vascular lesions as a marker for poor prognosis in patients with lupus nephritis. *Am J Kid Dis* 18:240–248, 1991
40. Miranda JM, Garcia-Torres R, Jara LJ, *et al*: Renal biopsy in SLE: Significance of glomerular thrombosis. Analysis of 108 cases. *Lupus* 3:25-29,1994
42. Farrugia E, Torres VE, Gastineau D, *et al*: Lupus anticoagulant in systemic lupus erythematosus: A clinical and renal pathological study. *Am J Kid Dis* 20:463–471, 1992
43. Bandari S, Harnden P, Brownjohn AM, *et al*: Association of anticardiolipin antibodies with intraglomerular thrombi and renal dysfunction in lupus nephritis. *Q J Med* 91:401–409, 1998
44. Perez-Vaquez ME, Villa A, Drenkard C, *et al*: Influence of disease duration, continued follow-up and further antiphospholipid antibody testing on the frequency and classification category of antiphopholipid syndrome in a cohort of patients with SLE. *J Rheumatol* 20:437–442, 1993
45. Leaker B, MacGregor A, Griffiths M, *et al*: Insidious loss of renal function in patients with anticardiolipin antibodies and absence of overt nephritis. *Br J Rheumatol* 30:422–425, 1991
46. Coggins HC, McCluskey RT: Rapidly progressive renal failure in a 35-year-old woman with SLE. Case Records of Massachusetts

General Hospital. Case 11–2001. *N Engl J Med* 344:1152–1158, 2001
47. Daugas E, Nochy D, Huong DT, *et al*: Antiphospholipid nephropathy in systemic lupus erythematosus. *J Am Soc Nephrol* 13:42–52, 2002
48. Stratta P, Canavese C, Ferrero S, *et al*: Catastrophic antiphospholipid syndromes in systemic lupus erythematosus. *Ren Fail* 21:49–61, 1999
49. Nochy D, Daugas E, Droz D, *et al*: The intra renal vascular lesions associated with primary antiphospholipid syndrome. *J Am Soc Nephrol* 10:507–518, 1999
50. Lacueva J, Enriquez R, Cabezuelo JB, *et al*: Acute renal failure as the first clinical manifestation of the primary antiphospholipid antibody syndrome. *Nephron* 64:479–480, 1993
51. Sokunbi D, Miller F, Wadhwa NK, Nord EP: Reversible renal failure in the primary antiphospholipid syndrome. A report of two cases. *J Am Soc Nephrol* 3:28–35, 1993
52. D'Agati V, Kinus C, Williams G, *et al*: Anticardiolipin antibody and renal disease. A report of three cases. *J Am Soc Nephrol* 1:777–784, 1990
53. Simniah R, Gan H, Yoon K: Primary antiphospholipid antibody syndrome and mesangial 1gA glomerulonephritis. *Am J Nephrol* 21:134–140, 2001
54. Silva MF, Pimentel FL, Faria MS, *et al*: IgA nephropathy and antiphospholipid syndrome. *Nephron* 83:95–96, 1999
55. Perez RE, McClendon JR, Lie JT: Primary antiphospholipid antibody syndrome with multiorgan arterial and venous thrombosis. *J Rheumatol* 19:1289–1292, 1992
56. Asherson RA, Buchanan N, Baguley E, *et al*: Postpartum bilateral renal vein thrombosis in the primary antiphospholipid syndrome. *J Rheumatol* 20:874–876, 1993
57. Triplett DA, Asherson RA: Pathophysiology of the catastrophic antiphospholipid syndrome (CAPS). *Am J Hematol* 65:154–159, 2000
58. Harris EN, Bos K: An acute disseminated coagulopathy-vasculopathy associated with the antiphospholipid antibody syndrome. *Arch Intern Med* 151:231–233, 1991
59. Peddi VR, Kant KS: Catastrophic secondary antiphospholipid syndrome with concomitant antithrombin III deficiency. *J Am Soc Nephrol* 5:1882–1887, 1995
60. Nochy D, Daugas E, Huong DL, *et al*: Kidney involvement in the antiphospholipid syndrome. *J Autoimmun* 15:127–132, 2000
61. Asherson RA, Cervera R, Piette JC, *et al*: Catastrophic antiphospholipid syndrome. Clues to pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 80:355–377, 2001
62. Griffiths MH, Papadaki L, Neild GH: The renal pathology of primary antiphospholipid syndrome: A distinctive form of endothelial injury. *Q J Med* 93:457–467, 2000
63. Cisternas M, Guttierrez MA, Rosenberg H, *et al*: Catastrophic antiphospholipid syndrome associated with crescentic glomerulonephritis: A clinicopathologic case. *Clin Exp Rheumatol* 18:252–254, 2000
64. Poux JM, Boudet R, Lacroix P, *et al*: Renal infarction and thrombosis of the infrarenal aorta in a 35-year-old in with primary antiphospholipid syndrome. *Am J Kid Dis* 27:721–725, 1996
65. Gherman RB, Tramont J, Connito DJ: Post partum hemolytic-uremic syndrome associated with lupus anticoagulant. *J Reprod Med* 44:471–474, 1999
66. Knauz D, Eisenberg GM, Elrad H, *et al*: Postpartum hemolytic uremic syndrome associated with antiphospholipid antibodies. A case report and literature review. *Am J Nephrol* 12:126–133, 1992
67. Kleinknecht D, Bobrie G, Meyer O, *et al*: Recurrent thrombosis and renal vascular disease in patients with a lupus anticoagulant. *Nephrol Dial Transpl* 4:854–858, 1989
68. Caccoub P, Wechsler b, Piette JC , *et al*: Malignant hypertension in anti phospholipid syndrome without overt lupus nephritis. *Clin Exp Rheum* 11:479–485, 1993
69. Riccialdelli L, Arnaldi G, Giacchetti G, *et al*: Hypertension due to renal artery occlusion in a patient with the antiphospholipid syndrome. *Am J Hypertens* 14:62–65, 2001
70. Sirvent AE, Euriquez R, Antholin A, *et al*: Malignant hypertension in antiphospholipid syndrome. *Nephron* 73:368–369, 1996
71. Serino R, Osajima A, Hiroshige K, *et al*: Renovascular hypertension associated with antiphospholipid antibodies in a woman with systemic lupus erythematosus. *Jap J Nephrol* 38:417–422, 1996
72. Ames PR, Cianciaruso B, Bellizi V, *et al*: Bilateral renal artery occlusion in a patient with primary antiphospholipid syndrome: Thrombosis, vasculitis or both. *J Rheumatol* 19:1802–1806, 1992
73. Asherson RA, Noble GE, Hughes GR: Hypertension, renal artery stenosis and primary antiphospholipid syndrome. *J Rheumatol* 18:1413–1415, 1991
74. Rossi E, Sani C, Zini M, *et al*: Anticardiolipin antibodies and renovascular hypertension. *Ann Rheum Dis* 51:1180–1181, 1992
75. Gronhagen-Riska C, Teppo AM, Helantera A, *et al*: Raised concentrations of antibodies to cardiolipin in patients receiving dialysis. *Br Med J* 300:1696–1697, 1990
76. Quereda C, Pardo A, Lamas S, *et al*: Lupus-like in vitro anticoagulant activity in end-stage renal disease. *Nephron* 49:39–44, 1988
77. Sitter T, Spannal M, Schiffl H: Anticardiolipin antibodies and lupus anticoagulant in patients treated with different methods of renal replacement therapy compared to patients with systemic lupus erythematosus. An epiphenomenon? *Nephron* 64:655–656, 1993
78. Garcia Morton F, De Arriba G, Carrascosa T, *et al*: Anticardiolipin antibodies and lupus anticoagulant in end-stage renal disease. *Nephrol Dial Transpl* 6:543–547, 1991
79. Quereda C, Otero GG, Pordo A, *et al*: Prevalence of antiphospholipid antibodies in nephropathies not due to systemic lupus erythematosus. *Am J Kid Dis* 23:555–561, 1994
80. Brunet P, Ailland M, San Morgo M, *et al*: Antiphospholipids in hemodialysis patients. Relationship between lupus anticoagulant and thrombosis. *Kid Int* 48:794–800, 1995
81. Fastenau DR, Wagenknecht DR, McIntyre JA: Increased incidence of antiphospholipid antibodies in left ventricular assist system recipients. *Ann Thorac Surg* 68:137–142, 1999
82. Gharavi AE, Pierangeli S: Origin of antiphospholipid antibodies: Induction by viral peptides. *Lupus* 7(Suppl 2):S52–S54, 1998
83. Matsuda J, Saitoh N, Gohchi K, *et al*: Beta 2-Glycoprotein I-dependent and independent anticardiolipin antibody in patients with end-stage renal disease. *Thromb Res* 72:109–117, 1993
84. Sitter T, Spannagl M, Schiffl H: Anticardiolipin antibodies and lupus anticoagulant in patients treated with different methods of renal replacement therapy in comparison to patients with systemic lupus erythematosus. *Annal Hematol* 65:79–82, 1992
85. Philips AO, Jones HW, Hambley H, *et al*: Prevalence of lupus anticoagulant and anticardiolipin antibodies in dialysis patients. *Nephron* 65:350–353, 1993
86. Chew SL, Lins RL, Daelemans R, *et al*: Are antiphospholipid antibodies clinically relevant in dialysis patients? *Nephrol Dial Transp* 14:1194–1198, 1992
87. Fabrizi F, Sangiorgio R, Pontoriero G, *et al*: Antiphospholipid (APL) antibodies in end-stage renal disease. *J Nephrol* 12:89–94, 1999
88. Prieto LN, Suki WN: Frequent hemodialysis graft thrombosis: Association with antiphospholipid antibodies. *Am J Kid Dis* 23:587–590, 1994
89. Prakash R, Miller CC, Suki W: Anticardiolipin antibody in patients on maintenance hemodialysis and its association with recurrent arteriovenous graft thrombosis. *Am J Kid Dis* 26:347–352, 1995
90. Haviv YS: Association of anticardiolipin antibodies with vascular access occlusion in hemodialysis patients: Cause or effect? *Nephron* 86:447–454, 2000
91. Lesar CJ, Merrick HW, Smith MR: Thrombotic complications resulting from hypercoagutable states in chronic hemodialysis vascular access. *J Am Coll Sur* 189:73–79, 1999
92. Ducloux D, Pellet, Fournier V, *et al*: Prevalence and clinical significance of antiphospholipid antibodies in renal transplant recipients. *Transplantation* 67:90–93, 1999
93. Radhakrishnan J, Williams GS, Appel GB, Cohen DJ: Renal transplantation in anticardiolipin antibody-positive lupus erythematosus patients. *Am J Kid Dis* 23:286–289, 1994
94. Joseph RE, Radhakrishnan J, Appel GB: Antiphospholipid antibody and renal disease. *Curr Opin Nephrol Hypertens* 10:175–181, 2001
95. Stone JH, Amend WJ, Criswell LA: Antiphospholipid antibody

syndrome in renal transplantation: Occurrence of clinical events in 96 consecutive patients with system lupus erythematosus. *Am J Kid Dis* 34:1040–1047, 1999
96. Baid S, Pascual M, Williams WW, *et al*: Renal thrombotic microangiopathy associated with anticardiolipin antibodies in hepatitis C-positive allograft recipients. *J Am Soc Nephrol* 10:146–153, 1999
97. Amigo ML, Mondragon G, Bochicchio T, *et al*: Adverse outcome after renal transplantation in two patients with the primary antiphospholipid syndrome. *Arthritis Rheum* 36:S117–119, 1993
98. Mengarelli A, Minotti C, Palumbo G, *et al*: High levels of antiphospholipid antibodies are associated with cytomegalovirus infection in unrelated bone marrow and cord blood allogeneic stem cell transplantation. *Br J Haematol* 108:126–131, 2000
99. Wagen Knecht DR, Fastenau DR, Torry RJ, *et al*: Risk of early allograft failure is increased for patients with antiphospholipid antibodies. *Transpl Int* 13(Suppl 1):S78–S81, 2000
100. Wagen Knecht D, Becker DG, Lefor WM, McIntyre JA: Antiphosphospholipid and antibodies are a risk factor for early renal allograft failure. *Transplantation* 68:241–246, 1999
101. Vaidya S, Wang CC, Gugliuzza C, Fish JC: Relative risk of post-transplant renal thrombosis in patients with antiphospholipid antibodies. *Clin Transpl* 12:439–444, 1998
102. Abramowicz D, Pradier O, Marchant A, *et al*: Induction of thrombosis within renal grafts by high dose prophylactic OK T3. *Lancet* 339:777–780, 1992
103. Fischereder M, Gohring P, Schneeberger H, *et al*: Early loss of renal transplants in patients with thrombophilia. *Transplantation* 65:936–939, 1998
104. Torry RJ, Labarrere CA, Gargiulo P, Faulk WP: Natural anticoagulant and fibrinolytic pathways in renal allograft failure. *Transplantation* 58:926–931, 1994
105. Faulk WP, Labarrere CA, Pitts D, Halbrook H: Vascular lesions in biopsy specimens devoid of cellular infiltrates: qualitative and quantitative immunocytochemical studies of cardiac allografts. *J Heart Lung Transplant* 12:219–229, 1993
106. Labarrere CA, Nelson DR, Faulk WP: Endothelial activation and development of coronary artery disease in heart-transplant recipients. *JAMA* 278:1169–1175, 1997
107. Wagen Knecht DR, Fastenau DR, Torry RJ, *et al*: Antiphospholipid antibodies are implicated in early renal allograft failure: isolation of APA from a thrombosed renal allograft. *Transplant Proc* 31:285–288, 1999
108. Wagen Knecht DR, McIntyre JA: Interaction of heparin with beta2-glycoprotein I and antiphospholipid antibodies in vitro. *Thromb Res* 68:495–500, 1992
109. Liano F, Mampaso F, Garcia-Morton F: Allograft membranous glomerulonephritis and renal vein thrombosis in a patient with a lupus anticoagulant factor. *Nephrol Dial Transpl* 3:684–689, 1988
110. Chitalia VC, Kolhe N, Kothari J, Almeida AF: Acute renal failure in a renal transplant donor due to primary antiphospholipid syndrome. *Am J Nephrol* 21:55–57, 2001
111. Harris EN, Pierangeli S, Gharavi AE: Diagnosis of antiphospholipid antibody syndrome: a proposal for use of laboratory tests. *Lupus* 7(Suppl 2):S144–S148, 1998
112. Greaves M, Cohen H, Machin SJ, Machin I: Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Haematol* 109:704–715, 2000
113. Pierangeli S, Gharavi, Harris EN. Testing for antiphospholipid antibodies: problems and solutions. *Clin Obstet Gynecol* 44:48–57, 2001
114. Merkel PA, Chang Y, Pierangeli S, *et al*: Comparison between the standard anticardiolipin antibody test and a new phospholipid test in patients with connective tissues. *J Rheumatol* 26:591–596, 1999
115. Ardiles L, Ramirez P, Moya P, *et al*: Anticardiolipin antibodies in acute post-streptococcal glomerulonephritis and streptococcal impetigo. *Nephron* 83:47–52, 1999
116. Harris EN, Pierangeli SS: Equivocal antiphospholipid syndrome. *J Autoimmun* 15:81–85, 2000
117. Amengual O, Atsumi T, Khamashta MA, *et al*: Specificity of ELISA for antibody to beta2-glycoprotein I in patients with antiphospholipid syndrome. *Br J Rheumatol* 35:1239–1243, 1996
118. Khamashta MA, Cuadrado MJ, Mujic F, *et al*: The management of thrombosis in the antiphospholipid antibody syndrome. *N Engl J Med* 332:993–997, 1995
119. Petri M: Pathogenesis and treatment of the antiphospholipid antibody syndrome. *Med Clin North Am* 81:151–177, 1997
120. Krnic-Barrie S, O'Connor CR, Looney S, *et al*: A retrospective review of 61 patients with antiphospholipid syndrome: Analysis of factors influencing recurrent thrombosis. *Arch Intern Med* 157:2101–2108, 1997
121. Costedoat-Chalumeau N, Amoura Z, Aymard G, *et al*: Potentiation of vitamin K antagonists by high dose intravenous methyl prednisolone. *Ann Intern Med* 132:631–635, 2000
122. Faria MS, Mota C, Barbot J, *et al*: Haemolytic uraemic syndrome, cardiomyopathy, cutaneous vasculopathy and anti-phospholipid activity. *Nephrol Dial Transpl* 15:1891–1892, 2000
123. Kon SP, Kwan JT, Raftery MJ: Reversible renal failure due to antiphospholipid antibody syndrome, pre-eclampsia and renal thrombotic microangiopathy. *Clin Nephrol* 44:271–273, 1995
124. Dupont P, Jackson J, Warrens A, Lightstone L: Life-threatening thrombosis 18 years after first presentation of primary antiphospholipid antibody syndrome. *Nephrol Dial Transpl* 16:843–845, 2001
125. Janicinova V, Nosal R, Petrikova M: On the inhibitory effect of chloroquine on blood platelet aggregation. *Thromb Res* 74:495–504, 1994
126. Nasal R, Janicinova V, Petrikova M: Chloroquine inhibits stimulated platelets at the arachidonic acid pathway. *Thromb Res* 77:531–542, 1995
127. Edwards MH, Pierangeli S, Xiao W, *et al*: Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. *Circulation* 96:4380–4384, 1997
128. Piette JC, Le Thi Huong D, Wechsler B: Therapeutic use of intravenous immunoglobulins in the antiphospholipid syndrome. *Ann Med Intern* 151(Suppl 1):1551–1554, 2000
129. Takeshita Y, Turumi Y, Touma S, Takagi N: Successful delivery in a pregnant woman with lupus anticoagulant positive systemic lupus erythematosus treated with double plasmapheresis. *Ther Apher* 5:22–24, 2001
130. Harris EN, Pierangeli S: Utilization of intravenous immunoglobulin therapy to treat recurrent pregnancy loss in the antiphospholipid syndrome: A review. *Scan J Rheumatol* 107:S97–S102, 1998
131. Pierangeli SS, Espinola RG, Liu X, *et al*: Identification of an Fc receptor independent mechanism by which intravenous immunoglobulin ameliorates antiphospholipid antibody-induced thrombogenic phenotype. *Arthritis Rheum* 44:876–882, 2001
132. Blank M, Tomer Y, Slavin S, Shoenfeld Y: Induction of tolerance to experimental anti- phospholipid syndrome (APS) by syngeneic bone marrow cell transplantation. *Scan J Immunol* 42:226–234, 1995.