The Antiphospholipid Syndrome

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Summary: The antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the clinical association of antiphospholipid autoantibodies (aPL) with a syndrome of hypercoagulability that can affect any blood vessel, irrespective of type or size. Involvement of larger vessels, such as arteries or veins, manifests in the form of thrombosis or embolism, whereas involvement of smaller vessels, including capillaries, arterioles, and venules, manifests as thrombotic microangiopathy. Virtually any organ in the body, including the kidney, can be affected. Here, we review the basic principles and recent advances in our understanding of APS, and discuss the broad spectrum of renal diseases that have been observed in association with this syndrome. We also discuss the impact that APS may have on pre-existing renal disease as well as current recommendations for treatment of APS.
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Anti-phospholipid antibodies (aPLs) are a heterogeneous group of autoantibodies encompassing a broad range of target specificities and affinities, all recognizing various combinations of phospholipids and/or phospholipid-binding proteins. The term *antiphospholipid syndrome* (APS) was first coined in the mid-1980s to denote the clinical association of aPL with a syndrome of hypercoagulability. Although we now appreciate the prominence and variety of renal manifestations in APS, initial descriptions of the syndrome did not even include the kidney among the many organ systems affected in APS. Despite burgeoning interest in the effects of APS on the kidney, the full range of renal manifestations still may be underestimated, especially the more chronic effects of APS. In this review, we focus on basic principles and recent advances in our understanding of APS. A more detailed discussion of APS in general, and its renal manifestations in particular, as well as a more complete list of references, may be found in several earlier reviews.[1,2]

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TERMINOLOGY AND BASIC PROPERTIES OF aPL

The nomenclature for aPL, which is historically based, can be very confusing. aPL is the general term for autoantibodies recognizing phospholipids and/or phospholipid-binding proteins. Division of aPL into subsets is based on the method of detection (see Table 2 in reference 1). When aPL are detected functionally, by their ability to prolong clotting times in various coagulation assays, they are referred to as *lupus anticoagulants* (LAs). In contrast, when detected immunologically, by their ability to bind to surfaces coated with either phospholipids (most commonly, cardiolipin [CL]) or phospholipid-binding proteins (most commonly, β2-glycoprotein I [β2GPI]), they are referred to as *anticardiolipin antibodies* (aCLs) or *anti-β2GPI antibodies* (anti-β2GPI), respectively.

Although aPLs occur in association with a broad range of diseases and physiologic conditions, including maintenance hemodialysis, the two most important associations are with autoimmune diseases, especially systemic lupus erythematosus (SLE) and infectious diseases such

as syphilis. Despite their name, aPLs found in the setting of autoimmunity, of which LAs are the classic example, most often are directed against a complex of phospholipid and protein, and tend not to recognize phospholipid alone. In contrast, aPLs in the setting of infectious diseases usually recognize phospholipid alone, but not the phospholipid–protein complex. For example, the antibody detected by the Venereal Disease Research Laboratory (VDRL) serologic assay for syphilis binds to CL alone; proteins such as β2GPI, which bind to CL, interfere with the recognition of CL by the VDRL antibody. Another important distinction between aPLs occurring in these two settings is their health-related consequences. In general, aPLs associated with infectious diseases lack a clinically important impact on coagulation. We will therefore focus exclusively on aPLs occurring in association with autoimmunity.

Despite the frequent concordance between LAs and either aCLs or anti-β2GPI, these antibodies are not necessarily identical. Some patients have LAs, without detectable aCLs or anti-β2GPI, most likely because the aPLs of these patients react with phospholipids other than CL or phospholipid-binding proteins other than β2GPI (such as prothrombin, protein C, protein S, annexin V, and several kininogens). Other patients have aCLs and/or anti-β2GPI that possess no discernible effect on coagulation.

Although CL is the phospholipid most frequently used in immunologic assays for aPLs, the reactivity of aPLs in general is unaffected by substitution of CL with another negatively charged (anionic) phospholipid, such as phosphatidylserine. In marked contrast, substitution of CL with a net neutrally charged phospholipid, such as phosphatidylethanolamine, virtually eliminates reactivity. The basis for this preference lies in the phospholipid-binding proteins, which in conjunction with CL comprise the antigenic targets of most aCLs. β2GPI and most other phospholipid-binding proteins recognized by aPLs interact strongly with anionic phospholipids, but only weakly with net neutrally charged phospholipids.

Despite their name, LAs are associated with thromboembolic events rather than clinical bleeding. aPLs can interfere with both anticoagulant and procoagulant pathways (see Table 3 in reference 1). Although the phospholipid surface used in most in vitro coagulation assays favors inhibition of procoagulant pathways, and therefore prolongation of clotting, the microenvironment of cell membranes in vivo may promote greater inhibition of anticoagulant pathways and therefore thrombosis.

As noted earlier, aPLs comprise a broad family of autoantibodies. We presume that the initial target of the autoimmune response that leads to the generation of aPLs is a cell-surface complex between one of several phospholipid-binding proteins circulating in the plasma and an anionic phospholipid on the external cell membrane. The absence of anionic phospholipids on the surface of resting viable cells (with the exception of trophoblasts and possibly endothelial cells) suggests that perturbation of the cell membrane may be required for binding of aPLs to cells. A number of cells or particles that express negatively charged phospholipids on their surface have been proposed as the natural targets for aPLs. These include activated platelets, activated or injured endothelial cells, sickled red blood cells, apoptotic cells, and oxidized low-density lipoprotein (Ox-LDL) particles. In each of the cellular examples, there is an induced loss of normal membrane phospholipid asymmetry with resultant exposure of anionic phospholipids on the outer cell surface.

Once the autoimmune response to the phospholipid/phospholipid-binding protein complex has been initiated, then the immune response presumably can spread to other antigenic specificities including isolated phospholipids or phospholipid-binding proteins. Strong support for the role of epitope spread, and the primacy of the aPL response in human SLE, comes from recent data showing that SLE autoantibodies emerge in a remarkably consistent order and can precede the development of clinical disease by 7 or 8 years, with aPLs being among the very first autoantibodies to appear.[3,4]

DIAGNOSIS

A recent consensus statement has modified the criteria for classification of APS.[5] There are a number of important changes from previous

criteria. A patient with APS must manifest at least 1 of 2 clinical criteria (vascular thrombosis or pregnancy morbidity) and at least 1 of 3 laboratory criteria (LAs, aCLs, and/or anti-β2GPI). Laboratory criteria must be met on two or more occasions, at least 12 weeks apart. Although prolongation of a single phospholipid-dependent coagulation assay is sufficient to establish the presence of LAs, current criteria recommend using at least two coagulation assays before excluding LAs. The two assays should evaluate distinct portions of the coagulation cascade (extrinsic, intrinsic, or final common pathways). A suitable combination would be the activated partial thromboplastin time (APTT) and dilute Russell's viper venom time (dRVVT). As opposed to the earlier classification, clinical and laboratory criteria cannot be separated in time arbitrarily, but should be more than 12 weeks and less than 5 years apart. Although the laboratory criteria have been broadened to include anti-β2GPI antibodies (titer >99th percentile), the threshold for aCL positivity has been tightened considerably (titer >99th percentile or >40 immunoglobulin G phospholipid [GPL] or immunoglobulin M phospholipid [MPL] units). Only immunoglobulin M (IgM) and IgG isotypes of aPLs fulfill the laboratory criteria; IgA aPLs are still thought to lack sufficient specificity.

It is important to emphasize that these criteria are intended primarily to guide classification of patients entered into clinical studies on APS. To minimize the incorrect attribution of APS to unaffected patients (false positives), these criteria are designed to have very high specificity. Given the inexorable trade-off between sensitivity and specificity, the sensitivity of these criteria is somewhat limited. Hence, in the clinical setting, failure to fulfill these classification criteria should not necessarily preclude the diagnosis of APS.

None of the other protean clinical manifestations of APS, such as thrombocytopenia or livedo reticularis, is included in the clinical criteria. Although such features have been associated strongly with aPLs, they occur in a variety of disease states other than APS, and their specificity for APS does not reach that of vascular thrombosis. The consensus statement has proposed standardized definitions for multiple clinical features of APS not included in the classification criteria, such as aPL-associated nephropathy.

CLASSIFICATION OF APS

APS traditionally has been divided into several categories. Primary APS occurs in patients without clinical evidence of another autoimmune disease, whereas secondary APS occurs in association with autoimmune or other diseases. The recent consensus statement recommends documentation of the specific autoimmune disease(s) co-existing with APS.[5]

SLE is by far the most common disease with which APS occurs. Some patients with APS have evidence of an underlying autoimmune disorder but only partially fulfill the criteria for diagnosis of SLE. Such patients are referred to commonly as having *lupus-like disease*. The link between aPLs and other rheumatologic diseases, with the exception of rheumatoid arthritis and possibly also Sjögren's syndrome and systemic sclerosis, is more tenuous and based largely on case reports.[1,6] Many cases of Sneddon's syndrome, defined as the clinical triad of stroke, livedo reticularis, and hypertension, may represent undiagnosed APS. Although aPLs commonly occur in association with other conditions (including drugs, infections, malignancy, hemodialysis), they are usually low-titer IgM antibodies unassociated with thrombotic events. Catastrophic APS is discussed separately later.

EPIDEMIOLOGY

The frequency of aPLs among healthy controls is fairly low, about 1% to 5% for both aCLs and LAs. As for other autoantibodies, the frequency of aPLs increases with age, especially among elderly patients with co-existent chronic diseases. Among patients with SLE, the frequency of aPLs is much higher, ranging from 12% to 30% for aCLs and 15% to 34% for LAs. It should be noted that all of these percentages predate the most recent consensus statement, and that application of its revised stricter laboratory criteria may lead to a decrease of these estimates of prevalence.

Many patients have laboratory evidence of aPLs without clinical consequence. For otherwise healthy controls, there are insufficient data to determine what percentage of those with a positive aPL will eventually have a thrombotic event or pregnancy complication consistent with APS. In contrast, the percentage of patients with SLE and positive aPLs who have or develop APS is as high as 50% to 70% after 20 years of follow-up evaluation. Nonetheless, up to 30% of patients with SLE and positive aCLs lacked any clinical evidence of APS over an average follow-up period of 7 years.

WHICH PATIENTS WITH aPLs WILL DEVELOP THROMBOSIS?

A critical issue, therefore, is identification of those patients with aPLs at increased risk for a thrombotic event. In general, LAs are more specific for APS, whereas aCLs are more sensitive. In a recent meta-analysis of 25 studies involving more than 7,000 patients, the mean risk for thrombosis was increased 11.0-fold by LAs versus 1.6-fold by aCL.[7] The specificities of aCLs and anti-β2GPI for APS increase with titer, and are higher for IgG versus IgM isotype. Still, there is no definitive association of specific clinical manifestations with particular aPL subsets. Therefore, multiple aPL tests should be used because patients may be positive in one test and negative in another.

The most important risk factor for thrombosis, and the only one sufficiently predictive to warrant treatment, is a previous history of thrombosis. Other risk factors, each of which may increase the risk for thrombosis up to 10-fold, include the presence of LAs, an increased titer of IgG aCLs, and persistence of aPLs.

Although not yet integrated into clinical practice, there are additional specific features of aPLs that may help to stratify risk. For example, LAs whose prolongation of clotting times is dependent on the presence of β2GPI show a much stronger association with thrombosis (odds ratio, ~42) than do LAs that are independent of β2GPI (odds ratio, ~1.6).[8] Moreover, among anti-β2GPI, those that recognize domain I of β2GPI were predictive of thrombosis (odds ratio, ~19), whereas antibodies that recognized domains other than domain I showed no association with thrombosis.[9]

PATHOGENESIS OF APS

The cellular and molecular mechanisms by which aPLs promote thrombosis remain largely unclear, but several hypotheses have been proposed. It has been suggested that aPLs interfere with or modulate the function of phospholipid-binding proteins involved in the regulation of coagulation. For example, although β2GPI seems to bind poorly to the cell membranes of viable cells, anti-β2GPI may increase the affinity of β2GPI for cell membranes via dimerization of surface-bound β2GPI molecules.[10] Moreover, binding of β2GPI to anionic phospholipids is thought to result in a conformational change, leading to exposure of domain I epitopes that are recognized by the pathogenic subset of anti-β2GPI.[10] Binding of complexes of β2GPI and anti-β2GPI may activate certain cells, including monocytes and endothelial cells. Although the signaling mechanisms remain unclear, receptors such as Toll-like receptor 4 (TLR4), which is used by endotoxin, may be involved.[11] Activation of endothelial cells results in increased expression of adhesion molecules, secretion of proinflammatory cytokines, and prostacyclin metabolism, potentially creating a more prothrombotic microenvironment.

A second mechanism focuses on the cross-reaction of aPLs with Ox-LDLs, a major contributor to atherosclerosis that is present at sites of oxidative injury to vascular endothelium. Recognition and uptake of aPL/Ox-LDL complexes by phagocytic cells would lead to an inflammatory reaction and increased tendency to coagulation. Finally, thrombosis in APS has been likened to that in heparin-induced thrombocytopenia.

DIFFERENTIAL DIAGNOSIS

APS is one of several prothrombotic states in which thrombosis occurs within both the venous and arterial beds (see Table 4 in reference 1). Although other conditions predisposing to venous and arterial thrombosis may be detected through routine laboratory testing, the sole abnormality in a patient with primary APS may be

the existence of aPLs. Because a normal APTT does not exclude the presence of LAs, a patient presenting with a first thrombotic event should be screened by at least two LA-sensitive assays and for aCLs and anti-β2GPI. Importantly, diagnosis may be unsuspected in patients in whom APS results in a chronic, more indolent process, leading to ischemia and slowly progressive loss of renal or other organ function.

Secondary risk factors that increase the tendency to thrombosis should be surveyed. Such factors can affect the venous or arterial beds, and include stasis, vascular injury, medications such as oral contraceptives, and established risk factors for atherosclerotic disease. Eliminating or reducing the impact of these factors is especially important because the mere presence of aPLs may be insufficient to generate thrombosis. A second hit, most commonly thought to entail some form of endothelial cell activation or injury, in combination with aPLs, may be required for thrombosis to occur. Finally, even in patients with documented APS, disentangling cause and effect can sometimes be difficult. For example, APS is associated with the nephrotic syndrome, which is itself a risk factor for thromboembolism.

GENERAL CLINICAL FEATURES

Although attribution of clinical manifestations to aPLs is clearest in primary APS, there are no major differences in the clinical consequences of aPLs for patients with primary versus secondary APS. Virtually any organ can be involved, and the range of disorders observed within any one organ system spans a diverse spectrum (see Table 5 in reference 1). The effects of aPLs are best appreciated from a pathogenetic point of view, with emphasis placed on two key features: the nature and size of the vessels involved, and the acuteness or chronicity of the thrombotic process.

Venous thrombosis, especially deep venous thrombosis of the lower extremities, is the most common manifestation of APS. As many as 50% of these patients suffer pulmonary emboli. Arterial thromboses are less common than venous thromboses, and most commonly manifest with features consistent with ischemia or infarction. The severity of presentation relates to the acuteness and extent of occlusion. It should be emphasized that thrombotic episodes in association with APS frequently occur in vascular beds atypically affected by other prothrombotic states, such as the subclavian, renal, retinal, and pedal arteries. Moreover, not all arterial episodes of ischemia and/or infarction are thrombotic in origin. Emboli, especially from mitral or aortic valve vegetations, also can lead to vascular occlusion and organ ischemia, especially in the cerebrovascular circulation.

Acute involvement at the level of the capillaries, arterioles, or venules often results in a clinical picture virtually indistinguishable from hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) and other thrombotic microangiopathies. Thrombotic microangiopathy (TMA) also may occur as a more chronic process, resulting in slow progressive loss of organ function, the underlying reason for which may only be determined by biopsy. Thus, organ involvement in association with APS can present anywhere along a spectrum from explosive and rapidly progressive to clinically silent and indolent. Depending on the size of vessels affected, organ failure has two predominant causes, TMA and ischemia secondary to thromboembolic events.

Although the most characteristic clinical features of APS relate to thromboembolic phenomena, other prominent manifestations of APS include thrombocytopenia, hemolytic anemia, and livedo reticularis.

RENAL MANIFESTATIONS

A broad spectrum of renal diseases has been observed in association with APS (Tables 1 and 2).[2] There are no major differences in the renal lesions attributable to aPLs in APS patients with and without SLE.[12,13] As with the systemic findings of APS, the renal manifestations are best understood from a pathophysiologic perspective with emphasis on two features: the acuteness versus chronicity of the thrombotic process, and the size and nature of the involved vessels.

Renal Artery Lesions

Renal artery involvement can be bilateral and generally consists of occlusive lesions resulting

Table 1. Renal Lesions and Syndromes Associated With APS

Renal arterial lesions
Renal artery stenosis
Renal infarction
Renal ischemia
Renovascular hypertension
Ischemic acute renal failure
Chronic kidney disease
Renal vein lesions
Renal vein thrombosis
Thrombotic microangiopathy
Acute renal failure
Chronic kidney disease
Subnephrotic range proteinuria
Nephrotic syndrome
Malignant hypertension
Glomerular lesions
Membranous glomerulonephritis
Focal ischemic changes consistent with chronic TMA
Other (minimal change disease, focal segmental glomerulosclerosis, mesangial C3 deposition)
Adrenal failure

from in situ thrombosis or from embolism from either a pre-existing upstream arterial lesion or a bland cardiac valvular lesion. These lesions can manifest in multiple ways, ranging from renal infarction to ischemic acute renal failure (ARF) to slowly progressive ischemic chronic renal failure (CRF) to renovascular hypertension. The clinical features for these syndromes in aPL-positive patients exactly parallel those in patients lacking aPLs. In the absence of concomitant cardiac disease, hypertension almost always is present. The prevalence of renal artery lesions is difficult to estimate because many lesions are clinically silent and incidentally detected by radiographic procedures or autopsy. Among unselected patients with APS, the prevalence of renal infarction is probably about 1% to 2%. The prevalence of renal artery stenosis is probably greater, up to 7% in unselected patients with APS, and perhaps more than 10% in APS patients selected for evidence of renal involvement of any sort such as hypertension or proteinuria.

Renal Vein Lesions

Renal vein thrombosis occurs more commonly in APS patients with SLE (~10%) than in APS patients without SLE (≤1%). The major reason for this would seem to be the multiple additional causes for heavy proteinuria and nephrotic syndrome in patients with SLE. Similar to renal artery lesions, renal vein thrombosis can be bilateral. Clinical features resemble those from renal vein thrombosis of any cause, and can include loin pain, hematuria, enlarged kidneys, and pulmonary embolism.

TMA

Perhaps the most important renal manifestation of APS is TMA, which can vary widely in presentation from an explosive ARF requiring dialysis to a mild progressive CRF with bland urine. The frequency of TMA may be 50% or more in primary APS patients with renal findings of any sort, including hypertension and minimal levels of proteinuria. Among SLE patients with APS and renal findings, the frequency of TMA is somewhat lower (although still ≥10%), because these patients have additional non-APS–related reasons for renal abnormalities.

The pathologic changes of TMA are nonspecific and can occur as part of several well-defined clinical entities or syndromes. For this reason, depending on the dominant mode of clinical presentation, TMA in association with APS (both primary and secondary) has been variously described in the literature as any of the following: HUS/TTP; malignant hypertension; renal crisis of scleroderma; or pregnancy-related events such as eclampsia, pregnancy-associated renal failure, post-partum renal failure, or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). It is critical to recognize that, irrespective of the name, the pattern of injury seen on renal biopsy for all these entities is remarkably similar. Renal pathologic and/or clinical differences relate far less to the associated syndrome or state (eg, pregnancy versus nonpregnancy) than to the acuteness or chronicity of the underlying thrombotic process. Acute TMA presents suddenly, often with widespread intrarenal thrombosis and rapidly progressive ARF, whereas

Table 2. Histopathologic Manifestations of APS

Pathophysiologic Process	Renal Parenchymal Element		
	Glomeruli	**Vasculature**	**Tubules and Interstitium**
Acute TMA	Light: Intracapillary fibrin thrombi Glomerular congestion Endothelial cell swelling and degeneration Focal mesangiolysis and mesangial hypercellularity IF: Glomerular capillary wall staining for fibrin-related antigens Virtual absence of staining for complement or immunoglobulins EM: Separation of endothelium from glomerular basement membrane by fluffy electrolucent material Absence of electron-dense deposits	Light: Fibrin and/or fibrocellular thrombi (arteries and arterioles) Medial accumulation of fibrinous or cellular material Fibrinoid necrosis Degeneration and loss of endothelial lining	Light: Mild edema Mild cellular infiltrate (plasma cells and lymphocytes) Acute tubular necrosis
Chronic TMA	Light: Global glomerulosclerosis Occasional focal segmental glomerulosclerosis Glomerular hypoperfusion Double-contour or tram-tracking of capillary walls Mesangial sclerosis IF: Trace staining for fibrin-related antigens EM: Glomerular basement membrane widening with mesangial interposition	Light: Thrombotic organization with recannulization Fibrous intimal hyperplasia Intimal accumulation of connective tissue components (collagen and elastin) Arteriosclerosis and arteriolosclerosis	Light: Interstitial fibrosis Tubular atrophy Focal cortical atrophy Tubular thyroidization
Ischemia caused by large-vessel thrombosis	Light: Global glomerulosclerosis (late) Retraction or shrinkage of glomerular tuft Capillary collapse Wrinkling of capillary walls Hyperplasia of juxtaglomerular apparatus Cystic enlargement of Bowman's space	Light: Arteriosclerosis and arteriolosclerosis	Light: Interstitial fibrosis Tubular atrophy Focal cortical atrophy Tubular thyroidization

Abbreviations: IF, immunofluorescence; EM, electron microscopy.

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chronic TMA is a more smoldering process, characterized by extensive healing and scarring, and may be overlooked clinically and morphologically because of the focal, nonspecific, and often subtle nature of the vascular lesions.

The clinical presentation of TMA is extraordinarily varied, mainly dependent on the acuity of the underlying thrombotic process. The following generalizations may be helpful. First, hypertension, frequently severe or malignant, is extremely common (≥80%). Second, proteinuria exceeding 100 mg/d occurs in up to 90% of patients, and may achieve the nephrotic range in as many as 20% of patients. Many of these cases of nephrotic range proteinuria had primary APS, without evidence of SLE or other autoimmunity, so the heavy proteinuria truly can be attributed to APS. Third, renal insufficiency frequently is found at presentation, ranging from anuric ARF requiring dialysis to seemingly stable mild CRF. Although not clearly studied, several case series suggest that APS can lead to a slow loss of renal function, without history or evidence of overt nephritis; renal biopsy in these cases reveals focal ischemic changes consistent with a chronic TMA.

Glomerular Disease

An expanding spectrum of glomerular lesions has been reported in association with APS.[14] Renal biopsy in most cases of nephrotic range proteinuria associated with TMA reveals a variety of nonspecific changes consistent with chronic glomerular ischemia. However, true glomerular pathology does seem to occur in patients with APS. The best documented is membranous glomerulonephritis. Among 29 primary APS patients with a variety of renal abnormalities who underwent biopsy, 3 cases of membranous glomerulonephritis were found.[14] Other glomerular lesions that have been reported include minimal change, focal segmental glomerulosclerosis, and mesangial deposition of C3.

Other

Adrenal failure, especially in association with catastrophic APS, may lead to profound disturbances of fluid and electrolyte levels.

PATHOLOGY

The histopathologic features of APS reflect a combination of several major pathophysiologic processes: TMA; ischemia secondary to upstream arterial thromboses or emboli; and peripheral embolization from venous, arterial, or intracardiac sources (Table 2).[1,2] The histopathology of arterial and venous thromboses in association with APS does not differ from that seen in other prothrombotic states. Similarly, regions of ischemia and infarction downstream of thrombotic or embolic occlusions lack unique features.

TMA is a consequence of microvascular involvement. Its histologic features also are not specific to APS and can be seen in a variety of other diseases and syndromes, including HUS/TTP, malignant hypertension, scleroderma, radiation-induced injury, pregnancy-associated renal failure, and various drug-induced thrombotic microangiopathies (cyclosporine, FK506, and chemotherapeutic agents, such as mitomycin C). Although the acute changes of TMA usually are fairly prominent, the chronic changes can be quite subtle and easily overlooked. Acute changes include capillary congestion and intracapillary fibrin thrombi, generally without inflammation. Immunofluorescence reveals a predominance of fibrin-related antigens. Immune complexes are not seen. On electron microscopy, the endothelium is separated from the glomerular basement membrane by an accumulation of fluffy electron-lucent material.

Chronic changes, ranging from ischemic hypoperfusion to atrophy and fibrosis, reflect healing and scarring of acute lesions. The capillary walls often are thickened, with a double-contour or tram-track appearance. The mesangium may have areas of sclerosis. Fibrin staining is much less intense than that seen in acute TMA. Electron microscopy shows widening of the glomerular basement membrane, with areas of mesangial interposition accounting for the double contours on light microscopy. Effacement of the visceral epithelial cells from the glomerular basement membrane also may be seen, especially in patients with significant proteinuria. Significantly less electron-lucent material is seen, and there are again no electron-dense deposits.

Regions of focal cortical atrophy occur within the superficial cortex, just beneath the renal capsule, and in the appropriate context are highly suggestive of APS. They appear as well-demarcated foci or triangles of scarring and atrophy. Their sharp borders suggest previous infarction. Features associated with focal cortical atrophy include dense interstitial fibrosis, tubular atrophy and thyroidization, global sclerosis of glomeruli with occasional cystic dilatation, and fibrous intimal hyperplasia of arteries and arterioles with positive intimal staining for fibrin.

Vascular involvement extends from the nonmuscular precapillary arterioles to small muscular arteries. During the acute phase, fibrin thrombi containing fragmented blood cells narrow or occlude the vascular lumen. Thrombi eventually organize into fibrocellular and fibrous vascular occlusions, which can be recannulated by endothelialized channels. An onion-skin arrangement of intimal fibrosis is a frequent end result. The lesions of fibrous intimal hyperplasia, suggestive of APS, are usually much more cellular than those of arteriosclerosis and arteriolosclerosis.

True vasculitis is rarely, if ever, seen in primary APS. Vasculitis in secondary APS is attributable to SLE, not APS. Although enormous confusion exists regarding terminology for the vascular lesions associated with SLE, vaso-occlusive disease in association with APS, irrespective of the size of the vessel involved, universally is caused by thrombosis.

IMPACT OF aPLs ON LUPUS NEPHROPATHY

Two important and unresolved questions relate to the impact of aPLs on the natural history of lupus nephropathy. The first question is whether TMA or other APS-like pathology can occur in SLE patients through mechanisms independent of aPLs. A recent, well-performed study strongly suggests that the answer to this first question is no, because it was found that APS-like pathology virtually always occurs in association with a positive aPL.[15] The investigators examined 151 consecutive renal biopsy specimens for SLE. The definitions were precise and specific. aPLs were positive only if detected on two occasions, at least six weeks apart. APS-like nephropathy required the presence of one of the following: TMA, focal cortical atrophy, fibrous intimal hyperplasia, or organized thrombi with or without recannulation. APS-like nephropathy was found in 32 of 81 aPL-positive patients, and only three of 70 aPL-negative patients. Of the three aPL-negative patients, two had single measurements of high-titer aCL.

The second question is the potential impact of aPLs on the course and progression of renal disease in patients with SLE. Data from earlier studies are conflicting. In general, those studies finding a positive association between aPLs and renal disease were based on meticulous analysis of biopsy findings rather than broad definitions of nephropathy. A recent prospective follow-up study of 111 SLE patients compared the course of aPL-positive ($n = 29$) versus aPL-negative ($n = 82$) patients.[16] By Kaplan-Meier analysis, the incidence of renal insufficiency (creatinine level ≥ 1.5 mg/dL) was significantly greater in aPL-positive patients. A significant difference did not emerge until fairly late (>10 y). By multivariable analysis, the presence of aPLs was associated independently with an approximately 2.0-fold increased risk for the development of renal insufficiency.

CATASTROPHIC APS

In most patients with APS, thrombotic events occur singly. Recurrences may occur months or years after the initial event. However, a minority of APS patients present with an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. Preliminary criteria for the classification of this syndrome, termed *catastrophic APS*, recently have been published and validated.[17,18] Definitive diagnosis requires the simultaneous clinical involvement by APS of at least three different organ systems in a period of less than a week with histopathologic confirmation of small-vessel occlusion in at least one organ system. The high mortality rate of catastrophic APS may preclude laboratory confirmation of the presence of aPLs on a second occasion at least six weeks later. For this reason, preliminary criteria

for a probable diagnosis of catastrophic APS also have been provided.[17]

Although the same clinical manifestations seen with primary and secondary APS also occur as part of catastrophic APS, there are important differences in prevalence and in the caliber of the vessels predominantly affected. Large-vessel venous or arterial thrombosis is less common in patients with catastrophic APS, who tend to present with an acute TMA affecting small vessels of multiple organs. The kidney is the organ most commonly affected by catastrophic APS (70%-80%), followed by lungs, central nervous system, heart, and skin, each of which is involved in more than 50% of cases. Hypertension is found in virtually 100% of patients. Another fulminant process that can affect up to 25% of patient with catastrophic APS is disseminated intravascular coagulation, which does not occur in primary or secondary APS. Microvascular manifestations of catastrophic APS include the following: renal TMA; adult respiratory distress syndrome; cerebral microthrombi and microinfarctions; and myocardial microthrombi. Virtually all patients with renal involvement have hypertension, often malignant, and up to 25% require dialysis. The mortality rate is 50%, usually secondary to multi-organ failure.

Precipitating factors of catastrophic APS included infections, surgical procedures (including such minor procedures as biopsies or dental extractions), withdrawal of or inadequate anticoagulation, neoplasm, lupus flares, and drugs such as oral contraceptives.[18] A precipitating event cannot be identified in approximately 30% of patients.[18] Although the pathophysiology of this disorder is understood poorly, thrombosis can be self-perpetuating in patients with an underlying hypercoagulable state. Thus, an initial thrombosis in an APS patient may upset the balance of hemostasis and set in motion a process termed *thrombotic storm*, leading to multiple coagulative events throughout the body.

Recommendations for the treatment of catastrophic APS are based entirely on case reports and series.[17,18] Initial treatment in suspected cases involves anticoagulation with intravenous heparin plus high doses of steroids. If life-threatening, plasma exchange and/or administration of intravenous immunoglobulin should be added. The rationale for plasmapheresis derives from the documented effectiveness of plasmapheresis in treating HUS/TTP. In the absence of clinical improvement, other therapies may be used, such as cyclophosphamide, prostacyclin, fibrinolytic agents such as streptokinase and urokinase, or defibrotide. Because thrombosis tends to be a self-perpetuating process, an early aggressive therapeutic approach is warranted in these patients.

The long-term outlook for patients surviving an episode of catastrophic APS depends on one's perspective. Of 58 patients followed-up for an average of 5.5 years, none had a recurrence of catastrophic APS, and 38 (65%) were alive without further complications of APS.[19] Mortality occurred in nine patients (16%), and an additional 11 patients (19%) had further manifestations of APS.[19]

TREATMENT

Treatment decisions fall into four main areas: prophylaxis, prevention of further large-vessel thromboses, treatment of acute TMA, and management of pregnancy in association with aPL. This section reviews data on treatment in the first two areas. Treatment of acute TMA is covered in the section on catastrophic APS,[17-19] and treatment of obstetric complications was covered in a previous review.[1]

Prophylaxis

A nested case-control study within the Physicians' Health Study examined the role of aspirin (325 mg/d) as a prophylactic agent.[20] Aspirin did not offer protection against deep venous thrombosis and pulmonary embolus in male physicians with aCLs.[20] In contrast, a retrospective analysis of women with APS, identified solely by pregnancy loss, showed that low-dose aspirin (81 mg/d) significantly reduced the rate of nongravid thrombotic events.[21] A cross-sectional study also suggested a prophylactic benefit of low-dose aspirin in aPL-positive patients without SLE.[22] An ongoing study comparing low-dose aspirin versus placebo in asymptomatic aPL-positive patients should resolve the

question of aspirin's effectiveness as a prophylactic agent.[23]

Hydroxychloroquine also may be protective against the development of thrombosis in aPL-positive patients with or without SLE.[22,24] Certainly any factors predisposing to thrombosis should be eliminated (see Table 4 in reference 1). In addition, modification of secondary risk factors for atherosclerosis seems prudent, based on the putative role of vascular injury in promoting aPL-associated thrombosis and the association of aPL with Ox-LDL.

Treatment After a Thrombotic Event

A beneficial role for anticoagulation in decreasing the rate of recurrent thrombosis has been shown in three retrospective studies.[25-27] In a small series of 19 APS patients, recurrence at eight years was 0% for those patients receiving oral anticoagulation.[27] Among patients whose anticoagulation was stopped, recurrence was 50% at 2 years, and 78% at eight years.[27] In two larger series, protection (venous and arterial) correlated directly with the level of anticoagulation.[25,26] Among 70 APS patients, intermediate-intensity (INR [International Normalized Ratio], 2.0-2.9) and high-intensity (INR $\geq$ 3.0) treatment with warfarin significantly reduced the rate of thrombotic recurrence, whereas low-intensity treatment (INR $\leq$ 1.9) conferred no protection.[26] Similar results were found in a series of 147 APS patients.[25] In both studies, aspirin alone was ineffective in reducing the rate of thrombotic recurrence.[25,26]

Several additional points warrant mention. First, two recent prospective randomized controlled trials have established that intermediate-intensity treatment with warfarin (INR, 2.0-3.0) is equally as effective as high-intensity treatment (INR, 3.0-4.0) for APS patients with no history of thrombosis while on anticoagulation.[28,29] Some authorities suggest that these results should be applied only to patients for whom APS was diagnosed on the basis of a venous thrombosis because a majority of patients in both studies (70%-80%) had venous events, and patients with recurrent thromboses were excluded.[30] These authorities recommend that high-intensity warfarin should be used for APS patients with an arterial thrombosis.[30] Second, discontinuation of warfarin seems to be associated with an increased risk of thrombosis, and even death, especially in the first six months after stopping anticoagulation. Because the rate of recurrence among patients who are not anticoagulated optimally can be as high as 70%, treatment with warfarin probably should be long term, if not lifelong. Finally, monitoring the level of anticoagulation in APS patents is complicated by the lack of a standardized thromboplastin for determination of INR and the potential interference of aPLs in this measurement.

Additional Treatments

A theoretic basis exists for suggesting that statins and angiotensin-converting enzyme inhibitors (ACEIs), two agents already commonly prescribed by nephrologists, may be effective in decreasing thrombotic events in patients who have aPLs. Statins were effective in an in vivo animal model of APS,[31] and appear to have beneficial anti-inflammatory and antithrombotic effects on the vascular endothelium.[30,31] Both statins and ACEIs inhibit monocyte expression of tissue factor, a cofactor in the coagulation cascade that is up-regulated by interaction with aPLs.[32] Given the favorable therapeutic profile of these agents, and the prevalence of renal disease among APS patients, the use of ACEIs, and probably statins, seems to be justified. Other potential therapies, poised for clinical trials, include thrombin inhibitors, rituximab (anti-CD20 chimeric monoclonal antibody), recombinant human activated protein C, prostacyclin, and prostaglandin E1.[30,32]

REFERENCES

1. Levine JS, Branch DW, Rauch J. Anti-phospholipid syndrome. N Engl J Med. 2002;346:752-63.
2. Levine JS, Rauch J. Renal involvement in the antiphospholipid syndrome. In: Adu D, Emery P, Madaio MP, editors. Rheumatology and the kidney. New York: Oxford University Press Inc; 2001. p. 132-66.
3. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med. 2003; 349:1526-33.
4. McClain MT, Arbuckle MR, Heinlen LD, et al. The prevalence, onset, and clinical significance of antiphospholipid antibodies prior to diagnosis of sys-

temic lupus erythematosus. Arthritis Rheum. 2004; 50:1226-32.
5. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4:295-306.
6. Cervera R, Piette J-C, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002;46:1019-27.
7. Galli M, Luciani D, Bertolini G, et al. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood. 2003;101:1827-32.
8. de Laat HB, Derksen RH, Urbanus RT, et al. Beta2-glycoprotein I-dependent lupus anticoagulant highly correlates with thrombosis in the antiphospholipid syndrome. Blood. 2004;104:3598-602.
9. de Laat B, Derksen RH, Urbanus RT, et al. IgG antibodies that recognize epitope Gly40-Arg43 in domain I of beta 2-glycoprotein I cause LAC, and their presence correlates strongly with thrombosis. Blood. 2005;105:1540-5.
10. de Laat B, Derksen RH, van Lummel M, et al. Pathogenic anti-beta2-glycoprotein I antibodies recognize domain I of beta2-glycoprotein I only after a conformational change. Blood. 2006;107:1916-24.
11. Raschi E, Testoni C, Bosisio D, et al. Role of the MyD88 transduction signaling pathway in endothelial activation by antiphospholipid antibodies. Blood. 2003;101:3495-500.
12. Nochy D, Daugas E, Droz D, et al. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol. 1999;10:507-18.
13. Daugas E, Nochy D, Huong du LT, et al. Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. J Am Soc Nephrol. 2002;13:47-52.
14. Fakhouri F, Noel L-H, Zuber J, et al. The expanding spectrum of renal diseases associated with antiphospholipid syndrome. Am J Kidney Dis. 2003;41:1205-11.
15. Tektonidou MG, Sotsiou F, Nakopoulou L, et al. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associations, and long-term outcome. Arthritis Rheum. 2004;50:2569-79.
16. Moroni G, Ventura D, Riva P, et al. Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. Am J Kidney Dis. 2004;43:28-36.
17. Asherson RA, Cervera R, de Groot FG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003;12:530-4.
18. Cervera R, Font J, Gómez-Puerta JA, et al. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis. 2005;64:1205-9.
19. Erkan D, Asherson RA, Espinosa G, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis. 2003;62:530-3.
20. Ginsburg KS, Liang MH, Newcomer L, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med. 1992;117: 997-1002.
21. Erkan D, Merrill JT, Yazici Y, et al. High thrombosis rate after fetal loss in antiphospholipid syndrome: effective prophylaxis with aspirin. Arthritis Rheum. 2001;44:1466-7.
22. Erkan D, Yazici Y, Peterson MG, et al. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. Rheumatology. 2002;41:924-9.
23. Erkan D, Sammaritano L, Levy R, et al. APLASA study 2004 update: primary thrombosis prevention in asymptomatic aPL-positive patients with aspirin [abstract]. Arthritis Rheum. 2001;50:S640-1.
24. Petri M. Hydroxychloroquine use in the Baltimore lupus cohort: effects on lipids, glucose and thrombosis. Lupus. 1996;5:S16-22.
25. Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med. 1995;332:993-1007.
26. Rosove MH, Brewer PMC. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med. 1992;117:303-8.
27. Derksen RH, de Groot PG, Kater L, et al. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. Ann Rheum Dis. 1993;52:689-92.
28. Crowther MA, Ginsberg JS, Julian J, et al. Comparison of two intensities of warfarin for the prevention of recurrent of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med. 2003;349:1133-8.
29. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost. 2005;3:848-53.
30. Erkan D, Lockshin MD. New treatments for antiphospholipid syndrome. Rheum Dis Clin North Am. 2006; 32:129-48.
31. Ferrara DE, Liu X, Espinola RG, et al. Inhibition of the thrombogenic and inflammatory properties of antiphospholipid antibodies by fluvastatin in an *in vivo* animal model. Arthritis Rheum. 2003;48:3272-80.
32. Roubey RAS. New approaches to prevention of thrombosis in the antiphospholipid syndrome: hopes, trials, and tribulations. Arthritis Rheum. 2003;48: 3004-8.