Review Article

Medical Progress

THE ANTIPHOSPHOLIPID SYNDROME

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ANTIPHOSPHOLIPID antibodies are a family of autoantibodies that exhibit a broad range of target specificities and affinities, all recognizing various combinations of phospholipids, phospholipid-binding proteins, or both. The term "antiphospholipid syndrome" was first coined to denote the clinical association between antiphospholipid antibodies and a syndrome of hypercoagulability.[1,2] Revision of the criteria for diagnosis of the antiphospholipid syndrome and the terminology used to describe the disease is an ongoing process[3] (Table 1).

BACKGROUND

The first antiphospholipid antibody, a complement-fixing antibody that reacted with extracts from bovine hearts, was detected in patients with syphilis in 1906.[10] The relevant antigen was later identified as cardiolipin, a mitochondrial phospholipid.[11] This observation became the basis for the Venereal Disease Research Laboratory (VDRL) test for syphilis that is currently used. Mass screening of blood for syphilis led to the finding that many patients with systemic lupus erythematosus had a positive VDRL test, without clinical or serologic evidence of syphilis.[12] In 1983, a solid-phase immunoassay for anticardiolipin antibodies was developed.[13] This assay was several hundred times more sensitive than the VDRL test for detecting anticardiolipin antibodies in patients with systemic lupus erythematosus, and the anticardiolipin antibodies detected were strongly associated with lupus anticoagulant antibodies, false positive VDRL tests, and thrombosis.[13]

In the early 1990s, two groups discovered that some anticardiolipin antibodies require the presence of the plasma phospholipid-binding protein β_2-glycoprotein I in order to bind to cardiolipin.[14,15] This requirement is a feature of anticardiolipin antibodies from patients with systemic lupus erythematosus or the antiphospholipid syndrome but not from patients with syphilis or other infectious diseases.[14-16] Antibodies in the latter group of patients react directly with cardiolipin; they are not only independent of β_2-glycoprotein I but are also inhibited by it.[16] The demonstration that autoimmune anticardiolipin antibodies are directed against a phospholipid-binding protein rather than against a phospholipid led to the discovery that some autoantibodies bind directly to β_2-glycoprotein I in the absence of phospholipids.[14,17] This has resulted in a change of focus from phospholipids to phospholipid-binding proteins.[6]

DETECTION OF CLINICALLY RELEVANT ANTIPHOSPHOLIPID ANTIBODIES

The most commonly detected subgroups of antiphospholipid antibodies are lupus anticoagulant antibodies, anticardiolipin antibodies, and anti–β_2-glycoprotein I antibodies. Division into these subgroups is broadly based on the method of detection (Table 2). Lupus anticoagulant antibodies are identified by coagulation assays, in which they prolong clotting times. In contrast, anticardiolipin antibodies and anti–β_2-glycoprotein I antibodies are detected by immunoassays that measure immunologic reactivity to a phospholipid or a phospholipid-binding protein (cardiolipin and β_2-glycoprotein I, respectively). Despite the frequent concordance between lupus anticoagulant antibodies and either anticardiolipin[19] or anti–β_2-glycoprotein I[20] antibodies, these antibodies are not identical. Some lupus anticoagulant antibodies react with phospholipids other than cardiolipin or proteins other than β_2-glycoprotein I,[7,21] whereas some anticardiolipin[19] and anti–β_2-glycoprotein I[20] antibodies have no lupus anticoagulant activity. Most β_2-glycoprotein I–dependent anticardiolipin antibodies recognize β_2-glycoprotein I equally well whether bound to cardiolipin or bound to other anionic phospholipids. This is because β_2-glycoprotein I interacts strongly with anionic phospholipids but weakly with phospholipids with a net neutral charge.[22] In general, lupus anticoagulant antibodies are more specific for the antiphospholipid syndrome, whereas anticardiolipin antibodies are more sensitive.[23] The specificity of anticardiolipin antibodies for antiphospholipid syndrome increases with titer and is higher for the IgG than for the IgM isotope. However, there is no

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TABLE 1. INTERNATIONAL CONSENSUS STATEMENT ON PRELIMINARY CRITERIA FOR THE CLASSIFICATION OF THE ANTIPHOSPHOLIPID SYNDROME.*

Clinical criteria
Vascular thrombosis
One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ
Complications of pregnancy
One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation; or
One or more premature births of morphologically normal neonates at or before the 34th week of gestation; or
Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria†
Anticardiolipin antibodies
Anticardiolipin IgG or IgM antibodies present at moderate or high levels in the blood on two or more occasions at least six weeks apart‡
Lupus anticoagulant antibodies
Lupus anticoagulant antibodies detected in the blood on two or more occasions at least six weeks apart, according to the guidelines of the International Society on Thrombosis and Hemostasis§

*A diagnosis of definite antiphospholipid syndrome requires the presence of at least one of the clinical criteria and at least one of the laboratory criteria. No limits are placed on the interval between the clinical event and the positive laboratory findings.

†The following antiphospholipid antibodies are currently not included in the laboratory criteria: anticardiolipin IgA antibodies, anti–β_2-glycoprotein I antibodies, and antiphospholipid antibodies directed against phospholipids other than cardiolipin (e.g., phosphatidylserine and phosphatidylethanolamine)[4,5] or against phospholipid-binding proteins other than cardiolipin-bound β_2-glycoprotein I (e.g., prothrombin, annexin V, protein C, or protein S).[6-8]

‡The threshold used to distinguish moderate or high levels of anticardiolipin antibodies from low levels has not been standardized and may depend on the population under study. Many laboratories use 15 or 20 international "phospholipid" units as the threshold separating low from moderate levels of anticardiolipin antibodies. Others define the threshold as 2.0 or 2.5 times the median level of anticardiolipin antibodies or as the 99th percentile of anticardiolipin levels within a normal population. Until an international consensus is reached, any of these three definitions seems reasonable.

§Guidelines are from Brandt et al.[9]

definitive association between specific clinical manifestations and particular subgroups of antiphospholipid antibodies. Therefore, multiple tests for antiphospholipid antibodies should be used, since patients may be negative according to one test yet positive according to another.

Despite their name, lupus anticoagulant antibodies are associated with thromboembolic events rather than clinical bleeding. Antiphospholipid antibodies can interfere with both anticoagulant and procoagulant pathways[24] (Table 3). 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.[24] Current criteria for the detection of lupus anticoagulant antibodies require prolongation of coagulation in at least one phospholipid-dependent coagulation assay. To rule out the presence of lupus anticoagulant antibodies, two or more assays that are sensitive to these antibodies must be negative[3,9,18] (Tables 1 and 2 and Fig. 1).

Current criteria for the classification of the antiphospholipid syndrome recommend the use of standardized enzyme-linked immunoassays that measure β_2-glycoprotein I–dependent IgG and IgM anticardiolipin antibodies[3,25] (Table 1). The observation that many anticardiolipin antibodies are directed at an epitope on β_2-glycoprotein I led to the development of anti–β_2-glycoprotein I antibody immunoassays.[6,14,15,17] Although their presence is not currently included in the criteria for the antiphospholipid syndrome,[3] anti–β_2-glycoprotein I antibodies are strongly associated with thrombosis and other features of the antiphospholipid syndrome.[20,26,27] The clinical utility of antiphospholipid-antibody assays for autoantibodies to phospholipids other than cardiolipin and to phospholipid-binding proteins other than β_2-glycoprotein I remains unclear.[4-8]

PATHOGENESIS

Several hypotheses have been proposed to explain the cellular and molecular mechanisms by which antiphospholipid antibodies promote thrombosis (Table 3). The first implicates activation of endothelial cells. Binding of antiphospholipid antibodies induces activation of endothelial cells, as assessed by upregulation of the expression of adhesion molecules, the secretion of cytokines, and the metabolism of prostacyclins.[28] Antiphospholipid antibodies recognize β_2-glycoprotein I bound to resting endothelial cells, although the basis for the interaction of β_2-glycoprotein I with viable endothelial cells remains unclear.[29]

A second theory focuses on oxidant-mediated in-

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TABLE 2. CLASSIFICATION AND DETECTION OF ANTIPHOSPHOLIPID ANTIBODIES.

ANTIBODY	METHOD OF DETECTION
Lupus anticoagulant antibodies	The first step is prolongation of coagulation in at least one phospholipid-dependent in vitro coagulation assay with the use of platelet-poor plasma.*† These assays can be subdivided according to the portion of the coagulation cascade that they evaluate as follows‡: The extrinsic coagulation pathway (dilute prothrombin time) The intrinsic coagulation pathway (activated partial-thromboplastin time, dilute activated partial-thromboplastin time, colloidal-silica clotting time, and kaolin clotting time) The final common coagulation pathway (dilute Russell's viper-venom time, Taipan venom time, and Textarin and Ecarin times).§
	The second step is a failure to correct the prolonged coagulation time by mixing the patient's plasma with normal plasma.*†
	The third step is confirmation of the presence of lupus anticoagulant antibodies by shortening or correction of the prolonged coagulation time after the addition of excess phospholipid or platelets that have been frozen and then thawed.*
	The fourth step is ruling out other coagulopathies with the use of specific factor assays if the confirmatory test is negative or if a specific factor inhibitor is suspected.*
Anticardiolipin antibodies	Solid-phase immunoassay (usually enzyme-linked immunosorbent assay) is performed on cardiolipin-coated plates, usually in the presence of bovine serum β_2-glycoprotein I. Anticardiolipin antibodies from patients with the antiphospholipid syndrome are β_2-glycoprotein I–dependent; antibodies from patients with infectious diseases are β_2-glycoprotein I–independent.¶
Anti–β_2 glycoprotein I antibodies	Solid-phase immunoassay (usually enzyme-linked immunosorbent assay) is performed on human β_2-glycoprotein I–coated plates (usually γ-irradiated polystyrene).‖ Anti–β_2-glycoprotein I antibody assays detect antibodies to human β_2-glycoprotein I, rather than bovine β_2-glycoprotein I (as in anticardiolipin antibody assays).

*Data are from Brandt et al.[9]

†The use of two or more assays sensitive to lupus anticoagulant antibodies is recommended before the presence of lupus anticoagulant antibodies is excluded. At least one of these assays should be based on low phospholipid concentration (dilute prothrombin time, dilute activated partial-thromboplastin time, colloidal-silica clotting time, kaolin clotting time, or dilute Russell's viper-venom time). The two assays should evaluate distinct portions of the coagulation cascade (e.g., activated partial-thromboplastin time and dilute Russell's viper-venom time).

‡Data are from Triplett.[18]

§The Ecarin-time assay differs from the other coagulation assays listed in that it is a phospholipid-independent assay. It should be used in combination with the phospholipid-dependent Textarin time as a confirmatory test for lupus anticoagulant antibodies. In the presence of lupus anticoagulant antibodies, Textarin times are prolonged, whereas Ecarin times are unaffected.

¶Data are from Galli et al.,[14] McNeil et al.,[15] and Hunt et al.[16]

‖Data are from Roubey.[6]

jury of the vascular endothelium. Oxidized low-density lipoprotein (LDL), a major contributor to atherosclerosis, is taken up by macrophages, leading to macrophage activation and subsequent damage to endothelial cells.[30] Autoantibodies to oxidized LDL occur in association with anticardiolipin antibodies, and some anticardiolipin antibodies cross-react with oxidized LDL.[31] Moreover, anticardiolipin antibodies bind to oxidized, but not reduced, cardiolipin, suggesting that anticardiolipin antibodies recognize oxidized phospholipids, phospholipid-binding proteins, or both.[32]

A third theory proposes that antiphospholipid antibodies interfere with or modulate the function of phospholipid-binding proteins involved in the regulation of coagulation. Although little is known about the biologic function of β_2-glycoprotein I, it is thought to act as a natural anticoagulant.[33] Mechanisms by which antiphospholipid antibodies interfere with the regulatory functions of prothrombin, protein C, annexin V, and tissue factor have also been proposed.[7,22,25,34,35]

Finally, thrombosis in the antiphospholipid syndrome has been likened to that in heparin-induced thrombocytopenia.[36] Both syndromes induce thrombosis in multiple arterial and venous beds.[36,37] In heparin-induced thrombocytopenia, the site of thrombosis is often determined by prior cardiovascular disease, whereas in the antiphospholipid syndrome, there is a high rate of recurrence of similar thrombotic events. A "second hit" such as vascular injury may be necessary for thrombosis to occur in both syndromes.

It remains unclear which cellular phospholipids and phospholipid-binding proteins are targeted by antiphospholipid antibodies in vivo. The absence of anionic phospholipids on the cell surface and the apparent lack of reactivity of antiphospholipid antibodies with intact cells suggest that perturbation of the cell

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TABLE 3. OPPOSING EFFECTS OF ANTIPHOSPHOLIPID ANTIBODIES ON COAGULATION.*

PROCOAGULANT EFFECT	ANTICOAGULANT EFFECT
Inhibition of the activated protein C pathway	Inhibition of activation of factor IX
Up-regulation of the tissue factor pathway	Inhibition of activation of factor X
Inhibition of antithrombin III activity	Inhibition of activation of prothrombin to thrombin
Disruption of annexin V shield on membranes	
Inhibition of anticoagulant activity of β_2-glycoprotein I	
Inhibition of fibrinolysis	
Activation of endothelial cells	
Enhanced expression of adhesion molecules by endothelial cells and adherence of neutrophils and leukocytes to endothelial cells	
Activation and degranulation of neutrophils	
Potentiation of platelet activation	
Enhanced platelet aggregation	
Enhanced binding of β_2-glycoprotein I to membranes	
Enhanced binding of prothrombin to membranes	

*Two major factors that probably modulate the balance between procoagulant and anticoagulant effects of antiphospholipid antibodies are the phospholipid surface on which the reaction takes place and the antigenic specificity of the antibody.

membrane may be required for antiphospholipid antibodies to bind to cells. Indeed, some antiphospholipid antibodies react with activated platelets[38] and apoptotic cells,[39] which have undergone a loss of the normal asymmetric distribution of membrane phospholipids and expose anionic phospholipids on their cell surface. Binding of antiphospholipid antibodies to apoptotic cells is dependent on β_2-glycoprotein I,[39] as is induction of antiphospholipid antibodies by apoptotic cells.[40]

CRITERIA FOR CLASSIFICATION AND DIAGNOSIS

A recent consensus statement provides simplified criteria for the diagnosis of the antiphospholipid syndrome[3] (Table 1). A patient with the antiphospholipid syndrome must meet at least one of two clinical criteria (vascular thrombosis or complications of pregnancy [as defined in Table 1]) and at least one of two laboratory criteria. None of the other protean clinical manifestations of the antiphospholipid syndrome,[2,41-46] such as thrombocytopenia, are included in the clinical criteria. Although such features have been associated with antiphospholipid antibodies, they occur in a variety of disease states other than the antiphospholipid syndrome, and the strength of their association does not reach that of vascular thrombosis.

The antiphospholipid syndrome may be divided into several categories. "Primary" antiphospholipid syndrome occurs in patients without clinical evidence of another autoimmune disease, whereas "secondary" antiphospholipid syndrome occurs in association with autoimmune or other diseases. Since systemic lupus erythematosus is by far the most common disease with which the antiphospholipid syndrome occurs, tentative exclusion criteria have been proposed to distinguish primary antiphospholipid syndrome from that related to systemic lupus erythematosus.[47] The link between antiphospholipid antibodies and other rheumatologic diseases, with the exception of rheumatoid arthritis,[48] is more tenuous and is based largely on case reports. Many cases of Sneddon's syndrome, defined as the clinical triad of stroke, livedo reticularis, and hypertension, may represent undiagnosed antiphospholipid syndrome.[49] Although antiphospholipid antibodies also occur in association with other conditions (including infections, cancer, and the use of drugs or hemodialysis), they are usually IgM antibodies that are present at low levels and are not associated with thrombotic events.[50] "Catastrophic" antiphospholipid syndrome will be discussed separately.

EPIDEMIOLOGY

Antiphospholipid antibodies are found among young, apparently healthy control subjects at a prevalence of 1 to 5 percent for both anticardiolipin antibodies and lupus anticoagulant antibodies.[51] As with other antibodies, the prevalence of antiphospholipid antibodies increases with age, especially among elderly patients with coexistent chronic diseases.[51] Among patients with systemic lupus erythematosus, the prevalence of antiphospholipid antibodies is much higher, ranging from 12 to 30 percent for anticardiolipin antibodies[48,52] and 15 to 34 percent for lupus anticoagulant antibodies.[52,53]

Many patients have laboratory evidence of antiphospholipid antibodies without clinical consequences. For otherwise healthy control subjects, there are insufficient data to determine what percentage of those with antiphospholipid antibodies will eventually have a thrombotic event or a complication of pregnancy consistent with the antiphospholipid syndrome. In contrast, the antiphospholipid syndrome may develop in 50 to 70 percent of patients with both systemic lupus erythematosus and antiphospholipid antibodies after 20 years of follow-up.[43,51] Nonetheless, up to 30 percent of patients with systemic lupus erythematosus and anticardiolipin antibodies lacked any clinical evidence of the antiphospholipid syndrome over an average follow-up of seven years.[43]

Prospective studies have shown an association between antiphospholipid antibodies and the first episode of venous thrombosis,[54] the first myocardial in-

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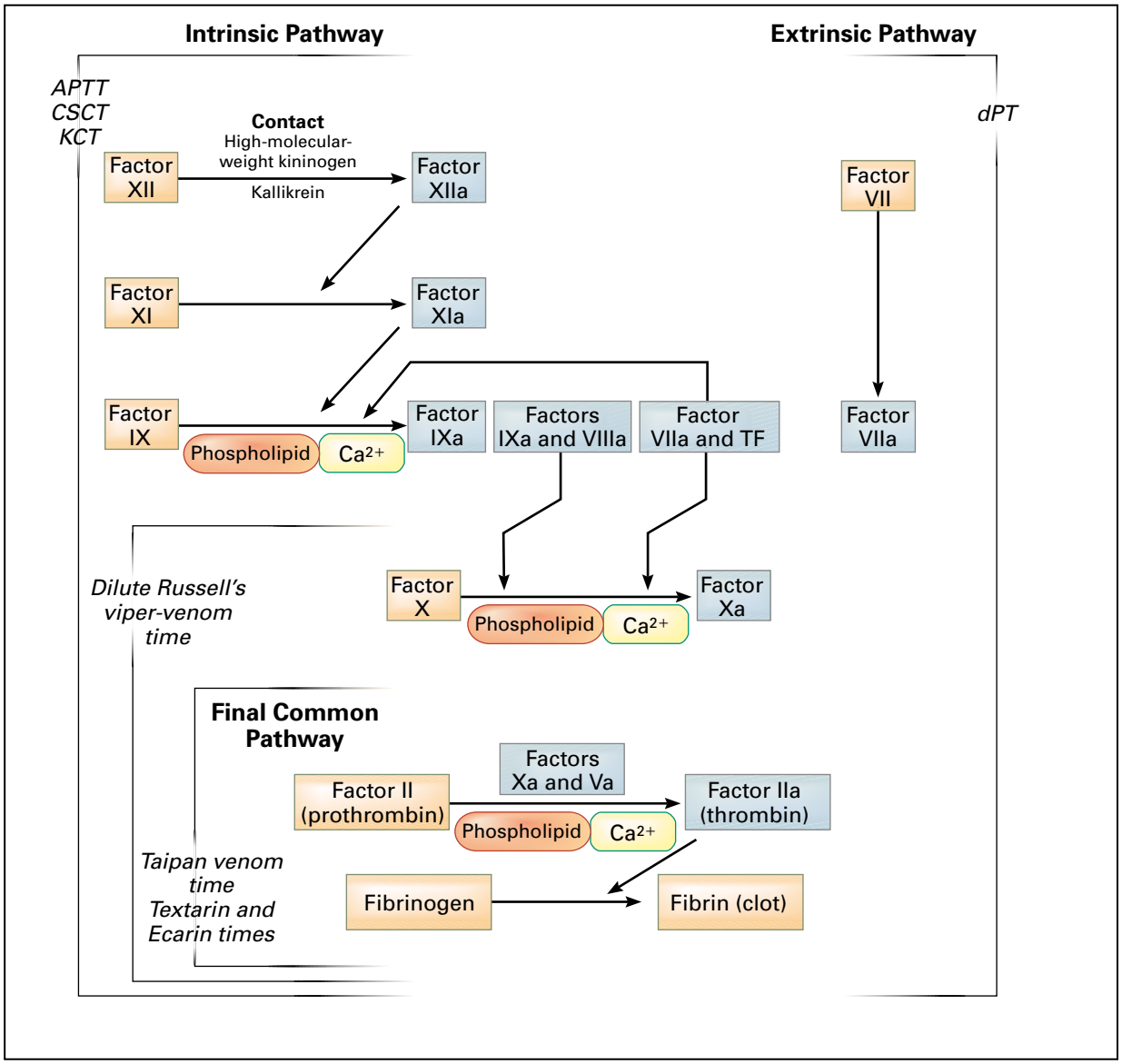

Figure 1. Detection of Lupus Anticoagulant Antibodies by in Vitro Coagulation Assays.

The various coagulation tests used to detect lupus anticoagulant activity are indicated in italics, and the figure shows a simplified schematic diagram of the coagulation pathway evaluated by each of these tests. The coagulation cascade is a result of the enzymatic conversion of each factor (orange boxes) to its activated, or enzymatic, form (blue boxes), which then, in combination with an activated cofactor, catalyzes the subsequent reaction. The intrinsic coagulation pathway is initiated by contact activation on glass, silica, or kaolin (as in the activated partial-thromboplastin time [APTT], colloidal-silica clotting time [CSCT], and kaolin clotting time [KCT] assays), whereas the extrinsic coagulation pathway is initiated by the formation of a complex between tissue factor (TF) and factor VIIa (as in the dilute prothrombin time [dPT] assay). Both the intrinsic and extrinsic pathways result in the conversion of factor X to activated factor X (factor Xa). Finally, both intrinsic and extrinsic pathways converge on the final common pathway, the activation of prothrombin to thrombin followed by the conversion of fibrinogen to fibrin. Russell's viper venom directly activates factor X. Taipan, Textarin, and Ecarin snake-venom extracts directly activate prothrombin but have different cofactor requirements. Taipan venom activation of prothrombin requires phospholipid and calcium but not factor Va. Textarin activation of prothrombin requires phospholipid, calcium, and factor Va, whereas Ecarin activation of prothrombin is independent of cofactors and does not require phospholipid, calcium, or factor Va. The activation of prothrombin to thrombin, like several other reactions in the coagulation cascade, requires the presence of phospholipid and calcium. These phospholipid-dependent reactions are believed to be targeted by lupus anticoagulant antibodies in vitro. Although both the intrinsic and extrinsic pathways are invaluable for understanding clot formation in vitro, the extrinsic pathway has the dominant role in vivo.

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farction,[55] and recurrent stroke.[56] A critical issue, therefore, is the identification of patients with antiphospholipid antibodies who are at increased risk for a thrombotic event. Important risk factors appear to be a history of thrombosis,[57,58] the presence of lupus anticoagulant antibodies,[18,59] and an elevated level of IgG anticardiolipin antibodies,[2,55,57] each of which increases the risk of thrombosis up to five times, although not all studies agree.[60] Persistence of antiphospholipid antibodies also appears to increase the risk of thrombosis.[2] Except for a previous thrombotic event, none of the above individual risk factors are sufficiently predictive to warrant treatment.

DIFFERENTIAL DIAGNOSIS

The antiphospholipid syndrome is one of several prothrombotic states in which thrombosis occurs within both the venous and arterial beds[61] (Table 4). Although other conditions predisposing the patient to venous and arterial thrombosis (e.g., heparin-induced thrombocytopenia, homocysteinemia, myeloproliferative disorders, and hyperviscosity) can be detected through routine laboratory testing, the sole abnormality in a patient with primary antiphospholipid syndrome may be the existence of antiphospholipid antibodies. It is important to note that since a normal activated partial-thromboplastin time does not exclude the presence of lupus anticoagulant antibodies (Table 2), a patient presenting with a first thrombotic event should be screened for anticardiolipin antibodies and with other assays that are sensitive to lupus anticoagulant antibodies. The diagnosis may be unsuspected in patients in whom the antiphospholipid syndrome results in a chronic, more indolent process, leading to ischemia and slow, progressive loss of organ function.

Secondary risk factors that increase the tendency to thrombosis should be pursued. Such factors can affect the venous or arterial beds and include stasis, vascular injury, the use of medications such as oral contraceptives, and traditional risk factors for atherosclerotic disease. Eliminating or reducing the effect of these factors is especially important, since the mere presence of antiphospholipid antibodies may be insufficient to generate thrombosis; a "second hit," in combination with antiphospholipid antibodies, may be required for thrombosis to occur. Finally, even in patients with documented antiphospholipid syndrome, disentangling cause and effect can at times be difficult. For example, the antiphospholipid syndrome is associated with the nephrotic syndrome, itself a risk factor for thromboembolism.

CLINICAL FEATURES

Although the association of clinical manifestations with the presence of antiphospholipid antibodies is clearest in primary antiphospholipid syndrome, there are no major differences in the clinical consequences of antiphospholipid antibodies between patients with primary antiphospholipid syndrome and those with secondary antiphospholipid syndrome.[44] Virtually any organ can be involved, and the range of disorders observed within any one organ system spans a diverse spectrum (Table 5). The effects of antiphospholipid antibodies 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 legs, is the most common manifestation of the antiphospholipid syndrome, occurring in 29 to 55 percent of patients with the syndrome during an average follow-up of less than six years.[42-44] Up to half these patients have pulmonary emboli.[42-44] Arterial thromboses are less common than venous thromboses[42-44] and most frequently manifest with features consistent with ischemia or infarction. The severity of presentation relates to the acuteness and extent of occlusion. The brain is the most common site, with strokes and transient ischemic attacks accounting for almost 50 percent of arterial occlusions.[42] Coronary occlusions account for an additional 23 percent; the remaining 27 percent involve diverse beds, including subclavian, renal, retinal, and pedal arteries.[42] It should be emphasized that thrombotic episodes associated with the antiphospholipid syndrome may occur in vascular beds that are infrequently affected by other prothrombotic states (Table 5).

Not all arterial episodes of ischemia or infarction are thrombotic in origin. Emboli, especially from mitral-valve or aortic-valve vegetations, can also lead to cerebral events. The frequency of cardiac valvular abnormalities appears to be quite high, with up to 63 percent of patients with the antiphospholipid syndrome revealing at least one valvular abnormality on echocardiography.[44] Although many of these abnormalities are of little clinical consequence, vegetations of the mitral or aortic valves are present in approximately 4 percent of patients with primary or secondary antiphospholipid syndrome.[44]

Acute involvement at the level of the capillaries, arterioles, or venules often results in a clinical picture virtually indistinguishable from those of the hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura as well as other thrombotic microangiopathies. Thrombotic microangiopathy may also 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 patients with the antiphospholipid syndrome can present on a spectrum from rapidly progressive to clinically silent and indo-

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TABLE 4. DISEASE STATES AND RISK FACTORS PREDISPOSING PATIENTS TO THROMBOEMBOLISM.

ABNORMALITY	AFFECTED VASCULAR BEDS		
	VENOUS	VENOUS AND ARTERIAL	ARTERIAL
Defects in coagulation factors	Resistance to activated protein C (factor V Leiden) Deficiency of protein C Deficiency of protein S Deficiency of antithrombin III Mutation of prothrombin		
Defects in clot lysis	Deficiency of plasminogen Deficiency of tissue plasminogen activator	Dysfibrinogenemia* Deficiency of plasminogen-activator inhibitor type 1*	
Metabolic defects		Homocysteinemia	
Platelet defects		Heparin-induced thrombocytopenia and thrombosis Myeloproliferative disorders Paroxysmal nocturnal hemoglobinuria* Polycythemia vera (with thrombocytosis)	
Stasis	Immobilization Surgery Congestive heart failure		
Hyperviscosity		Polycythemia vera Waldenström's macroglobulinemia Sickle cell anemia Acute leukemia	
Defects in vessel walls		Trauma Vasculitis	Atherosclerosis Turbulence
Other	Cancer (Trousseau's syndrome) Use of oral contraceptives Estrogen therapy Pregnancy or puerperium Nephrotic syndrome	Antiphospholipid syndrome Foreign bodies Cyclooxygenase-2 inhibitors†	Hypertension Diabetes Smoking Atrial fibrillation Hyperlipidemia Chronic inflammation Systemic lupus erythematosus‡

*In this disorder, the venous involvement far exceeds the arterial involvement.

†Specific inhibitors of cyclooxygenase-2 reduce systemic production of the antithrombotic prostaglandin prostacyclin. A recent series described four patients with secondary antiphospholipid syndrome in whom acute thrombosis developed in conjunction with a cyclooxygenase-2 inhibitor.[62]

‡A prothrombotic effect of systemic lupus erythematosus, separate from that of antiphospholipid antibodies, has been suggested but not definitely established.

lent. Depending on the size of the vessels affected, organ failure has two predominant causes, thrombotic microangiopathy and ischemia secondary to thromboembolic events.

Other prominent manifestations of the antiphospholipid syndrome include thrombocytopenia (in 40 to 50 percent of patients), hemolytic anemia (in 14 to 23 percent), and livedo reticularis (in 11 to 22 percent).[42-44] Although renal manifestations are a very common feature of systemic lupus erythematosus, they were only recently recognized as part of the antiphospholipid syndrome. Among patients with the antiphospholipid syndrome with renal involvement, hypertension is almost invariably present.[63]

PATHOLOGICAL FEATURES

The histopathological features of the antiphospholipid syndrome reflect a combination of several major pathophysiological processes: thrombotic microangiopathy, ischemia secondary to upstream arterial thromboses or emboli, and peripheral embolization from venous, arterial, or intracardiac sources.[46,63,64] The histopathological features of arterial and venous thromboses seen in association with the antiphospholipid syndrome do not differ from those seen in other prothrombotic states. Similarly, regions of ischemia and infarction downstream from thrombotic or embolic occlusions lack unique features.

Thrombotic microangiopathy, an emerging clinical concern in the antiphospholipid syndrome, is a consequence of microvascular involvement. Its histologic features also are not specific to the antiphospholipid syndrome and can be seen in a variety of other diseases and syndromes, including hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura, malignant hypertension, scleroderma, radiation-induced injury, pregnancy-associated renal failure, and various thrombotic microangiopathies induced by

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TABLE 5. CLINICAL MANIFESTATIONS OF THE ANTIPHOSPHOLIPID SYNDROME.

ORGAN SYSTEM	PRIMARY PATHOGENIC PROCESS*	
	THROMBOEMBOLISM OF LARGE VESSELS†	THROMBOTIC MICROANGIOPATHY
Arterial	Thrombosis of the aorta or axillary, carotid, hepatic, ileofemoral, mesenteric, pancreatic, popliteal, splenic, or subclavian artery	
Cardiac	Angina, myocardial infarction, cardiac valvular vegetations, valvular abnormalities, intracardiac thrombi, nonbacterial thrombotic (Libman–Sacks) endocarditis, peripheral embolization, or atherosclerosis	Myocardial infarction, myocardial microthrombi, myocarditis, or valvular abnormalities
Cutaneous	Superficial thrombophlebitis, splinter hemorrhages, leg ulcers, distal cutaneous ischemia, infarcts of the skin, blue toe syndrome, or acrocyanosis	Livedo reticularis, superficial gangrene, purpura, ecchymoses, or subcutaneous nodules
Endocrine or reproductive	Adrenal infarction, adrenal failure, testicular infarction, prostate infarction, necrosis of the pituitary gland, or pituitary failure	
Gastrointestinal	Budd–Chiari syndrome, hepatic infarction, intestinal infarction, splenic infarction, esophageal perforation, ischemic colitis, infarction of the gall bladder not attributable to gallstones, pancreatitis, or ascites	Intestinal, hepatic, pancreatic, and splenic infarctions or gangrene
Hematologic	Thrombocytopenia, hemolytic anemia, or hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura	Disseminated intravascular coagulation (catastrophic antiphospholipid syndrome only)
Miscellaneous	Perforation of the nasal septum or avascular necrosis of bone	
Neurologic	Transient ischemic attack, cerebrovascular accident (thrombotic or embolic), chorea, seizures, multi-infarct dementia, transverse myelitis, encephalopathy, migraines, pseudotumor cerebri, cerebral venous thrombosis, mononeuritis multiplex, or amaurosis fugax	Microthrombi or microinfarctions
Obstetrical	Pregnancy loss, intrauterine growth retardation, HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count in association with preeclampsia), oligohydramnios, uteroplacental insufficiency, or preeclampsia	
Ophthalmologic	Thrombosis of the retinal artery, thrombosis of the retinal vein, or amaurosis fugax	Retinitis
Pulmonary	Pulmonary emboli, pulmonary hypertension, pulmonary arterial thrombosis, or alveolar hemorrhage	Acute respiratory distress syndrome or alveolar hemorrhage
Renal	Thrombosis of the renal vein, thrombosis of the renal artery, renal infarction, hypertension, acute renal failure, chronic renal failure, proteinuria, hematuria, or the nephrotic syndrome	Acute renal failure (often requiring dialysis), thrombotic microangiopathy, or hypertension
Venous	Deep venous thrombosis of the legs or thrombosis of the adrenal, hepatic, mesenteric, portal, or splenic vein or of the inferior vena cava	

*Many of the clinical manifestations of the antiphospholipid syndrome listed in this table can occur as a result of thromboembolism of large vessels, thrombotic microangiopathy, or both. For convenience, these are listed as manifestations of thromboembolism of large vessels. Only manifestations that are seen exclusively with thrombotic microangiopathy or that constitute a major feature of this syndrome are listed under thrombotic microangiopathy.

†Manifestations of the antiphospholipid syndrome whose pathogenic origin is uncertain (e.g., thrombocytopenia) are also listed as manifestations of thromboembolism of large vessels.

drugs (cyclosporine, tacrolimus, and chemotherapeutic agents such as mitomycin C). Although the acute changes of thrombotic microangiopathy are usually fairly prominent, the chronic changes can be quite subtle and easily overlooked. Acute changes include capillary congestion and intracapillary fibrin thrombi, generally without inflammation.[45,46,63,65,66] Immunofluorescence reveals a predominance of fibrin-related antigens. Immune complexes are not seen.[63,66] Chronic changes, ranging from ischemic hypoperfusion to atrophy and fibrosis, reflect healing and scarring of acute lesions.[45,63,66,67] 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.[63,66] Thrombi eventually organize into fibrocellular and fibrous vascular occlusions. Blood flow may be restored by the development of new endothelialized channels that traverse the occlusion.[63]

True vasculitis is rarely, if ever, seen in primary antiphospholipid syndrome.[46,63] Vasculitis in secondary antiphospholipid syndrome is attributable to systemic lupus erythematosus, not the antiphospholipid syndrome. Although there is enormous confusion regarding terminology for the vascular lesions associated with systemic lupus erythematosus, vaso-occlusive disease associated with the antiphospholipid syndrome, irrespective of the size of the vessel involved, is universally due to thrombosis.[46]

OBSTETRICAL CONSIDERATIONS

Women with antiphospholipid antibodies have an unusually high proportion of pregnancy losses within the fetal period (10 or more weeks of gestation).[68,69] In contrast, in unselected women with sporadic or recurrent miscarriage, pregnancy losses occur more commonly in the preembryonic period (less than six weeks of gestation) or the embryonic period (six to nine weeks of gestation). Pregnancies in women who

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are positive for antiphospholipid antibodies can also be complicated by premature delivery due to pregnancy-associated hypertensive disease and uteroplacental insufficiency.[70,71] More recent studies have extended the deleterious effects of antiphospholipid antibodies to women with recurrent preembryonic and embryonic losses,[72-74] among whom 10 to 20 percent have antiphospholipid antibodies without other medical conditions.[72-77] The 1999 international consensus statement provides separate criteria for these two seemingly different populations[3] (Table 1).

Adverse pregnancy outcomes in women with the antiphospholipid syndrome may result from poor placental perfusion[78] due to localized thrombosis, perhaps through interference with trophoblastic annexin V that is mediated by antiphospholipid antibodies.[35] Antiphospholipid antibodies may also impair trophoblastic invasion and hormone production, thereby promoting not only preembryonic and embryonic loss but also fetal loss and uteroplacental insufficiency.[79]

Treatment has evolved considerably. Early enthusiasm for glucocorticoids waned when a small, randomized trial found heparin administered to pregnant women to be as effective as prednisone.[80] Recently, two prospective trials showed that heparin plus low-dose aspirin is more effective than aspirin alone for achieving live births among women with antiphospholipid antibodies and predominantly preembryonic and embryonic pregnancy loss.[75,76] A third prospective trial of women who were positive for antiphospholipid antibodies and had repeated pregnancy loss but no history of thrombosis or systemic lupus erythematosus found similar rates of live births (approximately 80 percent) with the use of either low-dose aspirin or placebo,[77] suggesting that treatment may be unnecessary in some women. Although intravenous immune globulin has been used to treat some autoimmune conditions in pregnancy, a randomized, controlled study found no benefit of intravenous immune globulin as compared with heparin and aspirin in reducing adverse obstetrical outcomes in women with the antiphospholipid syndrome.[81]

Concern about patient selection notwithstanding,[82] most experts recognize the antiphospholipid syndrome as a proven, treatable cause of recurrent pregnancy loss.[83] Currently, heparin administered to pregnant women after ultrasonographic demonstration of a live embryo is the treatment of choice, although the dose is debated. Women with recurrent preembryonic and embryonic pregnancy loss and no history of thromboembolism may be treated with 5000 U of heparin twice daily,[75] but experts recommend higher doses, sufficient to produce full anticoagulation, for women with prior thromboembolism.[84] The optimal treatment for women with pregnancy loss during the fetal period but no history of thromboembolism is controversial because of the potential risk of maternal thromboembolism. Generous thromboprophylaxis (15,000 to 20,000 U of heparin per day) or adjusted thromboprophylaxis is favored by some,[70,71,80] but there are no properly designed studies for guidance. Experts agree that low-molecular-weight heparin may be substituted for standard heparin in the treatment of pregnant women with the antiphospholipid syndrome.[84]

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

In most patients with the antiphospholipid syndrome, thrombotic events occur singly. Recurrences may occur months or years after the initial event. However, a minority of patients with the antiphospholipid syndrome present with an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. This syndrome, termed "catastrophic antiphospholipid syndrome," is defined by the clinical involvement of at least three different organ systems over a period of days or weeks with histopathological evidence of multiple occlusions of large or small vessels.[85] Although the same clinical manifestations seen with primary and secondary antiphospholipid syndrome also occur as part of catastrophic antiphospholipid syndrome, there are important differences in prevalence and in the caliber of the vessels predominantly affected. Our discussion will rely heavily on a comprehensive review through 1998 of 50 cases of catastrophic antiphospholipid syndrome.[85]

Venous or arterial thrombosis of large vessels is less common in patients with catastrophic antiphospholipid syndrome, who tend to present with an acute thrombotic microangiopathy affecting small vessels of multiple organs.[85] The kidney is the organ most commonly affected (in 78 percent of patients), followed by the lungs (in 66 percent), the central nervous system (in 56 percent), the heart (in 50 percent), and the skin (in 50 percent). Disseminated intravascular coagulation, which does not occur in primary or secondary antiphospholipid syndrome, occurs in approximately 25 percent of patients with catastrophic antiphospholipid syndrome. Microvascular manifestations include renal thrombotic microangiopathy, adult respiratory distress syndrome, cerebral microthrombi and microinfarctions, and myocardial microthrombi. Most patients with renal involvement have hypertension, often malignant, and approximately 25 percent require dialysis. The mortality rate is 50 percent, and death is usually due to multiorgan failure.[85]

Precipitating factors of catastrophic antiphospholipid syndrome include infections, surgical procedures, withdrawal of anticoagulant therapy, and the use of drugs such as oral contraceptives.[85] Although the

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pathophysiology of this disorder is poorly understood, thrombosis can be self-perpetuating in patients with an underlying hypercoagulable state. Thus, an initial thrombosis in a patient with the antiphospholipid syndrome may upset the balance of hemostasis and set in motion a process termed "thrombotic storm," leading to multiple coagulative events throughout the body.[86]

Recommendations for the treatment of catastrophic antiphospholipid syndrome are based entirely on case reports. In the above series of 50 patients, recovery occurred in 14 of 20 patients (70 percent) treated with a combination of anticoagulants and steroids plus either plasmapheresis or intravenous immune globulin.[85] The rationale for plasmapheresis derives from its documented effectiveness in treating the hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura. The fibrinolytic agents streptokinase and urokinase have also been used to treat acute thrombotic microangiopathy with varying success.[85,86] Since thrombosis tends to be a self-perpetuating process,[86] an aggressive therapeutic approach is warranted in these patients.

TREATMENT

Treatment decisions fall into four main areas: prophylaxis, prevention of further thromboses of large vessels, treatment of acute thrombotic microangiopathy, and management of pregnancy in association with antiphospholipid antibodies. This section will review data on treatment in the first two areas. Treatment of thrombotic microangiopathy and management of pregnancy have been covered in the sections on catastrophic antiphospholipid syndrome and obstetrical considerations, respectively.

Prophylaxis

A case–control study nested within the Physicians' Health Study examined the role of aspirin (325 mg per day) as a prophylactic agent.[54] Aspirin did not offer protection against deep venous thrombosis and pulmonary embolism in male physicians with anticardiolipin antibodies.[54] In contrast, aspirin may provide protection against thrombosis in women with the antiphospholipid syndrome and previous pregnancy loss.[87] Hydroxychloroquine may be protective against thrombosis in patients with systemic lupus erythematosus and secondary antiphospholipid syndrome.[88] Certainly, any factors predisposing the patient to thrombosis (Table 4) should be eliminated. In addition, modification of secondary risk factors for atherosclerosis seems prudent, given the putative role of vascular injury in promoting thrombosis associated with antiphospholipid antibodies[30,36] and the association between antiphospholipid antibodies and oxidized LDL.[31,32,56]

Treatment after a Thrombotic Event

A beneficial role for anticoagulation in decreasing the rate of recurrent thrombosis has been shown in three retrospective studies.[60,89,90] In a small series of 19 patients with the antiphospholipid syndrome, the rate of recurrence at eight years was 0 percent for the patients receiving oral anticoagulants.[90] Among patients whose anticoagulant therapy was stopped, the rate of recurrence was 50 percent at two years and 78 percent at eight years.[90] In two larger series, the level of protection against venous and arterial thrombosis correlated directly with the level of anticoagulation.[60,89] Among 70 patients with the antiphospholipid syndrome, warfarin treatment of intermediate intensity (to achieve an international normalized ratio [INR] of 2.0 to 2.9) and high intensity (INR, 3.0 or more) significantly reduced the rate of recurrent thrombosis, whereas low-intensity treatment (INR, 1.9 or less) did not confer significant protection.[89] Similar results were found in a series of 147 patients with the antiphospholipid syndrome.[60] In both studies, aspirin alone was ineffective in reducing the rate of recurrent thrombosis.[60,89]

Several additional points warrant mention. First, discontinuation of warfarin seems to be associated with an increased risk of thrombosis[59,60,90,91] and even death,[59] especially in the first six months after anticoagulant therapy is stopped. Since the rate of recurrence among patients who have not received optimal anticoagulation can be as high as 70 percent,[60,89,90] treatment with warfarin should probably be long term, if not lifelong. Second, it remains unclear whether patients with the antiphospholipid syndrome can be safely treated with intermediate-intensity warfarin treatment (INR, 2.0 to 2.9) or whether they require high-intensity treatment (INR, 3.0 or more). This is an important unresolved issue, since high-intensity warfarin carries a higher risk of hemorrhagic complications.[92] In some studies, intermediate-intensity warfarin has appeared to be fully effective in suppressing coagulation, as assessed according to the levels of prothrombin fragments[93] and the prevention of recurrent thrombosis.[59,91,94,95] Finally, monitoring the level of anticoagulation in patients with the antiphospholipid syndrome is complicated by the lack of standardized reagents for the determination of the INR and the potential interference of antiphospholipid antibodies in this measurement.[96]

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