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