Vasculitis in Antiphospholipid Syndrome

Lindsay Lally, MD*, Lisa R. Sammaritano, MD

KEYWORDS

• Antiphospholipid syndrome • Vasculitis • Lupus anticoagulant
• Anticardiolipin antibody • Anti-β2-glycoprotein 1 antibody

KEY POINTS

- Systemic vasculitis may rarely coexist with antiphospholipid syndrome (APS), despite the fact that the classic APS manifestations are thrombosis and vasculopathy.
- Vasculitic-like manifestations attributed to antiphospholipid antibodies (aPL) include livedoid vasculitis, retinal vasculitis, and diffuse alveolar hemorrhage.
- Antiphospholipid antibodies are increased in certain primary vasculitic disorders; a causative association of aPL with thrombosis in these patients has not been shown, however, and routine testing for aPL in primary vasculitis is not recommended.
- Differentiating between vasculitis and antiphospholipid-associated thrombosis, especially in patients with known primary vasculitis or systemic lupus, is critical in determining appropriate immunosuppressive or anticoagulant therapy.

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by vascular thrombosis and/or pregnancy morbidity occurring in conjunction with serologically detectable antiphospholipid antibodies (aPL). aPL, defined as autoantibodies directed against phospholipid-binding plasma proteins, include lupus anticoagulant (LAC), anticardiolipin antibody (aCL), and anti–β2-glycoprotein I (aβ2GPI), and should be persistently positive when measured at least 12 weeks apart to meet the criteria for APS (**Box 1**).[1] Detection of positive aPL in the absence of characteristic clinical events does not equate to a diagnosis of APS; many individuals with positive aPL remain asymptomatic indefinitely. Because transient aPL positivity can be triggered by certain infections, malignancies, or medications, demonstration of persistent serologic

Disclosure Statement: The authors have nothing to disclose.
Division of Rheumatology, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA
* Corresponding author.
E-mail address: lallyl@hss.edu

Rheum Dis Clin N Am 41 (2015) 109–123
http://dx.doi.org/10.1016/j.rdc.2014.09.009 **rheumatic.theclinics.com**
0889-857X/15/$ – see front matter

Box 1
Updated classification criteria for definite antiphospholipid syndrome (APS)

Clinical Criteria

1. Vascular thrombosis:

   At least 1 clinical episode of arterial, venous, or small vessel thrombosis, in any tissue or organ

2. Pregnancy morbidity:

   a. At least 1 unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation, or

   b. At least 1 premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency, or

   c. At least 3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities, and paternal and maternal chromosomal causes excluded

Laboratory Criteria[a]

1. Lupus anticoagulant present in plasma
2. Anticardiolipin antibody of immunoglobulin (Ig)G and/or IgM isotype, in medium or high titer (>40 IgG or IgM phospholipid units)
3. Anti–β2-glycoprotein I antibody of IgG and/or IgM isotype in medium or high titer (>99th percentile)

Definite APS is present if at least 1 of the clinical and 1 of the laboratory criteria are met.
[a] Laboratory criteria must be present on 2 or more occasions at least 12 weeks apart.

positivity is critical when considering a diagnosis of APS. APS may occur alone or in the setting of another autoimmune disease, most commonly systemic lupus erythematosus (SLE).

Although venous or arterial thrombosis and fetal loss are the commonest clinical manifestations of APS, this is a multisystem disease with many noncriteria manifestations including thrombocytopenia, skin ulcers, nephropathy, and cardiac valvular disease.[2] The pathogenic vascular lesions in APS are predominantly related to thrombosis or microangiopathy and not inflammation. However, vascular inflammation, namely, vasculitis, may rarely be a component of APS.[3] Furthermore, aPL positivity or secondary APS may occur in patients with an underlying primary systemic vasculitis.[4,5]

ANTIPHOSPHOLIPID ANTIBODIES, ANTIPHOSPHOLIPID SYNDROME, AND VASCULITIS

The mechanistic interplay between aPL and vascular inflammation is complex. Although the pathogenesis of thrombosis in APS is not entirely understood, the interactions of aPL with antigenic components of the phospholipid complex are essential in mediating the pathologic prothrombotic phenotype.[6] Subsequent endothelial cell activation and damage contributes to the vasculopathy of APS.

Despite the persistent presence of aPL, clinically evident thrombosis occurs only occasionally, suggesting that a “second hit” is required for the development of thrombosis. Inflammation driven by the nuclear factor κB pathway and/or complement activation has been hypothesized as a link between the aPL-induced hypercoagulable state and frank thrombus development.[7] Endothelial cell activation, production of