Venous Thrombosis in the Antiphospholipid Syndrome

Mary Katherine Farmer-Boatwright, Robert A.S. Roubey

Abstract—The antiphospholipid syndrome is a relatively common acquired cause of venous thrombosis. Up to 20% of cases of deep vein thrombosis, with and without pulmonary embolism, may be associated with antiphospholipid antibodies. These antibodies are typically detected in lupus anticoagulant assays and tests for anticardiolipin antibodies. Most antiphospholipid antibodies are directed against several phospholipid-binding plasma proteins. The most common antigens are β2-glycoprotein I and prothrombin. Immunoassays using these purified antigens are now available. In addition to being markers for thrombotic risk, antiphospholipid antibodies have been shown to directly contribute to hypercoagulability in animal models and in various in vitro studies. Prevention of recurrent venous thrombosis in patients with the antiphospholipid syndrome requires long-term anticoagulation. The optimal intensity of warfarin therapy is an ongoing issue, but most clinicians currently favor a target INR in the 2.0 to 3.0 range. In certain patients, antiphospholipid antibodies may interfere with determination of the INR, requiring other approaches to monitor and adjust the warfarin dose. Low-dose aspirin is typically recommended for primary prevention of thrombosis in asymptomatic patients with moderate to high levels of antiphospholipid antibodies, although strong supporting data are lacking. (Arterioscler Thromb Vasc Biol. 2009;29:321-325.)

Key Words: antiphospholipid ■ anticardiolipin ■ lupus anticoagulant ■ β2-glycoprotein I ■ thrombosis

The antiphospholipid syndrome (APS) is the association of thrombosis or recurrent pregnancy loss with persistent antiphospholipid antibodies (aPLs). The spectrum of thrombosis in APS includes both venous and arterial events and thrombosis at nearly every site in the vasculature has been reported. This review will focus on venous thrombosis (VT) in the setting of APS. The most common type of venous thrombosis associated with APS is lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE). APS is one of the more common acquired causes of venous thrombophiliA in. In one prospective cohort study, approximately 20% of patients with DVT or PE had moderate to high levels of aPLs before the thrombotic event.1 About one-third of patients present with VT at the time of diagnosis of APS.2

APS occurring in the absence of other autoimmune diseases is termed primary APS. Secondary APS refers to APS in the setting of other autoimmune diseases, most commonly systemic lupus erythematosus (SLE). International consensus criteria for the classification of definite APS were initially published in 1999 and updated in 2006.4 The classification criteria, summarized in the Table, are useful in research studies but are not intended as diagnostic criteria for clinical purposes. The criteria do not include a number of clinical manifestations associated with aPLs including thrombocytopenia, livedo reticularis, valvular heart disease (Libman-Sacks endocarditis), a form of nephropathy, and certain neurological abnormalities.4

Antiphospholipid Antibodies and Antigens
The terminology of aPLs can be confusing. aPLs were originally classified based on the type of assay in which they were detected without a clear understanding of their antigenic specificity. Lupus anticoagulants (LACs) are antibodies detected based on their ability to prolong phospholipid-dependent coagulation reactions. Anticardiolipin antibodies (ACA) are detected in immunoassays, typically enzyme-linked immunosorbent assays (ELISAs), in which cardiolipin, an anionic phospholipid, is the putative antigen. The antigenic specificities of LAC and ACA were elucidated in the early 1990s. Most aPLs are directed against phospholipid-binding plasma proteins not anionic phospholipids.5 The two best characterized antigens are β2-glycoprotein I (β2GPI) and prothrombin. β2GPI is a 50-kDa plasma glycoprotein. A number of physiological roles for β2GPI have been suggested, including apoptotic cell clearance,6 binding to oxidized low density lipoproteins,7 and an interaction with coagulation factor XI.8 Inherited deficiency of β2GPI does not have a clear phenotype.9 Prothrombin, of course, is the precursor of thrombin, and plays a major role in coagulation.
Most antibodies detected in ACA assays recognize 2GPI ELISAs is an area of ongoing research.

Clinical criteria
1. Vascular thrombosis:
   - One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.
2. Pregnancy morbidity:
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
   b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or recognized features of placental insufficiency, or
   c) Three or more 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
1. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA).
3. Anti-β2-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma, (in titer >99th percentile) present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

*Classification of APS should be avoided if <12 weeks or >5 years separate the positive aPL test and the clinical manifestation.

Most LACs are directed against either β2GPI or prothrombin. Most antibodies detected in ACA assays recognize β2GPI. It should be noted that ACA assays may detect both antibodies to β2GPI as well as antibodies that directly bind to cardiolipin. The former are associated with APS, whereas the latter occur in various infections such as syphilis and sometimes in normal individuals, and do not appear to be associated with APS. ELISAs using purified protein antigens are now available to detect anti-β2GPI and antiprothrombin antibodies. Anti-β2GPI ELISAs are clinically useful, and anti-β2GPI antibodies have been incorporated into the consensus classification criteria for APS. The clinical utility of antiprothrombin ELISAs is an area of ongoing research.

**aPLs and Risk of Thrombosis**

The thrombotic risk associated with aPLs has been studied in patients with SLE and in the general population. There are consistent data demonstrating an association between aPLs and an increased risk of venous thrombosis in SLE patients. Approximately one-third of SLE patients have aPLs, and SLE patients have an increased lifetime risk for thrombosis. Horbach et al found that LAC was the strongest risk factor for VT in SLE, with an odds ratio of 6.6. In a 1997 meta-analysis, Wahl and colleagues found odds ratios for VT of 5.6 for LAC and 2.2 for ACA.11 In the large Euro-Lupus study, 9.2% of SLE patients experienced one or more episodes of thrombosis during the 10-year follow-up period; 26.5% of deaths were attributable to thrombosis.12 aPLs were strongly associated with thrombosis in this cohort. In the LUMINA Study, 9% of SLE patients had at least one VT.13 VT was independently associated with LAC and several other risk factors (smoking, older age, disease activity, and glucocorticoid dose).

The association of thrombosis with aPLs in the absence of SLE or related conditions has been assessed in groups of patients with VT as well as in population-based prospective studies. Gali and colleagues systemically reviewed data from 25 primary studies including more than 7000 patients and controls, the large majority of whom did not have SLE.14 LAC was found to be a strong risk factor for thrombosis with odds ratios ranging from 5 to 16. A weaker association was found for ACA, and did not reach statistical significance in about half of the studies reviewed. Differences in ACA assay methodology, quantitation, and cut-off values may explain some of this disparity. A separate, but partly overlapping, meta-analysis of VT risk associated with aPLs in the absence other autoimmune diseases found an overall odds ratio of 11.1 for LAC.15 In this study, the odds ratio for ACA of any titer was approximately 1.6, and for high titer ACA the odds ratio was 3.2.

Three large population-based prospective studies have examined the association of VT and ACA.1,16-17 Ginsburg and colleagues investigated a cohort from the Physicians’ Health Study and found a relative risk of approximately 8 for medium to high titer IgG ACA.1 In contrast, in the HUNT 2 study no statistically significant association between ACA levels and VT was observed.16 A possible explanation for the absence of an association may be the older age of the patients in the latter study. In the Physicians Health Study article, the average age of patients with VT was 58. In contrast, half of the VT patients in the HUNT 2 study were 70 years old or older. Like many other autoantibodies, ACA, particularly at low titers, are more common in older individuals and may not have much clinical significance in this population. In an analysis of 1000 European APS patients, only 13% were diagnosed after the age of 50.2 The third population-based report, from the LITE study, also did not find an association of ACA with VT.17 The median age of VT patients in this paper was 63. Cut-off values for ACA positivity were relatively low (IgG ACA >15 GPL and >23 GPL were both analyzed). In the earlier Ginsburg study, the elevated relative risk for VT was seen with IgG ACA levels ≥38 GPL. The association of ACA titer with thrombosis risk is well-established.18 The revised classification criteria for APS use an ACA cutoff of 40 U. Low levels of ACA, although statistically abnormal, may not be associated with a significant risk of thrombosis.

**Other Thrombotic Risk Factors in Patients With aPLs**

In evaluating patients with aPLs, other risk factors for thrombosis should be identified and modifiable risk factors should be addressed. Among individuals with persistent aPLs, only about one-third will experience a thrombotic event.
or other APS manifestations. Approximately half of aPL-positive patients with thrombosis have coincident non-aPL risk factors at the time of thrombosis. These risk factors include oral contraceptives, hormone replacement therapy, cigarette smoking, and inherited thrombophilias (eg, factor V Leiden, prothrombin 20210A, and methylenetetrahydrofolate reductase mutation). The combination of aPLs with one or more inherited risk factors significantly increased the risk of VT.

Pathophysiology of VT in APS

There is strong evidence that aPLs are not an epiphenomenon but directly contribute to a thrombotic diathesis. Extensive studies have been performed using a murine passive transfer model of aPL-mediated VT developed by Pierangeli and colleagues. In this model, aPLs or control antibodies are transferred to a mouse via intraperitoneal injections and plasma levels of aPLs comparable to those seen in APS patients are achieved. The animal is then anesthetized, the femoral vein is surgically isolated and transilluminated, and a controlled “pinch” or laser-induced injury is administered to the vessel. This injury induces thrombus formation and thrombus size, and kinetics are measured. In animals receiving aPLs, thrombus size and persistence are markedly increased, as compared to animals receiving the control antibody. To understand the molecular mechanisms involved in aPL-mediated thrombosis, various gene “knockout” mice and pathway inhibitors have been studied in this model. For example, thrombosis is mediated by endothelial adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin), complement activation, p38 mitogen-activated protein kinase, and nuclear factor-κB.

The effects of aPLs on various coagulation and hemostatic pathways have also been studied, and numerous mechanisms of aPL-mediated thrombosis have been suggested. Data from a number of research groups suggest that aPLs have a procoagulant effect by inhibiting the anticoagulant protein C pathway. Consistent data also suggest that aPLs act by upregulating the expression of tissue factor (TF). TF, a high-affinity receptor and cofactor for factor VII/VIIa, is the procoagulant effect by inhibiting the anticoagulant protein C pathway. Consistent data also suggest that aPLs act by upregulating the expression of tissue factor (TF). TF, a high-affinity receptor and cofactor for factor VII/VIIa, is the physiological trigger of normal blood coagulation and, in many cases, of thrombosis. In vitro, aPLs induce TF expression and activity on normal monocytes and vascular endothelial cells. In vivo, TF expression is increased on monocytes from APS patients. In SLE patients, monocytocyte TF expression is increased and strongly associated with aPLs. In the murine model of aPL-mediated thrombosis, aPLs induce TF activity in carotid arteries and peritoneal cells. In many of these studies, anti–β2GPI antibodies have been specifically implicated. APS patient sera and purified IgG have also been shown to upregulate TF on normal human neutrophils.

Management of VT in APS

The treatment of acute VT in patients with APS is the same as for other patients with VT. Anticoagulation with unfractionated heparin or low-molecular-weight heparin, followed by warfarin is the standard of care. Longer term, the intensity and duration of warfarin anticoagulation necessary to prevent recurrent thrombosis in APS are important issues. Retrospective studies of APS patients suggest that high-intensity treatment with an international normalized ratio (INR) ≥3.0 is more effective than less intensive regimens. However, two more recent randomized controlled trials found that high intensity treatment (INR 3.1 to 4.0) was no better than moderate intensity (INR 2.0 to 3.0). In most cases, moderate intensity anticoagulation is now the standard of care. In a recent review, Ruiz-Irastorza and colleagues recommended a target INR of 2.0 to 3.0 for APS patients after a first VT and >3.0 after a recurrent VT. It should be noted that these retrospective and prospective studies included both patients with VT and arterial thrombosis. It is not known whether larger studies separating these two groups would yield similar results.

An important issue in monitoring warfarin therapy in APS patients involves the reliability of INR determinations. In 6.5% to 10% of patients with LAC, aPLs may prolong the prothrombin time assay leading to an unreliable INR. To address this issue, it is helpful to validate the INR in individual patients using a coagulation assay that is not affected by aPLs, eg, a factor II activity assay. After an APS patient is on warfarin with a stable INR of 2.0 to 3.0, an INR and factor II activity assay should be checked simultaneously. If the INR is in range and the factor II level is therapeutic (approximately 15% to 25%), the level of anticoagulation is adequate and the INR is reliable. If the INR is in range but the factor II level is >30%, the level of anticoagulation is inadequate. For such a patient, an individualized INR target range corresponding to a therapeutic factor II level should be established, or the factor II level itself could be followed.

The duration of anticoagulation for VT in APS is also an important issue. The risk of recurrent VT in APS patients off anticoagulation is high, 10% to 29% per year according to one report. Another study found that the risk of recurrent VT after stopping anticoagulation was 50% at 2 years and 78% at 8 years. Based on these observations, long-term anticoagulation is generally recommended. In some APS patients, aPL tests may become persistently negative years after a thrombotic event. It is not known whether it is safe to discontinue anticoagulation in such patients.

In general, immunosuppressive drugs, such as corticosteroids, are not thought to be effective preventing recurrent VT associated with aPLs. Limited data from case reports suggest that rituximab may be helpful for resistant APS, but additional data are needed to recommend its use.

Primary Prevention of VT in Patients With aPLs

Individuals with persistently positive LAC or medium or high titer ACA/anti–β2GPI antibodies and without a history of thrombosis are identified in a number of clinical situations. These include SLE patients who are routinely screened for aPLs, women with aPLs and pregnancy loss, and patients incidentally found to have a positive LAC on routine coagulation screening reason. Many physicians recommend daily low-dose aspirin for such patients. However, in a recent prospective controlled trial low-dose aspirin was no better
than placebo in preventing a first thrombotic event. The overall incidence of thrombosis in this study was very low, and the majority of subjects with thrombosis had coexisting thrombosis risk factors. To prevent VT in aPL-positive patients it is important to consider such risk factors and modify them when possible, as previously discussed. In SLE, hydroxychloroquine may be useful in preventing an initial thrombotic event in aPL-positive patients.

Conclusions

APS is a relatively common acquired cause of VT in patients with SLE, as well as in the general population. aPLs, particularly LAC, are important thrombotic risks factors. Growing evidence demonstrates that aPLs, particularly anti-β2GPI, are not merely a marker of thrombophilia but are pathogenic, directly contributing to hypercoagulability. The mainstay of treatment for VT in APS is long-term anticoagulation. Key ongoing issues in the treatment of APS include the optimal intensity of warfarin treatment of APS include the optimal intensity of warfarin. Dr Roubey serves as a consultant for Quest Diagnostics.

Disclosures

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References


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