Antiphospholipid Antibody Syndrome: Often a Conundrum in Clinical Practice

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Introduction

Thrombosis is one of the common causes for hospital admission and emergency room visits.[1] Thrombosis is associated with significant morbidity and mortality. Hypercoagulability is a condition characterized by tendency to have thrombosis as a result of inherited and/or acquired defects.

The prevalence of hypercoagulable state is low in the general population but is greater in people with genetic predisposition.[2] Antiphospholipid antibody syndrome (APS) accounts for approximately 28% of cases with hypercoagulability conditions, followed by activated protein C resistance (25%) and malignancy (15%).[1] Other conditions associated with hypercoagulability states include pregnancy and medications. Geographic variations have been reported in APS as follows: Sweden 15%, Cyprus 13% and the Middle East 5%.[3,4]

Clinicians must have a high index of suspicion for APS in patients with multiple thrombotic episodes, idiopathic DVT, or spontaneous abortions. An investigation for antiphospholipid antibodies early at presentation is important as it may influence the course of the disease.

We present a discussion of a case, where a patient initially had negative lab work-up for APS but had positive clinical features. He developed positive lab work-up for APS during later years and was managed with optimum anticoagulation therapy and education of the patient.

Case Report

A 57-year-old Caucasian male presented to the emergency department with complaints of right upper arm pain and erythema. The pain was acute in onset, radiating towards his palm, and rated as 5/10 (10 being the most severe pain) with no aggravating or relieving factors. For the prior month, the patient had intermittent pain in his right upper arm, but he did not seek medical treatment as the symptoms resolved spontaneously.

The patient had a history of multiple hospitalizations. The first one was in 1970 when he was admitted for deep vein thrombosis (DVT) and placed on warfarin for three months. After a hospitalization in 2003 for pulmonary embolism, he was placed on lifelong warfarin therapy. He was re-admitted to the hospital in 2003 for DVT. He had a negative work-up for APS in terms of following lab parameters: APTT, lupus anti-coagulant, cardiolipin screen, and hexagonal phospholipid test. In 2010, he was diagnosed with APS with the following lab parameters: APTT of 48 seconds, lupus anti-coagulant was positive, cardiolipin screen was negative, and hexagonal phospholipid test was positive. He

underwent a right above knee amputation in 2012 secondary to ischemia. He was non-compliant with his medications from 2010 to 2013. Also suspecting warfarin resistance due to non-compliance or due to decrease sensitivity of vitamin K 2,3-epoxide reductase to warfarin, he was switched from warfarin to enoxaparin. The patient's father also had a history of recurrent clots.

On physical exam, the patient's right upper extremity was cool to touch, capillary refill was greater than ten seconds, and a purple discoloration of the skin extended from his fingertips to mid forearm. There was an inability to palpate a radial, ulnar, or brachial pulse of the right upper extremity. The left upper extremity had diminished, but had palpable pulses. There was no pain to palpation of either extremity. No clubbing or edema of either upper extremity was noted. A peripheral angiogram showed thrombi in the right brachial artery extending into right radial artery. He subsequently underwent suction thrombectomy along with tissue plasminogen activator infusion to the clot. A follow-up angiogram showed a patent right brachial artery. He was placed on heparin for twenty-four hours, then switched to enoxaparin sodium, and finally bridged to warfarin successfully.

At the time of his recent admission, lab values included hemoglobin of 12.9 g/L, white blood count of 11,100 cells/mcL, mean corpuscular volume of 93.8 fL, glucose of 90 mg/dL, creatinine of 0.96 mg/dL, fibrinogen of 390, INR of 1.1, and activated partial thromboplastin time of 61 seconds. Labs on discharge included hemoglobin of 12.3 g/L, creatinine of 0.87 mg/dL, blood urea nitrogen of 9 mg/dL, activated partial thromboplastin time of 25.5 seconds, prothrombin time of 10, and INR of 2.5. He was advised on discharged to continue warfarin of 5 mg per day, enoxaparin 120 mg per day, and atenolol of 50 mg per day, and follow-up with the surgical vascular clinic. His INR goal was set at 2.5-3.0. He was educated about the importance of being compliant with his management and follow up visits at time of discharge.

Discussion

APS is an autoimmune disease characterized clinically by hypercoagulable state.[4] Its diagnosis is confirmed by the presence of at least one type of antibody (lupus anticoagulant, anti-cardiolipin antibody, or anti-β2-glycoprotein-I anti-bodies) in the plasma, and the occurrence of at least one of the following clinical manifestations: venous or arterial thrombosis, or pregnancy morbidity[5] (see classification criteria in appendix). The antibodies are directed not only against the epitopes on plasma proteins that are uncovered or generated by the binding of these proteins to phospholipids, but also to phospholipid binding proteins.[6] Anti-phospholipid antibodies (aPL) can disturb both pro- and anticoagulant pathways. Screening for these antibodies should include at least two phospholipid dependent coagulation tests: activated partial thromboplastin time, diluted prothrombin time, and diluted Russell viper venom time to increase specificity (identify true negatives).[7] A mixing test should be done following abnormal screening and failure of correction of clotting time should be confirmed by demonstration of phospholipid dependence of the inhibitor (hexagonal phospholipid ethanolamine time).[8]

The exact pathogenesis of APS is unknown. However, proposed hypotheses include activation of endothelial cells by antiphospholipid antibodies, interference with functioning of phospholipid binding proteins involved in coagulation, or oxidant-mediated injury of vascular endothelium.[9] These antiphospholipid antibodies can be formed in the susceptible individual

secondary to infections, autoimmune disorders such as systemic lupus erythematosus or rheumatic disorder, or malignancy, such as colon cancer, prostate cancer, or leukemia leading to APS.[10,11] These antibodies bind to endothelial cells causing stimulation of adhesion molecule and creating a pro-thrombotic state.[9] Close association exists between systemic lupus erythematous and APS.[12,13] Keeling et al.[7] reported that patients with systemic lupus erythematosus who were lupus anticoagulant positive had a six times greater risk of having a thromboembolic event as compared to patients who were negative. Similarly, those with a positive cardiolipin antibody had twice the risk.

Given the broad clinical presentation of APS, primary and secondary prevention for thrombosis is crucial. However, two prospective randomized trials reported that recurrences of vascular event in a low intensity treatment group (INR of 2-3) was less as compared to those in the high intensity group (INR of 3.1-4).[14] Schluman et al.[15] and Kearon et al.[16] reported that the rate of recurrence of a thrombotic event is less if therapy is given for a longer duration of time. In both studies, bleeding was more in the high intensity group (INR 3.5-4). The Antiphospholipid Antibody and Stroke Study (APASS) showed aspirin (325 mg/day) and low-to-moderate anticoagulation were equally effective in patients with initial stroke irrespective of their antiphospholipid antibody status.[17] The current recommendation for the management for APS or DVT is to have a therapeutic INR of 2.5-3. The duration of therapy depends per individual case and the risk/benefit ratio.[14] Annual risk of bleeding within a therapeutic INR of 2-3 is 2%.[9]

The American College of Chest Physicians Guidelines[18] for arterial thrombosis is to treat with aspirin or low-to-moderate intensity anticoagulation (INR of 1.5-2.5). For cancer associated with DVT or pulmonary embolism, clinicians should treat for at least 3-6 months and preferably with long-term anticoagulation therapy, unless bleeding risk is very high. A pregnant patient with a history of recurrent pregnancy loss (< 10 weeks) should be screened for antiphospholipid antibodies. If positive, low molecular weight heparin and aspirin should be given throughout pregnancy. If there is a history of pre-eclampsia, low dose aspirin is recommended. If the thrombotic event recurs during warfarin therapy, despite INR levels that are within the target range of 2.0 to 3.0, then an alternate treatment could be low molecular weight heparin or anti-Xa therapy.

APS is present if at least one of the following clinical criteria and one of the laboratory criteria are met.[4] For vascular thrombosis, episodes of arterial, venous, or small vessel thrombosis must be present in any tissue or organ or plasma on two or more occasions at least 12 weeks apart. Thrombosis must be confirmed by objective and validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

For pregnancy morbidity, either one of three conditions must be present.[5] They include: (1) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10^{th} week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, (2) one or more premature births of a morphologically normal neonate before the 34^{th} week of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions, or recognized features of placental insufficiency, or (3) three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation,

with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes have been excluded.

Laboratory criteria for APS includes: (1) lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)[17], (2) anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e., > 40 GPL or MPL, or greater than the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, (3) anti-β_2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

Conclusion

Anti-phospholipid antibody syndrome is a pro-thrombotic condition but with varied clinical presentation.[19] Therefore, treatment needs to be individualized depending on the clinical presentation. Education regarding medication administration is essential. More research is required to understand the patho-physiology of this syndrome, to validate the criteria, and to identify optimal treatment.[20,21]

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Appendix

Revised Classification Criteria for the Antiphospholipid Antibody Syndrome[22]

Clinical criteria (one or more)

1. Vascular thrombosis: One or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring 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, pre-eclampsia or placental insufficiency; or c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation.

Laboratory criteria: (one or more, present on 2 or more occasions at least 12 weeks apart using recommended procedures)

1. Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Haemostasis.
2. Anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer (greater than 40 GPL or MPL, or greater than the 99th percentile), measured by a standardized ELISA
3. Anti-β2-glycoprotein-1 antibody of IgG and/or IgM isotype, present in titer greater than the 99th percentile, measured by an ELISA.

Current evidence-based guidelines for treatment[18, 22]

1. Venous Thrombosis
   Distal leg DVT:
   a) Severe symptoms: Treat with anticoagulants for three months
   b) No/mild/moderate symptoms: No anticoagulation needed

   Proximal leg DVT
   a) 3 months, unless idiopathic (long term)

   Cancer associated DVT or PE
   a) Treat for at least 3 months and preferably long-term, unless bleeding risk very high

   Arterial Thrombosis
   a) Aspirin or low/ moderate intensity anticoagulation (INR 1.5-2.5)
   b) In patients with atrial fibrillation; warfarin or aspirin + clopidogrel

It is recommended in the guidelines that patients who have had a first unprovoked (idiopathic/genetic) proximal DVT or pulmonary embolism be considered for long-term anticoagulation, independent of considerations such as the presence or absence of an identifiable genetic or acquired thrombophilia.[22] If the patient develops another event while being on warfarin or aspirin, there is evidence that they should be put on warfarin with higher INR or warfarin with aspirin.[18, 22]