Antiphospholipid Syndrome: Highlights for internal medicine physicians

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Abstract

This narrative review is an attempt to summarize the pathogenesis, diagnostic approach and latest guidelines for the treatment of antiphospholipid syndrome (APS) in adults. APS is a chronic autoimmune disease that is associated with the presence of antiphospholipid antibodies and is usually presented with thrombotic events or obstetric complications but can have other manifestations. Differential diagnosis can be challenging. Treatment options focus on antithrombotic medications and aim το prevent recurrent thrombotic events but also include immunosuppressants. Catastrophic antiphospholipid syndrome (CAPS) has a high mortality rate and is challenging to diagnose and treat. Laboratory tests for antiphospholipid antibodies should always be interpreted carefully according to clinical presentation. Finally, patients should be thoroughly informed and guided to lifestyle changes as well as compliance with necessary long term pharmacological therapy.

Key words: *Antiphospholipid syndrome; highlights; internal medicine*

INTRODUCTION

Antiphospholipid syndrome is a relatively rare disease. The overall estimated prevalence ranges between 40 and 50 cases per 100,000 worldwide [1]. It is a chronic autoimmune disease that is usually presented with thrombotic events or specific obstetric complications but can have other manifestations, as will be discussed later. It can be primary or secondary, mostly associated with systemic lupus erythematosus (SLE). Upon appropriate clinical suspicion, the diagnosis is confirmed by laboratory tests that detect the presence of antiphospholipid antibodies. Usually, lifelong treatment is necessary after initial rescue therapy.

MATERIALS AND METHODS

The aim of this literature review is to highlight the main aspects of the diagnostic approach and treatment of APS in everyday clinical practice of internal medicine physicians. The existing literature on the subject has been reviewed, including original research articles, reviews, books, as well as the latest EULAR/ACR (European Alliance of Associations for Rheumatology/American College of Rheumatology) guidelines.

Pathogenesis of APS

Pathogenesis of APS is not perfectly clear; however, it is believed that antiphospholipid antibodies play a key role. Antiphospholipid antibodies are a family of autoantibodies that recognize phospholipids or phospholipid-binding proteins. It is believed that the main target of antiphospholipid antibodies is β2 glycoprotein one (β2GPI), a normal plasma protein that binds avidly to phospholipid membranes. This connection is even stronger when β2-GPI is dimerized by binding to its antibody (anti- β2-GPI). This connection on a membrane surface is believed to cause activation of endothelial and inflammatory cells and finally lead to thrombosis. Some

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of the assumed mechanisms include increased expression of prothrombotic molecules, such as E-selectin and tissue factor (TF), as well as complement pathway activation and reduced activation of protein C [2,3]. Monocytes, neutrophils, and platelets are some of the involved cells. The result is thrombosis, which causes most of the clinical presentations of APS. Thrombotic events in trophoblast, decidua, or placenta can cause specific obstetric complications.

DIAGNOSTIC APPROACH

Antiphospholipid antibodies

In the appropriate clinical context, the diagnosis of APS is based on the detection of antiphospholipid antibodies in the patient's plasma. The three types of detectable antiphospholipid antibodies in everyday clinical practice are lupus anticoagulant (LA), anti-β2GPI and anti-cardiolipin (antiCL) antibodies. Their presence is not always clinically significant. They can be transiently present in almost 10% of the healthy population, according to some surveys [2]. Antiphospholipid antibodies can also be transiently detectible during infections such as syphilis [4]. Therefore, tests for antiphospholipid antibodies should be requested only when there is clinical suspicion of APS or as part of expert follow-up or investigation of patients with SLE as guidelines suggest. The interpretation is not always simple and should be discussed with a rheumatologist.

Among the three (LA, anti-β2GPI and antiCL), the LA is the most clinically significant in that it has the greatest statistical and seemingly pathogenetic correlation with thrombotic and other events of the disease. Unfortunately, the LA test can be unreliable (mostly false positive) when the patient is on anticoagulant medication, which can often lead to diagnostic problems. LA is an "anticoagulant" in vitro in that it prolongs aPTT (activated Partial Thromboplastin Time). A specific three-stage test should be performed in experienced laboratories to detect Lupus Anticoagulant, but prolonged aPTT measured before anticoagulant treatment could be useful to suspect LA presence in the appropriate clinical context. Anti-β2GPI and antiCL antibodies are usually detected using the ELISA (Enzyme-linked Immunosorbent Assay) method, which is not influenced by the possible administration of anticoagulant treatment. Now, what antiphospholipid profile is considered high-risk? Is of high risk in the presence (in at least two measurements at least 12 weeks apart) of LA or triple positivity or double positivity (any combination of LA, anti-β2GPI, antiCL) or persistent high titres of antiphospholipid antibodies. On the contrary, low-to-moderate titres of isolated anti-β2GPI or antiCL are considered low-risk, especially if they are transient [5]. IgG antibodies are more clinically significant than IgM, while IgA have unknown clinical significance.

Clinical presentation

Typical clinical presentations include thromboses (arterial or venous) and specific obstetric complications (included in Sapporo Classification Criteria for APS) [6]. Therefore, APS is usually categorized as thrombotic or obstetric. A history of obstetric APS is supposed to present a lower risk for thrombotic events and is mostly associated with the risk of complications in future pregnancies. Thromboses can be arterial or venous, possibly affecting blood vessels of any size, including microthrombotic lesions that require a biopsy of the affected tissue to be confirmed. The most common affected blood vessels are the same as in the general population, causing strokes, deep venous thromboses or pulmonary embolism. As far as obstetric complications are concerned, according to the revised Sapporo classification criteria and latest guidelines, only specific presentations should raise clinical suspicion. An unexplained spontaneous abortion or fetal death after the 10^{th} week of gestation requires exclusion of APS, while one spontaneous abortion before the 10^{th} week of gestation is not uncommon and is usually caused by chromosomal abnormalities of the fetus. Three or more consecutive spontaneous abortions before the 10^{th} week of gestation though, do require investigation. Maternal causes such as anatomical or hormonal disorders should always be excluded by the gynecologist. Another criterion is premature birth (before the 34^{th} week of gestation) caused by placental insufficiency, eclampsia, or severe pre-eclampsia. For a definite diagnosis, according to the revised Sapporo classification criteria, at least one confirmed thrombosis or one obstetric criterion must be positive in combination with at least one type of antiphospholipid antibodies (LA, anti-β2GPI or antiCL) detected at least two times at least 12 weeks apart.

However, there are other possible clinical manifestations of APS that are not included in the Sapporo Classification Criteria. These include hematologic disorders such as thrombocytopenia, usually mild (>50,000 platelets per mm^3) with or without thrombotic microangiopathy, as well as hemolytic anemia, either due to thrombotic microangiopathy or immune mediation.

Hemorrhage is uncommon. Renal manifestations are also caused by thrombotic microangiopathy and can be acute or chronic. The heart can also be affected; Libman–Sacks endocarditis usually affects the mitral or the aortic valve. Skin is sometimes affected as well, with livedo reticularis or racemosa being the most common presentation. Neurologic manifestations of the central nervous system (in the absence of stroke) are less common but possibly severe and challenging to diagnose. The 2023 ACR/EULAR classification criteria for APS [7] are generally more inclusive than Sapporo criteria, but stricter as far as obstetric complications are concerned, with placental insufficiency or severe pre-eclampsia being necessary to meet criteria.

Considering all the possible presentations listed above, when should a physician suspect APS? Mostly as part of the investigation of recurrent thrombosis or thrombosis in an uncommon vessel or unprovoked thrombosis at a young age. The obstetric complications that require investigation for APS are listed above. Moreover, mild thrombocytopenia or prolonged aPTT can cause further clinical suspicion. Clinical history and physical examination can also suggest underlying SLE or other rheumatic diseases (Table 1). The involvement of multiple organs or systems should be investigated. Livedo-like skin lesions, even though not specific, are quite typical and should raise suspicion for APS. On the contrary, in the absence of organ involvement or any of the clinical presentations described above, laboratory testing for antiphospholipid antibodies is not recommended as part of screening, except for SLE patients.

Catastrophic APS (CAPS) is characterized by rapid development of clinical presentations, typically within seven days, and multi-organ involvement (>=3), typically including histopathologically confirmed thrombotic microangiopathy and SIRS (Systemic Inflammatory Response Syndrome). The laboratory criterion for APS (persistent antiphospholipid antibodies) must be met. Manifestations may include acute renal failure, ARDS (Acute Respiratory Distress Syndrome), diffuse alveolar hemorrhage, encephalopathy and adrenal hemorrhage. Mild thrombocytopenia is common [10]. CAPS has a high mortality rate (20-45%) [8,9]. Therefore, an aggressive treatment approach is needed. Hemorrhagic complications can cause challenges in treatment decisions, considering the cost-benefit balance of administering anticoagulant medication. These are rare (<1% of APS cases) and relapses are uncommon. It is possibly triggered by treatment discontinuation, malignancy, infections, pregnancy, exogenous estrogens, trauma, surgery or SLE flare. In the differential diagnosis of CAPS, other forms of thrombotic microangiopathies must be considered e.g. hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia or diffuse intravascular coagulation [10], which may also be associated with underlying infections or malignancies. When CAPS is the first clinical presentation of APS, differential diagnosis is even more challenging.

Table 1. *Common "red flags" raising suspicion for APS.*

Recurrent or multiple thromboses
Thrombosis of uncommon blood vessel
Unprovoked thrombosis at a young age
Placental insufficiency or severe pre-eclampsia or eclampsia
Livedo reticularis or racemosa
SLE diagnosis
Prolonged aPTT
Mild thrombocytopenia

MANAGEMENT

Management includes antithrombotic treatment of acute clinical presentations, long-term treatment to prevent relapses, with specific guidelines for obstetric APS and a more aggressive approach, including immunosuppressants, for manifestations that are not included in the Sapporo classification criteria, such as renal involvement, hematologic disorders, and CAPS.

It must be emphasized that management includes much more than pharmacological therapy. Patients diagnosed with APS should be thoroughly informed and guided to make lifestyle changes and, in collaboration with their attending physicians, attempt to eliminate modifiable risk factors for thrombotic events, such as smoking, hypertension and hypercholesterolemia. Moreover, exogenous estrogens (e.g., oral contraceptives or hormone replacement therapy) should be avoided and aggressive prophylactic perioperative anticoagulant treatment should be administered. Recommended vaccination schedules should also be followed. These methods of prevention also apply to asymptomatic people with a high-risk antiphospholipid antibody profile. If APS is secondary, the underlying rheumatic disease should also be treated and closely monitored [2].

Thrombotic APS

According to the 2019 EULAR guidelines [5], even asymptomatic people with a high-risk antiphospholipid antibody profile should be prescribed with a low dose of aspirin (75-100mg daily), indefinitely (primary prevention).

In case of thrombotic APS with a history of venous thrombosis, after initial anticoagulant treatment (usually LMWH (low-molecular-weight heparin), vitamin K antagonists (such as warfarin) should be administered long-term, with target INR (International Normalized Ratio of Prothrombin Time) 2-3. If the thrombotic event was provoked, e.g. after surgery, there is less data to support indefinite anticoagulant therapy. At this point, it should be emphasized that DOACs (Direct-acting Oral Anticoagulants) are not part of the treatment options for APS, as data is insufficient. The existing trials are negative; rivaroxaban failed, specifically for triple-positive APS patients [11].

When the diagnosis of APS is based on arterial thrombosis, the main treatment approach is the same, except for the option to target INR 3-4 or to co-administer aspirin with vitamin K antagonists, especially if the patient is considered high-risk. In high-bleeding-risk, frail, elderly patients with unclear diagnosis (low-risk antiphospholipid antibody profile) after a stroke, monotherapy with aspirin could be considered. Relapse, as far as thromboses are concerned, is defined as a recurrent thrombotic event that is diagnosed while the patient is on proper anticoagulant treatment and reaching the target INR. If the patient had previously discontinued the anticoagulant treatment or INR is below target for any reason, then a new thrombotic event should not necessarily lead to treatment reevaluation and escalation. In case of true relapse besides treatment, therapeutic options include adding aspirin to warfarin (double antithrombotic therapy), increasing the target INR from 2-3 to 3-4 and switching to parenteral heparin.

Obstetric APS

As far as obstetric APS is concerned, treatment is necessary during future pregnancies. Moreover, for women with a history of obstetric APS, indefinite prophylaxis with low-dose aspirin is generally recommended. A prophylactic dose of LMWH is also recommended for the puerperium period (at least six weeks postpartum). During pregnancy, double antithrombotic therapy is recommended; with the co-administration of aspirin with LMWH (in prophylactic dose for women with a history of obstetric APS, especially with fetal death, or in therapeutic dose for women with a history of thrombotic APS). Vitamin K antagonists are of course contraindicated during pregnancy because of their teratogenicity. There is less evidence to support obstetric guidelines for asymptomatic women with high-risk antiphospholipid antibody profile, but aspirin should be considered during pregnancy [5].

Treatment beyond antithrombotic medication

Some manifestations of APS, most of which have an underlying pathogenetic mechanism of thrombotic microangiopathy, require immunosuppressive treatment.

Hematologic complications, specifically hemolytic anemia and severe thrombocytopenia (<20,000 platelets per mm^3), can be treated with high-dose glucocorticoids, IVIG (intravenous immunoglobulin) or rituximab (an anti-CD20 monoclonal antibody). Other options include cyclophosphamide, azathioprine and MMF (mycophenolate mofetil). Splenectomy is generally avoided, because surgery in patients with APS is a potential trigger for further thromboses or even CAPS.

Antiphospholipid-antibody-related nephropathy is less studied. It can be chronic or acute. In case of acute renal failure, plasmapheresis is recommended. Treatment options also include rituximab, eculizumab (anti-C5 monoclonal antibody) or conventional immunosuppressants such as MMF or azathioprine.

Livedo reticularis or racemosa or livedoid vasculopathy, with skin ulcers, is difficult to treat. Glucocorticoids are generally ineffective. Some therapeutic options are antiplatelet treatment (aspirin, clopidogrel, dipyridamole), sildenafil, thrombolysis e.g. with alteplase, and hyperbaric oxygen therapy.

Catastrophic antiphospholipid syndrome, because of its severity, is aggressively treated with intravenous pulses of glucocorticoids (followed by high-dose continuous treatment), parenteral anticoagulants (classic heparin intravenously) and plasmapheresis or IVIG. Refractory CAPS can be treated with rituximab or eculizumab. Underlying infections should also be treated. Therapeutic decisions can be challenging in case of severe infections or active bleeding [2].

CONCLUSIONS

APS may be challenging to diagnose, partly because of possible non-thrombotic or microangiopathic manifestations that may require histopathological confirmation. Moreover, laboratory findings, specifically

antiphospholipid antibody tests, can be difficult to interpret, especially if they are transiently positive. Reevaluation and exclusion of other underlying conditions, such as infections or malignancies, is usually necessary. Underlying rheumatic diseases such as SLE should also be investigated. CAPS is a rare presentation of the disease but should be considered in the differential diagnosis because it requires urgent aggressive treatment, considering its high mortality.

Treatment is based on antithrombotic agents, but many manifestations require immunosuppressive therapy. Regulating the modifiable traditional risk factors for cardiovascular disease as well as necessary vaccinations are part of the disease management approach. Finally, patients with APS, as most patients with chronic disease, should be informed about the importance of lifestyle changes along with complying with long term pharmacological treatment and medical follow-up.

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