ANTIPHOSPHOLIPID (HUGHES) SYNDROME

INTRODUCTION

In 1983, Hughes et al describe a syndrome characterized by arterial and venous thrombosis, recurrent foetal wastage, and thrombocytopenia, which were seen in a subset of patients with systemic lupus erythematosus (SLE). It was also showed that this syndrome was characterized by the presence of a family of autoantibodies called antiphospholipid antibodies (aPL). aPL were directed against anionic phospholipids of the prothrombin activator complex of the coagulation cascade. This syndrome was originally named the anticardiolipin syndrome, and is now more appropriately called the antiphospholipid syndrome (APS). The term primary APS (in contradistinction to APS secondary to SLE or other SLE-like disorders) is used for patients with APS who do not have underlying SLE or any other connective tissue disorder. According to some workers, APS is the most common form of acquired hypercoagulable state.

Clinical features

The major clinical features of APS include:

- Recurrent venous and/or arterial thrombosis.
- Recurrent foetal loss, usually at >1- weeks of gestation and other adverse pregnancy outcomes.
- Thrombocytopenia (usually mild and subclinical) and/or haemolytic anaemia.

Major thrombotic presentations of APS

The major presentation patterns identified are the following:

1. Deep venous thrombosis (DVT) with/without pulmonary embolism.
2. Coronary or peripheral arterial thrombosis.
3. Cerebrovascular-retinal vessel thrombosis.
4. Patients presenting with mixtures of the above.
DVT with/without pulmonary embolism

DVT is the most common presentation of APS, both in the lower and/or upper extremities. The DVT’s are often recurrent, multiple, bilateral, and with propensity for pulmonary embolism. Skin and subcutaneous tissue changes characteristically associated with chronic venous stasis (e.g. atrophic skin with loss of appendages and/or chronic leg ulcers) may be present. Other reported venous thromboses include renal vein thrombosis, hepatic vein thrombosis causing Budd-Chiari syndrome and hepatic veno-occlusive disease, portal vein thrombosis with non-cirrhotic portal hypertension, and mesenteric vein thrombosis with features of acute bowel infarction or a more subtle presentation with non-specific abdominal discomfort and small amount of bloody ascites. Inferior vena cava block may also occur. Vena caval thrombosis may produce features like distended neck veins, congested liver and generalized oedema that may be confused with congestive heart failure and/or pericarditis with tamponade. Small veins (adrenal veins, central retinal vein) may also get occluded producing specific syndromes.

Arterial thrombosis

Arterial thrombosis associated with APS may present with a wide variety of clinical manifestations depending upon the site of thrombosis. These would include isolated occlusions in the peripheral arteries or coronary arteries. Blocks in the carotids might cause transient ischemic attacks or focal paralysis. Aortic arch syndrome, digital gangrene, aortic occlusion with ischemic claudication for lower limbs, renal arterial involvement with renal hypertension, involvement of arteries in the leg with absent dorsalis pedis and/or posterior tibial arterial pulses, with resulting cyanosis or gangrene of toes, have all been reported. Involvement of proximal and distal aorta producing features of Takayasu arteritis has brought up the possibility of this being a disease of aortic thrombotic involvement rather than being a primary inflammatory arthritis. Mesenteric blocks with clinical features of acute small bowel infarction or ischemic colitis have also been reported. Small arteries in the extremities can also be involved, and nailbed lesions resembling “splinter haemorrhages” may appear. With APS having a propensity to involve the heart these “splinter hemorrhages” may cause confusion between it and infective endocarditis.
Cerebral and/or retinal thrombosis

Cerebral (intracranial) thrombosis can cause a variety of neurologic deficits, which has been described in APS. These include:

- Focal ischemia producing transient ischemic attacks or infarctions and related neurological syndromes
- Multiple small vessel occlusions producing multi-infarct dementia or ischemic encephalopathy
- Cerebral venous thrombosis including sagittal sinus or cavernous sinus thrombosis
- Focal neurologic syndromes including transverse myelitis
- Migraine-like headaches due to benign intracranial hypertension
- Diverse other neurologic disorders such as seizures, chorea, Guillain-Barre syndrome, pseudo-multiple sclerosis and acute subdural hematoma.

APS associated rare syndromes like Sneddon’s syndrome (livedo reticularis, ischemic stroke and occasional arterial hypertension) and Dego’s disease (multisystemic vasculopathy with thrombosis of skin, gastrointestinal and central nervous system) have also been reported. Embolic stroke secondary to APS-related deposition of thrombus on heart valves and APS-related Libman-Sacks endocarditis has been documented extensively. APS is clearly associated with retinal vaso-occlusive disease and optic neuritis, with transient partial or complete visual loss, diplopia, and field defects. These defects may be monocular or binocular.

ADVERSE PREGNANCY OUTCOMES

Adverse pregnancy outcomes include:

- Recurrent foetal wastage (occluding at > 10th week of gestation)
- Abortions
- Foetal growth retardation
- Pre-eclampsia, which is the second most common clinical presentation of APS.
Placental vascular thrombosis has been implicated in the syndrome of recurrent foetal lost. This suggests that foetal wastage and growth retardation could also be related to thrombosis of placental vessels with consequent ischemic damage of the foetus. It has been estimated that there is 50% change of fetal wastage in pregnancies in those patients with significant titres of lupus anticoagulant (LAC) or IgG class of anticardiolipin (aCL) antibody. Less common is maternal thromboytopenia or thrombosis seen in this presentation. An unusual post-partum syndrome of spiking fever, pleuritic chest pain, dyspnea, patchy pulmonary infiltrates, pleural effusion, cardiomyopathy and ventricular arrhythmia can occur with APS.

**APS ASSOCIATED THROMBOCYTOPENIA AND/OR AUTOIMMUNE HEMOLYTIC ANEMIA**
Thrombocytopenia is a known haematological manifestation of SLE. Trombocytopenia is included as diagnostic criteria for APS. The thrombocytopenia associated with APS is usually not severe enough to cause bleeding. Autoimmune haemolytic anaemia may occur in isolation or in association with thrombocytopenia (the latter being called Evan’s syndrome) and has been reported in the presence of anticardiolipin antibodies or LAC.

**OTHER CLINICAL ASSOCIATIONS OF APS**
There are a variety of other distinct clinical manifestations where APS has been implicated namely:

**Dermatological lesions**
Livedo reticularis (cutaneous vascular stasis with cyanosis due to thrombosis of deep dermal vessels causing appearance of reticular pattern of vessels in the skin), is the most specific lesion. Other lesions include chronic leg ulcers near the medial malleolus, cutaneous necrosis and infarcts, splinter hemorrhages under the nails, livedoid mottling, palpable purpuric vasculitis, and other forms of vasculitis. Pseudovasculitis lesions (with clinical picture mimicking that of skin vasculitis but biopsy not showing vasculitis) have
also been implicated as possible manifestations of APS. Digital gangrene can also present in APS.

**Cardiac lesions**
Coronary thrombosis with myocardial infarction can occur either prematurely or in premenopausal women. Valvular lesions with endocarditis like vegetations (Libman-Sacks endocarditis) causing valve thickening are fairly common, making APS (with or without SLE) an important cause of valvular heart disease, next only to rheumatic heart disease. The cardiovascular features of APS, which include:

- Cardiac murmurs
- Valvular vegetations
- Fever
- Splinter haemorrhages, may mimic those of infective endocarditis.

**Osteonecrosis**
Osteonecrosis of the femoral neck and other bones is not uncommon in patients with SLE. Of the several possible causes of osteonecrosis, thrombosis of the nutrient arteries due to APS has been mentioned as one.

**Lung conditions**
Possible associations with APS include:

- Primary pulmonary hypertension
- Fibrosing aveolitis
- Pulmonary capillaritis with alveolar hemorrhage

**Renal lesions**

- Renal thrombotic microangiopathy
- Renal artery stenosis
- Renal infarct producing renal hypertension
- Renal vein thrombosis with SLE with or without APS has also been reported.
Addison’s disease
There are a number of reports of Addison’s disease with APS, with occlusion of the adrenal vessels being the most likely cause.

Vasculitis in APS
- Cutaneous leucocytic vasculitis
- Cogan’s syndrome
- Polyarteritis nodosa-like vasculitis has been reported in APS.

Various other varieties of vasculitides have also been described. However, an important point to note is that as a rule, the occurrence of cerebral vasculitis in APS (with or without SLE) is distinctly uncommon.

Catastrophic APS
This is a rapidly progressive lethal form of APS with widespread vascular occlusion in multiple organs. The syndrome can closely mimic other conditions like systemic forms of necrotizing vasculitis, disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP). These can however be differentiated hematologically, since high platelet counts would occur in systemic vasculitis, low platelet counts with increased fibrinogen degradation products in urine (the hallmark of DIC), and low platelet counts with schistocytes and helmet cells would be seen in microangiopathic anemia of TTP.

SERUM MARKERS OF APS: ANTIPHOSPHOLIPID ANTIBODIES
The characteristic serum markers of APS are a family of autoantibodies reactive against different anionic phospholipids, and are required in the formation of prothrombin activator complex (PAC) of the blood coagulation cascade. These antibodies are anticardiolipin antibodies (aCL), lupus anticoagulant (LAC), biologically false positive serological test for syphilis (BFP-STS), and antibodies against cofactors associated with anionic phospholipid.

Secondary antiphospholipid syndrome:
Connective tissue diseases

- Systemic lupus erythematosus
- Undifferentiated connective tissue disease
- Discoid lupus
- Systemic sclerosis
- Primary Sjögren’s syndrome

Systemic inflammatory arthritides

- Rheumatoid arthritis
- Ankylosing spondylitis

Other immunological diseases

- Chrohn’s disease
- Systemic vasculitis disorders including leucocytoclastic vasculitis, giant cell/polymyalgia rheumatica syndrome
- Idiopathic thrombotic purpura
- Behcet’s disease
- Several others

In association with malignancy

- Lymphomas and leukemias
- Solid tumors e.g. renal-cell carcinoma, carcinoma lung, ovarian cancer
- Trousseau’s syndrome, others

Drug-induced aPL

- Oral contraceptives
- Quinine, quinidine*
- Phenytoin, procainamide
- Hydralazine
- Beta-blockers
- High dose interferon

*Although drugs may induce APL, development of actual clinical APS has only been reported with phenothiazines and oral contraceptives. It is possible that patients with underlying genetic abnormalities may develop clinical features while taking drugs that are known to induce aPL.

From among these marker autoantibodies, aCL and anti-β2GP1 are seen most often, followed in decreasing order of frequency by LAC and BFP-STS. There could be patients having only one, or any two, or all three of the above antibodies in their serum. The prevalence of LAC in the normal population is about 2% with about 0.2% showing high titres. It is unclear whether or not such apparently normal individuals are at greater risk for thrombosis.

**Interpretation of aCL and LAC levels**

Standardization of the anticardiolipin test recommend that the result be expressed in “phospholipid units” and the results be interpreted as follows:

- Below 5 units : Negative
- Between 5 to 20 units : Low positive
- Between 20 and 60 units : Moderate positive
- Above 60 units : High positive

Although there is no such “international standard” available for LAC, traditionally, the interpretation is as follows:

- Below 0.17 units : Negative
- Between 0.17-0.29 units : Low positive
- Between 0.3-0.7 units : Medium positive
- Above 0.7 units : High positive
Moderate to high levels of aCL and/or LAC seems to correlate with clinical manifestations of thrombosis and foetal loss.

**DIAGNOSTIC CRITERIA FOR APS**

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Laboratory</th>
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<tr>
<td>Venous thrombosis</td>
<td>IgG aCL in moderate/high levels</td>
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<tr>
<td>Arterial thrombosis</td>
<td>IgMaCL in moderate/high levels</td>
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<tr>
<td>Fetal loss</td>
<td>Positive LAC test</td>
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<td>Thrombocytopenia</td>
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At least one criteria each from clinical and laboratory categories must be present and aPL test must be found positive on at least two occasions, more than three months apart, for the diagnosis of APS.

**TREATMENT OF APS**

APS is a relatively recent discovery and controlled therapeutic trials in this disease are few and far between. Like other systemic inflammatory rheumatic and autoimmune diseases, it is a chronic illness with fluctuating course. Under the circumstances, most of the therapeutic recommendations are based on limited, and often anecdotal, clinical experience.

**General therapeutic recommendations**

1. Thromboembolic manifestations of APS

   Patients with thromboembolic manifestations of APS need acute anticoagulation with heparin (keep the activated partial thromboplastin time (APTT) 1.5 to 2 times above the patient’s pre-heparin APTT). This is usually achieved with heparin in a dose of approximately 1000 units per hour. (Note: In about 40% of APS patients who have prolonged baseline APTT due to presence of LAC in their serum, this method of monitoring of heparin dose cannot be used. In such situations, actual measurements of
blood heparin levels or low molecular weight heparin that does not require monitoring of APTT can be used. Patients are simultaneously started on oral anticoagulation with warfarin in the dose of 5 to 10mg per day). Combined therapy is given for 5 to 7 days, by which time the INR reaches therapeutic levels. While warfarin is continued for prolonged periods, heparin is discontinued. The effects of added aspirin (or other antiplatelet aggregants) for further improvement of results (or increases the risk of bleeding) has not yet been adequately studied.

It has been shown that steroids and/or immunosuppressive therapy have little to offer in APS and are therefore not recommended. These agents may be required for treating certain manifestations of SLE or other underlying diseases in patients with SAPS.

2. Recurrent foetal wastage:

It is recommended that low dose aspirin (75-150mg/d) should be given in the preconception period, switching over to low-dose heparin (5000 units SC 12-hourly) at diagnosis of pregnancy and carrying it through delivery. After delivery, the patient should be switched back to long-term low dose aspirin therapy. Significant haemorrhage is unlikely with this regime but good protection is provided in the peripartum period.

3. Thrombocytopenia/haemolytic anaemia:
Thrombocytopenia may not require any specific therapy since it is subclinical in most patients. In patients with clinical manifestations of thrombocytopenia and in those with haemolytic anaemia, corticosteroids remain the standard line of therapy. Anticoagulation has a role in corticosteroid resistant thrombocytopenia.