The antiphospholipid antibody syndrome: diagnosis, skin manifestations and current therapy

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ABSTRACT

Antiphospholipid antibody syndrome is characterized by venous and/or arterial thrombosis and/or pregnancy morbidity associated with antiphospholipid antibodies (aPL), such as anticardiolipin antibodies, anti beta 2 glycoprotein I antibodies and positive lupus anticoagulant test. This syndrome may potentially affects any organ system including the skin.

Livedo reticularis is the most frequently observed cutaneous lesion; other lesions, by order of frequency, are ulcerations, digital gangrene, subungueal splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, extensive cutaneous necrosis and primary anetoderma. Skin lesions are more frequently observed in the catastrophic antiphospholipid syndrome, characterized by widespread microvascular occlusions involving multiple organs simultaneously.

Patients with antiphospholipid associated thrombosis should receive long-term oral anticoagulants. The intensity of anticoagulation should be guided according to the nature of the thrombotic event (venous vs. arterial thrombosis). Patients with aPL-associated pregnancy morbidity should be treated with aspirin plus heparin and closely monitored during pregnancy.

The treatment of the catastrophic antiphospholipid syndrome remains unsatisfactory. High dose intravenous steroids and parenteral anticoagulation should be supplemented by intravenous gammaglobulin and repeated plasma exchanges using fresh frozen plasma early on in the course of the syndrome.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease with multifactorial etiology resulting from both genetic and environmental factors. It is characterized by the presence of venous and/or arterial thrombosis and/or pregnancy morbidity and the presence of antiphospholipid antibodies (aPL). It can appear either as isolated entity (primary APS) or in the context of other disease most commonly systemic lupus erythematosus (SLE). Mandatory for diagnosis of APS is the presence of a clinical finding in association with at least one laboratory criterion persistently positive.

In addition to vascular and obstetric manifestations there are other clinical findings, which are not included in the classification criteria, for example livedo reticularis, Libman-Sacks endocarditis, premature atherosclerosis, renal microangiopathy, thrombocytopenia and haemolytic anemia.

Over the last years the so called "catastrophic" syndrome (CAPS), characterized by multiple thrombotic events, above all at microvascular level, and an elevated mortality rate, has also been defined.

This review is focused on some relevant aspects of APS such as classification criteria, cutaneous manifestations, CAPS and treatment.

The diagnosis of APS

The preliminary classification criteria for definite APS were published in 1999 (1) but new clinical and laboratory insights have been recently addressed during the *ad hoc* Workshop held within the framework of the XIth International Congress on Antiphospholipid Antibodies (Sydney, 14-18 November 2004). This Workshop defined "criteria" and "non-criteria" features of APS

The recognized independent clinical criteria are one or more episodes of venous, arterial or small vessel thrombosis and/or pregnancy morbidity. Thrombosis can occur anywhere within the vascular tree and must be confirmed

by imaging techniques, Doppler or histopathology. Moreover additional factors contributing to thrombosis should be assessed and APS patients should be stratified according to the presence or absence of other risk factors. Pregnancy morbidity was instead defined as follows: 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 deaths at or before the 34th week of gestation because of severe preeclampsia, eclampsia or placental insufficiency or c) three or more unexplained consecutive abortions before the 10th week of gestation (anatomic, hormonal or chromosomic causes should be excluded). Other clinic conditions such as cardiac valve disease, livedo reticularis, thrombocytopenia, haemolytic anemia, renal microangiopaty, etc, although frequent in patients with APS, should be considered as non-criteria.

As far as laboratory criteria concerns, despite decades of extensive work in the understanding of the etiopathogenesis of APS, few biomarkers have been validated and widely accepted for this disease.

Relevant laboratory tests recommended as criteria for definite APS are lupus anticoagulant (LA) assay, anticardiolipin (aCL) IgG or IgM (medium to high positive titres) and IgG, IgM anti-β2-glycoprotein I (a β2GPI).

Lupus anticoagulant prolongs coagulation steps *in vitro* by interfering with binding of coagulation factors to phospholipid, it doesn't affect activities of individual coagulation factor and is rarely associated with bleeding. It's a functional assay which measures the ability of IgG, IgM or mixture of both autoantibodies that recognize plasma proteins (mainly β2GPI and prothrombin) bound to anionic surfaces (phospholipid dependent) to inhibit the conversion of prothrombin to thrombin and therefore affecting clot formation in vitro. *In vivo* LA is vice versa associated to clotting tendency. The LA must be investigated according to the guidelines of the International Society for Thrombosis and Haemostasis Standardization Subcommittee (ISTH-SSC) (2).

The aCL antibody test utilizes cardiolipin (negatively charged phospholipid) as an antigen in solid-phase immunoassays although the majority of aCL antibodies are directed against plasma proteins bound to anionic phospholipids, mainly β2GPI. β2GPI molecule is a glycosylated membrane adhesion glycoprotein present in blood plasma which exhibits anticoagulant property *in vitro* and immunogenic *in vivo*. Before the conference of Sydney, LA and aCL were the only laboratory test recognized for diagnosis of APS because the lack of standardization data and of validating studies did not support the use of a β2GPI as classification criterion. With the Sydney meeting, a β2GPI IgG and/or IgM antibodies (revealed by standardized ELISA) are considered an independent risk factor for thrombosis (high titres of anti-B2GPI are associated with a high risk of thrombosis) and pregnancy complications.

One of the main important hallmarks in autoantibodies screening is to have available a reproducible and easy to use method at the benchtop. The lack of standardization affect inter-laboratory variation in the field of aPL ELISAs (3). In addition these kits are now produced by an number of different companies and follow relatively diversified methods (4). Minimal requirements considered useful to decrease the variability are: to run the samples in duplicate; to determine the cut-off level in each laboratory analysing at least 50 samples from normal subjects, age and sex matched with the patient population afferent to the Centre; to calculate the cut-off level in percentiles since aPL ELISAs do not follow a normal distribution. Moreover, the use stable external controls and calibrators is recommended. In this respect, human or humanized monoclonal antibodies (HCAL and EY2C9) should be soon available from the Center for Disease Control and Prevention (CDC, Atlanta) to allow comparison between assay systems.(5)

An important task to be considered in the interpretation of IgM a β2GPI and aCL, (particularly in the low positive range) is the possibile interference of cryoglobulins and rheumatoid factors.

The new guidelines suggest that the positivity of laboroatory tests has to be confirmed after 12 weeks aiming to verify its stability and its relationship with a clinical criterion. In addition it is advised not to classify as affected with APS a patient if more than 5 years separate the clinical event from the detection of the positive laboratory test.

The most significant goal remains to pass from benchtop to bedsides. Accordingly it was observed that the simultaneous positivity of more than one diagnostic test was associated to an increased risk of thrombosis (6).

Possible future investigation area in the diagnosis of APS is the analysis of different tests now considered "non criteria". Among these, anti-phosphatidylethanolamine appear as the most different from classical aPL and therefore the most promising in term of new observations.

Dermatologic aspects of APS

Since the first description of APS, a wide variety of dermatologic manifestations have been reported. Their prevalence is highly variable depending on the series. In our series of 200 consecutive APS patients, they were present in 49% of cases (7). Livedo reticularis (LR) was the most frequently observed lesion, then, other lesions, by order of frequency, were ulcerations, digital gangrene, subungual splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, extensive cutaneous necrosis and primary anetoderma. Skin lesions are more frequently (70%) observed in the CAPS, characterized by widespread microvascular occlusions involving multiple organs simultaneously. LR, acrocyanosis, large cutaneous necrosis, palmar erythema, digital gangrene and ischemic ulcers were reported in this condition (8).

LR was a presenting manifestation in 17.5% of cases; its prevalence was 25.5% (7). When it is the sole cutaneous manifestation, its clinical features, although non-specific, is rather suggestive of APS. It is usually widespread, non-infiltrated, localized not only on the limbs but also on the trunk and/or buttock. The fishnet reticular pattern is mainly irregular (livedo racemosa). A significant association between LR and cerebral or ocular ischemic arterial events, seizures, all arterial events,

heart valve abnormalities detected on echocardiography, and arterial systemic hypertension was demonstrated. Conversely, LR was less frequently observed in patients with only venous thrombosis (7).

Different types of skin ulcerations may be encountered: post-phlebitic ulcers resulting from circumscribed skin necrosis or large ulcers resembling pyoderma gangrenosum. Digital gangrene was present in 3.3% to 7.5% of APS cases (7, 9). Subungueal splinter hemorrhages appear concomitantly to thrombotic events or lupus flares. Superficial venous thromboses (5 to 11.7%) have been included in the classification criteria for definite APS (1). The pseudovasculitis lesions may mimic cutaneous vasculitis and may be misdignosed if skin biopsies are not performed, especially in patients with SLE. Clinical features of widespread superficial cutaneous necrosis within APS are similar to those observed in other thrombophilic states.

Anetoderma may be primary or secondary to various dermatoses. When primary, it is frequently observed in patients with autoimmune diseases and especially related to antiphospholipid antibodies (10).

Non-inflammatory thrombosis in small arteries and/or veins throughout the dermis and the subcutaneous fat tissue are the main histological findings, observed in circumscribed skin ulcerations, widespread cutaneous necrosis and pseudo-vasculitis lesions. In contrast, thrombosis is rarely observed from biopsies of LR except in CAPS.

The histological features of anetoderma associated with APS are not usually different from those of other cases of primary anetoderma. In rare cases, thrombosis of dermal vessels was however reported.

In conclusion, the dermatological manifestations of the APS may be the presenting feature of the syndrome. They are extremely diverse and heterogeneous, ranging from minor signs to life-threatening conditions. LR is strongly associated with the " arterial subset" of APS. Scientific data are required to determine the optimum management of these patients, who might benefit from recently developed antithrombotic agents.

The catastrophic antiphospholipid (Asherson's) syndrome

This rapidly progressive, often fatal variant of the antiphospholipid syndrome was first defined in 1992 (11) with the publication of ten representative cases. Many more cases have been documented and over the past 14 years, primarily due to the establishment of a website based at the Systemic Autoimmune Diseases Unit of the Hospital Clinic in Barcelona (http:///www.med.ub.es/MIMMUN/FORUM/CAPS/HTM), almost 300 patients with this condition have been documented and many reviews published (8, 12). In 2003, the eponym, Asherson's syndrome was attached (13). The characteristic features of the condition are: i) the rapid onset of the condition resulting in multiple organ dysfunction syndrome, ii) small vessel occlusive disease predominating, iii) pathological evidence of thrombotic microangiopathy, iv) fulminant tissue necrosis, particularly involving the gastrointestinal tract, may result in evidence of the systemic inflammatory response syndrome manifest particularly as an acute respiratory distress syndrome (ARDS), v) a high frequency of unusual organ involvement e.g. reproductive organ infarctions, bone marrow necrosis, acalculous cholecystitis, olyneuropathy or splenic, hepatic and adrenal infarctions. Serological evidence of disseminated intravascular coagulation (DIC) is present in a significant proportion of patients.

Most patients end up in Intensive Care Units with a plethora of physicians in attendance. It seems that the attending physicians may often miss the diagnosis.

The condition is most frequently encountered in patients with a primary APS (49.9%), with SLE and "lupus-like" disease being slightly less frequent (45%) Other uncommon associations include rheumatoid arthritis, systemic sclerosis, dermatomyositis, Crohn's disease, ulcerative colitis and vasculitides (polychondritis, Behçet's disease).

Clearly some patients have already been identified as suffering from a simple or classic APS and may already have been on long term steroids or anticoagulation. The condition may arise "de novo" in others. A previous history of vascular occlusive events is therefore of great importance.

"Triggering" factors may be present in 60% of patients. These are infections (22%), trauma (13%), anticoagulation withdrawal (7.2%), neoplasia (6.8%), obstetric-related factors (4.2%), lupus "flares" (3%), others including drugs (captopril, oral contraceptives, danazol, thiazide diuretics), ovulation induction, and post-immunization in 4%.

Specific infections such as typhoid, malaria and dengue fever among others have been encountered; the majority have had a variety of infectious triggers which include viral upper respiratory, unidentified urinary tract or bacterial infections. Infected leg ulcers have featured prominently among the latter etiological triggers encountered.

Immunizations against Yellow Fever, Japanese "B" encephalitis, and influenza have been followed by CAPS in isolated cases. The trauma may be major or even minor surgical (eg biopsy), or even a simple fracture. In a percentage of patients multiple trigger factors may be present in the same patient (eg infection, anticoagulation withdrawal followed by a surgical procedure, or biopsy in patient with neoplasia who has aPL) This is the so-called "double" or "treble" hit hypothesis common in other patients who present with multiorgan failure.

The organs involved clinically are predominantly renal (70%), pulmonary (66%), brain (60%), heart (52%), skin (47%); cardiac and pulmonary complications are most likely to be associated with poorer prognosis and death. Patients do not however die from renal failure but a cardiopulmonary death is usual.

Often CAPS is accompanied by neurological complications. Patients, although initially conscious, rapidly deteriorate and coma often supervenes. Although small vessel occlusive disease predominates, stroke, because of large cerebral vessel occlusions, is not uncommon.

The pathogenesis of this condition has received as much attention as its clinical manifestations, and the prognosis is recognized completely different to that for large venous or arterial thrombosis encountered in patients with simple or classic APS. The commonality of the

demonstration of the aPL, often in high titres, make this a distinct "subset" of the APS.

A theory of "*molecular mimicry*" was proposed by Asherson and Shoenfeld (14). Others have referred to the condition as a "thrombotic storm" and hypothesized that the vascular occlusions in these patients themselves were responsible for the on-going thrombosis; "thrombosis begets thrombosis".

Merrill and Asherson recently pointed out that perhaps a "continuum" exists where localised and diffuse microvascular thrombosis exists (15). These include thrombotic thrombocytopenic purpura (TTP), haemolytic-uremic syndrome (where indeed a relationship to preceding infections with shiga-toxin producing organisms is seen) thrombotic microangiopathic haemolytic anemia (TMHA), as well as postpartum renal failure, malignant hypertension, preeclampsia and the HELLP syndrome as well as scleroderma renal crisis. In any of these conditions, similar complications such as severe thrombocytopenia, microangiopathic haemolytic anemia, fever, renal and neurological complications may occur. Antiphospholipids antibodies have indeed been reported in many of these conditions with or without the presence of SLE. The association of the aPL with these TMHA-like disorders might in fact be higher than previously appreciated (16). There may in fact be a continuum of illness leading up to CAPS or a significant overlapping of these disorders with CAPS as we already know. This is perhaps exemplified by the association of the HELLP syndrome with CAPS or the presence of schistocytes in CAPS patients, making the differential diagnosis between CAPS and TTP difficult in those patients with predominantly renal/CNS involvement who also have demonstrable titres of aPL (17).

The role of complement in aPL induced thrombosis has received great attention recently. Pierangeli *et al*. (18) stressed the role of complement fractions C3 and C5 in aPL mediated thrombosis.

The recent outstanding work on the role of complement in the etiopathogenesis of fetal loss from the Salmon group in New York (19) has been extended by the group from Harvard University in Boston and effectively attempts to explain some of the odd features of CAPS.

Hart *el al*. (20) and Fleming *et al*. (21) recently published two important papers, which clearly demonstrated that complement activation pays an important role not only in local tissue injury but also in remote injury. Gut barrier dysfunction (eg from ischemia induced by small vessel occlusive disease in CAPS) may lead to bacterial translocation to the lung resulting in increased complement neutrophil infiltration as a result of lectin complement pathway activation via *ficolins*. Mannose binding lectine (MBL) activates the lectin complement in the intestines; *ficolins* may be activating complement in the lungs. This hypothesis explains why with neutrophilic infiltration initially, secondary disruption of alveolar blood vessels might take place resulting in diffuse alveolar hemorrhage, a not infrequent accompaniment of CAPS. The high frequency of abdominal symptomatology in CAPS patients and the much higher frequency of pulmonary complications such as alveolar hemorrhage in the group of patients with CAPS lends great credence to this link. The ficolin hypothesis also ties in well with the high frequency of infections as "triggering" mechanisms for CAPS.

The second paper from this group (20) led them to conclude that aPL could bind to tissues subjected to I/R insult and mediated tissue damage, just as they had been shown to mediate fetal growth retardation and loss when injected into pregnant mice (19).

Recurrent CAPS is rare, only five such patients having been reported to date. In one patient two relapses were triggered by infections, in another, trauma was responsible and in the third, no obvious precipitating factors were detectable prior to two relapses. Simple cataract surgery was responsible for a third relapse. The patient survives.

Treatment of APS

The controversy concerning whether or not prophylactic treatment is indicated for patients with aPL who have no history of thrombosis remains unresolved. A prospective, randomised clinical trial comparing low-dose aspirin alone with aspirin plus low-intensity warfarin (INR ~ 1.5) in patients with aPL who have never had thrombosis is currently under way in the United Kingdom (22). Until these results are available, it is recommendeded that individuals with a persistently positive anticardiolipin antibodies (moderate/high titers) and/or unequivocally positive lupus anticoagulant tests take low-dose aspirin (75-100mg daily) indefinitely. It is worthnoting that hydroxychloroquine have been shown to be protective against the development of thrombosis in aPL-positive patients with SLE (23). Cessation of estrogen-containing oral contraceptive use, treatment of hypertension, hyperlipidemia or diabetes if present, and the avoidance of smoking are all additional recommended therapeutic measures.

Patients with the APS have a higher risk of recurrent thrombosis after a first episode than do patients without the APS and require long-term anticoagulation (24). Many patients with APS in whom anticoagulation has been stopped have had major recurrent thrombosis. It is not clear, however, whether prolonged anticoagulation is necessary in APS patients whose first thrombotic episode developed in association with surgery, oral contraceptive use, pregnancy or other circumstantial thrombotic risk factors.

Most patients requiring long-term anticoagulant therapy respond well to warfarin targeted to an International Normalised Ratio (INR) of 2.0-3.0. However, the optimal intensity of anticoagulation therapy is uncertain for patients with aPL-associated thrombosis. Retrospective studies in the 1990s suggested that thrombosis in APS patients should be managed by high-intensity (target INR 3.0-4.0) oral anticoagulation (25, 26). The more recent prospective studies suggest only an INR of 2.0-3.0 is required (27, 28). A major concern about these recent prospective and randomised studies is the fact that the majority of patients included had venous not arterial thrombosis. Furthermore, none of these studies achieved the expected sample size; a large number of patients were excluded because they had already had recurrent events

on oral anticoagulation; and in the Crowther's study (27) patients with recent stroke were excluded so that in the final study 76% of the patients had previous thrombosis only and review of the high-intensity arm showed that the patients were below the therapeutic range for 43% of the time.

Oral anticoagulation therapy carries an inevitable risk of serious haemorrhage. In APS, serious bleeding complications may occur but their risk is not higher than that observed in other thrombotic conditions warranting oral anticoagulation (29). In APS patients with previous arterial events, the dangers of thrombosis and stroke far outweigh the risk of anticoagulant-induced bleeding. The traditional fear of cerebral haemorrhage has almost certainly resulted in the undertreatment of many patients with cerebral APS. It is recommended that APS patients with previous thrombotic events should have moderate-intensity (INR 2.0-3.0) anticoagulation. However, those with previous arterial events merit high intensity (INR 3.0-4.0) until there is evidence to the contrary (30).

The role of steroids and immunosuppressive drugs in the treatment of patients with aPL and thrombosis is uncertain. Such drugs do not always suppress aPL and they have severe side effects when given for prolonged periods. Furthermore, in a large series of patients with APS, corticosteroids and immunosuppressive therapy, prescribed in some patients to control lupus activity, did not prevent further thrombotic events. The use of these drugs is probably justified only in patients with severe APS with repeated episodes of thrombosis despite adequate anticoagulation therapy.

Management of the pregnancy

The management of pregnancy in women known to have APS is the subject of much debate, and as yet there have been very few randomized controlled trials. Anticoagulation in one form or another is the preferred treatment, rather than steroids (once widely recommended). The current choices lie between aspirin, heparin or both. Recent trials showed that heparin plus low-dose aspirin is more effective than aspirin alone for achieving live births among women with aPL and first trimester recurrent pregnancy loss. However, such increased efficacy of the combination treatment was not seen in a later randomized controlled trial of similar design. Another prospective trial of aPL-positive women with repeated pregnancy loss but no history of thrombosis or SLE, found similar live birth rates (~80%) using either low-dose aspirin or placebo, suggesting that treatment may be unnecessary in some women (for review see 31). Although optimal treatment for women with one or more late pregnancy losses (second/third trimester) but no history of thromboembolism is controversial, most experts support the use of heparin therapy in addition to low-dose aspirin.

Pregnancy complicated by APS requires expert care and a team approach by obstetricians and physicians. Close monitoring of both mother and fetus is essential. Ultrasound monitoring of fetal growth and uteroplacental blood flow is crucial. This allows for timely delivery. Some authorities utilize uterine artery waveforms at 20 and 24 weeks' gestation, and those pregnancies with evidence of an early diastolic notch are monitored very closely with 2-weekly growth scans because of the high risk of intrauterine growth restriction. When there are no notches we recommend 4-weekly assessment of growth and amniotic fluid volume. Doppler flow studies of the umbilical artery may be used, as in other pregnancies at high risk of fetal compromise through uteroplacental insufficiency. Our recent experience demonstrated that a 90% live birth rate can be achieved in women with APS with significant past pregnancy morbidity and/or thrombosis (32).

Treatment of cutaneous manifestations of APS

Treatment of patients with skin lesions must be considered according to both the different dermatological manifestations and the presenting clinical situation.

Widespread cutaneous necrosis and/or digital gangrene are major thrombotic events, which require full anticoagulation with heparin. If extension of these skin lesions persists despite anticoagulation, other treatments may be added.

No treatment has been proven to be effective for livedo reticularis, which may extend or appear despite anticoagulant or anti-platelet therapy. Livedo reticularis is less visible on sun-tanned skin; but sun exposure is not recommended in SLE-related APS, and we think it should be proposed only to aPL-negative patients desiring to mask a troublesome livedo.

In isolated other skin lesions such as livedoid vasculitis-like ulcers or pseudo-vasculitis lesions, low dose-aspirin and dipyridamole has been reported as effective in some patients. If these lesions recur or extend despite anti-platelet agents, anticoagulation is usually prescribed.

Prevention of recurrence of skin lesions depends not only on their severity, but also on the other features of the disease. As widespread cutaneous necrosis and/or digital gangrene are considered as major thrombotic events, the current recommendations for such cases is long term warfarin as in patients with large vessel thrombosis. Prevention of recurrences of isolated "minor dermatological manifestations" (i.e. livedoid vasculitis-like ulcers, pseudo-vasculitis skin lesions, superficial thrombophlebitis) is unclear. Antiplatelet therapy such as low-dose aspirin (75 mg/day) is usually chosen as first-line treatment. Hydroxychloroquine has also well-documented antiplatelet effects and has been shown to reduce the risk of thrombosis in both SLE patients and animal models of APS. However, in our experience, these treatments are rarely effective and long term anticoagulation is frequently required.

Of major concern is the problem of patients presenting with isolated livedo reticularis and aPL (33). Some of them, at least, are prone to develop ischemic cerebral events with years, as illustrated by our above-mentioned experience of Sneddon's syndrome (10). Low dose aspirin is frequently prescribed in such patients for prevention of strokes, but its effectiveness is doubtful.

Treatment of CAPS

The treatment of the CAPS remains unsatisfactory but it is clear that many patients have not been given the benefit

of IV gammaglobulins and repeated plasma exchanges, which have been strongly recommended. High dose IV steroids and parenteral anticoagulation should be supplemented by IV gammaglobulins, fibrinolytic agents, and repeated plasma exchanges using fresh frozen plasma (FFP) early on in the course of CAPS and should not be withheld (34). The use of Rituximab in patients who demonstrate severe thrombocytopenia has been successful in those few cases, to whom it has been administered; IV antibiotics should also be administered if an infection is present or suspected.

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