Systemic Lupus Erythematosus and Antiphospholipid Syndrome

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14.1 Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-β_2-glycoprotein I (β_2GPI) antibodies [1]. The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS), or it may be associated with other diseases, mainly systemic lupus erythematosus (SLE), but occasionally with other autoimmune conditions [1], infections [2], drugs [1], and malignancies [3] (Table 14.1).

Primary APS patients rarely progress to SLE. Only 8 % of 128 patients, who were followed up for about 9 years, developed lupus, and a positive Coombs' test was a clinically significant predictor of progression [4].

The aPL can appear in different scenarios, such as asymptomatic "carrier" patients for aPL, "classical" APS with recurrent venous and/or arterial thrombosis, APS affecting otherwise healthy women with recurrent pregnancy loss, patients with aPL positivity with non-thrombotic aPL manifestations (i.e., thrombocytopenia, hemolytic anemia, or *livedo reticularis*) [5], or, in a small subset of patients, as a life-threatening form characterized by a rapid development of microthrombosis that led to rapid multiorgan failure, which is termed catastrophic APS [6].

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Table 14.1 Diseases where aPL have been described

Systemic autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, primary Sjogren's syndrome, dermato- and polymyositis, vasculitis (polyarteritis nodosa, microscopic polyarteritis, giant cell arteritis, Behçet's disease, relapsing polychondritis, leukocytoclastic vasculitis)
Infections: viral (HIV infection; mononucleosis; rubella; parvovirus; hepatitis A, B, C; mumps), bacterial (syphilis, Lyme disease, tuberculosis, leprosy, infective endocarditis, rheumatic fever, *Klebsiella*), protozoal (malaria, toxoplasmosis)
Malignancies: solid tumors (lung, colon, cervix, prostate, liver, kidney, thymus, esophagus, maxilla, ovary, breast), hematologic (myeloid and lymphatic leukemias, polycythemia vera, myelofibrosis), lymphoproliferative diseases (Hodgkin's disease, non-Hodgkin's lymphoma, lymphosarcoma, cutaneous T-cell lymphoma/Sezary syndrome), paraproteinemias (monoclonal gammapathies, Waldenström macroglobulinemia, myeloma)
Nonmalignant hematologic conditions: idiopathic thrombocytopenic purpura, sickle-cell disease, pernicious anemia
Drugs: procainamide, phenothiazines, ethosuximide, chlorothiazide, quinine, oral contraceptives, anti-TNFα therapies
Other conditions: diabetes mellitus, autoimmune thyroid disease, inflammatory bowel diseases, dialysis, Klinefelter's syndrome, Ehlers-Danlos syndrome

14.2 Epidemiology of aPL

Prevalence of the aPL in the general population ranges between 1 and 5 %. However, only a minority of these individuals develop the APS. Some estimates indicate that the incidence of the APS is around 5 new cases per 100,000 persons per year and the prevalence around 40–50 cases per 100,000 persons [7]. Cross-sectional studies of aPL in SLE underestimate the true prevalence, because many SLE patients make these antibodies intermittently. In fact, aPL can disappear after thrombotic events in some SLE patients, demonstrating the importance of prospective studies in SLE. Previous estimates have suggested that 30 % of SLE patients will develop APS. In the Hopkins Lupus Cohort, after 20 years of follow-up, there was a 50 % chance of having an arterial or venous thrombosis event if the SLE patient had aPL.

Recently, the APS ACTION (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking) group published a literature review focused in the prevalence of aPL in the general population with pregnancy morbidity, stroke, myocardial infarction (MI), and deep vein thrombosis (DVT). The authors estimated that aPL are positive in approximately 13 % of patients with stroke, 11 % with MI, 9.5 % of patients with DVT, and 6 % of patients with pregnancy morbidity [8].

The prevalence of the catastrophic APS is scarce (less than 1 % of all cases of APS) [6], but its potentially lethal outcome emphasizes its importance in clinical medicine today [9, 10]. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was created in 2000 by the *European Forum on Antiphospholipid Antibodies*. Currently, it documents the entire clinical, laboratory, and therapeutic data of more than 500 patients whose data has

been fully registered. This registry can be freely consulted on the Internet (http://ontocrf.costaisa.com/es/web/caps).

14.3 Pathogenesis of aPL-Mediated Events

Several mechanisms have been proposed for the development of thrombosis in relation with the presence of aPL. Available data indicate that many of the autoantibodies associated with APS are directed against a number of plasma proteins and proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets. The involvement of aPL in clinically important normal procoagulant and anticoagulant reactions and on certain cells altering the expression and secretion of various molecules may offer a basis for definitive investigations of possible mechanisms by which aPL may develop thrombotic events in patients with APS [11].

A major advance came in the early 1990s with the simultaneous recognition by different groups that aPL required a plasma protein "cofactor" to bind cardiolipin on ELISA plates. β_2-glycoprotein I (β_2GPI) was identified as this cofactor. β2GPI-dependent autoantibodies seem to be the main pathogenic subpopulation of aPL.

Some evidence shows that a second hit (i.e., infections, trauma, drugs, among others) is required for thrombus formation in APS. This requirement is less clear for fetal loss. The theory of a second hit is especially important in the case of catastrophic APS.

In addition to placental thrombosis, other mechanisms for direct effects of aPL on placental tissues have been proposed. aPL decrease the levels of annexin V, a potent natural anticoagulant present in placenta and vascular endothelium. Another postulated mechanism is that aPL displace annexin V from trophoblast with resulting increased exposure of anionic phospholipids and acceleration of thrombin generation. Annexin V appears to play a thrombomodulatory role in the placental circulation where it is necessary for maintenance of placental integrity (Table 14.2) [12, 13].

14.4 Clinical Manifestations

APS is characterized by either venous or arterial thrombosis affecting any kind of blood vessels. Single-vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. The baseline characteristics and new APS features during the follow-up of a cohort of 1,000 patients with APS ("Euro-Phospholipid Project") are collected in Table 14.3 [14].

14.4.1 Venous and Arterial Involvement

Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years.

Table 14.2 Possible pathogenic mechanisms of the aPL [11–13]

Inhibition of anticoagulant reactions:
Inhibition of β_2GPI anticoagulant activity
Inhibition of the protein C pathway
Inhibition of protein C activation
Inhibition of activated protein C
Inhibition of antithrombin activity
Displacement of annexin A5
Cell-mediated events:
On endothelial cells:
Enhanced endothelial cell procoagulant activity
Increased expression and activation of tissue factor
Expression of adhesion molecules
Impaired fibrinolysis
Dysregulation of eicosanoids
Decreased endothelial cell prostacyclin production
Increased platelet thromboxane A_2 production
Impaired function of endothelial nitric oxide synthase
On monocytes:
Expression of tissue factor
Increase oxidative stress
On platelets:
Enhanced platelet activation/aggregation
On plasmacytoid dendritic cells:
Increased expression of toll-like receptor 7 and toll-like receptor 8

Venous occlusions in form of DVT, particularly affecting the veins of the lower limbs, are the most common clinical manifestation of the APS [15].

Other less common manifestations include superficial thrombophlebitis, chronic venous stasis, secondary malleolar ulceration, and venous occlusions occurring at sites of venous access.

The thoracic branches of the aorta may be affected, and an "aortic arch syndrome" with absent brachial pulse has been documented. Patients with APS commonly present with thrombotic problems, but there is a subgroup of patients who develop aneurysms with no evidence of vasculitis. Arterial stenosis can also play a role in APS. It may affect arteries of varying sizes and sites. So far, arterial stenosis affecting the renal, celiac, and intracranial arteries has been observed. The underlying pathology and mechanism for these stenotic lesions are unknown but may

Table 14.3 Most common manifestations in the APS, according to the "Euro-Phospholipid Project" at baseline and during the 10-year follow-up

	Baseline	0–5 year	5–10 year
	(*n* = 1,000)	(*n* = 1,000)	(*n* = 796)[a]
Manifestations	%	%	%
Deep vein thrombosis	38.9	2.1	2.7
Superficial thrombophlebitis in legs	11.7	0.9	1.0
Stroke	19.8	2.4	3.6
Transient ischemic attack	11.1	2.3	3.0
Epilepsy	7.0	1.7	1.9
Pulmonary embolism	14.1	2.1	1.7
Cardiac manifestations			
Valve thickening/dysfunction	11.6	1.7	3.6
Myocardial infarction	5.5	0.9	1.2
Vegetations	2.7	1.4	0.9
Livedo reticularis	24.1	2.6	6.9
Thrombocytopenia (<100,000/μl)	29.6	3.7	6.3
Autoimmune hemolytic anemia	9.7	0.9	3.9
Obstetric manifestations	**(*n* = 1580)**	**(*n* = 105)**	**(*n* = 83)**
Preeclampsia	5.2	7.6	4.8
Early fetal losses (<10 weeks)	35.4	17.1	15.7
Late fetal losses (≥10 weeks)	16.9	6.7	2.4
Live births	47.7	76.2	68.7

Modified from Cervera et al. [22]

[a]Number of patients that continued in the study in 2004

[b]Obstetric manifestations related to number of pregnancies (*n*). Some women had more than one pregnancy

involve thrombosis, accelerated atherosclerosis, and/or proliferation of smooth muscle [16].

14.4.2 Neurologic Involvement

Involvement of cerebral large vessels is frequent in APS, and patients usually present clinically with transient ischemic attacks (TIA) and strokes. Additionally, a wide spectrum of other neurologic features has been described, including chorea, epilepsy, multiple sclerosis-like lesions, psychiatric features, migraine, and also dementia, among others.

The association of aPL with recurrent stroke has been demonstrated in prospective studies. Patients with cerebral ischemia and APS are younger than the general stroke population. In particular, the strongest association of aPL with stroke is seen in patients under 50 years of age, with a prevalence of aPL reported to be from 4 to 46 % in this population.

In a large prospective study [17], aCL were an independent risk factor for ischemic stroke and TIA in women after multivariate adjustment for other cardiovascular risk factors, including age, systolic blood pressure, diabetes, cigarette smoking, and plasma C-reactive protein and cholesterol levels.

Cognitive dysfunction varies from global dysfunction in the context of multi-infarct dementia to subtle cognitive deficits in otherwise asymptomatic patients with aPL.

14.4.3 Cardiac Involvement

A variety of cardiac valve lesions have been associated with aPL in primary APS and SLE. Echocardiographic studies have shown that SLE patients with aPL have a higher prevalence of valvular lesions (mainly mitral and aortic lesions) than those without aPL. The valvular lesions consist mainly of superficial or intravascular fibrin deposits and their subsequent organization: vascular proliferation, fibroblast influx, and rigidity, leading to functional abnormalities. These may represent a potential cardiac source of stroke. It has been shown that the prevalence of valvular abnormalities, particularly left-sided valve lesions, is higher in SLE patients with aPL than in those without. Our group [18] showed that patients with SLE and aPL have an increased frequency of mitral valve vegetations and mitral regurgitation than aPL-negative patients (16 % vs 1.2 % and 38 % vs 12 %, respectively). In this study, 9 of 50 patients with mitral valve disease had cerebrovascular occlusions during follow-up, showing that valvular lesions can be a source for emboli and a possible cause of ischemic stroke in aPL patients, as reported by other authors. In patients with SLE, particularly women between 35 and 44 years of age, the risk of cardiovascular events is over ten times higher than in healthy women of similar age.

14.4.4 Pulmonary Involvement

Pulmonary manifestations – including pulmonary embolism and infarction; pulmonary hypertension; adult respiratory distress syndrome (ARDS); intra-alveolar hemorrhage; primary thrombosis of lung vessels, both large and small; and pulmonary capillaritis – may be associated with this syndrome. Less commonly, a postpartum syndrome and fibrosing alveolitis associated with APS have been described.

The prevalence of pulmonary hypertension in APS associated with SLE and primary APS has been estimated to be between 1.8 % and 3.5 %, respectively. In a prospective analysis of 500 patients with SLE, a statistically significant association between pulmonary hypertension and the presence of IgA aCL above 2 SD has been described.

14.4.5 Renal Involvement

Renal involvement can be present in patients with either primary or SLE-associated APS. Clinical and laboratory features of renal involvement in APS include

hypertension, hematuria, acute renal failure, and progressive chronic renal insufficiency with mild levels of proteinuria that can progress to nephrotic-range proteinuria. The main lesions are renal artery stenosis, venous renal thrombosis, and glomerular lesions (APS nephropathy) that may be acute (thrombotic microangiopathy) and/or chronic (arteriosclerosis, arterial fibrous intimal hyperplasia, tubular thyroidization, arteriolar occlusions, and focal cortical atrophy). APS can also cause end-stage renal disease and allograft vascular thrombosis [19].

14.4.6 Osteoarticular Involvement

Osteonecrosis (ON) or avascular necrosis of bone is a well-recognized complication in patients with SLE and APS. The pathogenesis of ON is probably multifactorial, of which abnormal hemostatic state such as the presence of aPL may play an important role. In patients with aPL, bilateral involvement of the femoral head is often found, but some patients follow an asymptomatic course. Atypical site ON (talus, vertebral, carpal lunate) and/or multiple ON (more than three bones affected) are not uncommon in patients with APS.

By definition, frank and sustained arthritis are not usually seen in patients with primary APS. However, arthralgias are not uncommon. Other anecdotal features, such as stress fractures, have been occasionally reported in association with aPL. The management of patients with aPL and ON without venous or arterial thrombosis is still controversial. A high diagnostic suspicion is crucial in order to prevent the onset of ON in new territories and to avoid the need of joint replacement [20].

14.4.7 Obstetric APS

A large proportion of pregnancy losses related to aPL occurs in the fetal period (greater than 10 weeks of gestation). However, fetal deaths at these gestational ages normally account for only a small proportion of all pregnancy losses in the general population, which occur more frequently before 10 weeks of gestation.

The most characteristic feature of obstetrical APS is miscarriage. Currently, recurrent miscarriage is a potentially treatable condition when it is associated with aPL. Additionally, several other serious obstetric complications have been associated with APS, including preeclampsia, fetal growth restriction, uteroplacental insufficiency, fetal distress, and medically induced preterm delivery. Preeclampsia is also associated with APS. Although 11–17 % of women with preeclampsia will test positive for aPL, the association is strongest in women with severe preterm preeclampsia (less than 34 weeks of gestation). Other infrequent reported maternal APS complications include postpartum cardiopulmonary syndrome, chorea gravidarum, and postpartum cerebral infarct among others [21].

In the "Euro-Phospholipid Project," baseline obstetric manifestations included early fetal losses (<10 weeks) in 35 % of patients, late fetal losses (>10 weeks) in 17 %, and prematurity in 10 % of cases [14].

14.5 Follow-Up, Outcome, and Organ Damage in APS

Under an appropriate treatment (usually, anticoagulation), most patients with diagnosis of APS have a satisfactory outcome. However, some patients can develop new manifestations. The 10-year follow-up report from the "Euro-Phospholipid Project" was recently published [22]. During the 10-year period, the most frequent manifestation was thrombosis. The most common thrombotic events were strokes (5.3 %), TIA (4.7 %), DVT (4.3 %), and pulmonary embolism (3.5 %). Other APS-related manifestations were also commonly observed, including thrombocytopenia (8.7 %), *livedo reticularis* (8.1 %), autoimmune hemolytic anemia (4 %), valve thickening/dysfunction (4.6 %), epilepsy (3.2 %), and skin ulcers (3.1 %).

Given that APS affect predominantly young patients, assessment of organ damage is crucial, but publications in that field are limited. A retrospective analysis was recently published that focused in morbidity, mortality, and organ damage in 135 APS patients. Patients were clustered according to the initial event: arterial thrombosis, DVT, or pregnancy morbidity. One-fourth of the patients progressed to organ damage in a mean time of 10 years from disease onset. The highest morbidity was attributed to neurologic damage, which was more common among patients with arterial thrombosis as an initial manifestation.

In the "Euro-Phospholipid Project," a 5-year survival rate of 94 % was reported. During this follow-up period, 53 (5.3 %) patients died. The main causes of death included bacterial infection (21 %), MI (19 %), stroke (13 %), hemorrhage (11 %), malignancy (11 %), catastrophic APS (9 %), and pulmonary embolism (9 %), among others.

During the 10-year period, 93 (9.3 %) patients (72 female and 21 male) died, leading to a survival rate of 91 % at 10-year follow-up. There were no differences in survival probabilities between patients with primary APS and those associated with SLE. The most common causes of death were severe thrombotic events, including MI, strokes and pulmonary embolism (36 % of total deaths), infections (27 %: bacterial 21 %, other 6 %), and hemorrhages (11 %). Five out of the nine (56 %) patients who developed catastrophic APS died [22].

14.6 Laboratory Abnormalities in APS

A wide variety of laboratory abnormalities can be found in patients with APS, depending on the organ involvement. The most common immunological features are depicted in Table 14.4. Detection of the LA must be performed according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies) [23].

Table 14.4 Most common immunological findings in the APS, according to the "Euro-Phospholipid Project"

Parameter	%
aCL	87.9
IgG and IgM aCL	32.1
IgG aCL alone	43.6
IgM aCL alone	12.2
LA	53.6
LA alone	12.1
LA and aCL	41.5
ANA	59.7
Anti-dsDNA	29.2
Anti-Ro/SS-A	14
Anti-La/SS-B	5.7
Anti-RNP	5.9
Anti-Sm	5.5
Rheumatoid factor	7.8
Cryoglobulins	3.6

14.7 APS Classification Criteria

In 1999, a preliminary set of classification criteria was established after an expert workshop held in Sapporo, Japan [24]. Later, another workshop was held in Sydney, Australia, in which the experts proposed some modifications to the previous criteria, such as the inclusion of anti-β2GPI antibodies. Although no new clinical criteria were added, some particular features were remarked on, such as associated APS features, including cardiac valve involvement, *livedo reticularis*, thrombocytopenia, APS nephropathy, and non-thrombotic central nervous system manifestations (i.e., cognitive dysfunction) [25] (Table 14.5).

The preliminary classification criteria for catastrophic APS were formulated at a workshop in Taormina, Italy, in 2002, during the 10th International Congress on aPL, and published as a consensus statement in 2003 (Table 14.6) [26].

14.7.1 Assessment of the Classification Criteria

The revised APS classification criteria [25] provide a more uniform basis for selecting patients for APS research by emphasizing risk stratification. They strongly recommend investigating coexisting inherited and acquired thrombosis risk factors in patients with APS, especially in those who are included in clinical trials. A recent assessment of the 2006 revised APS classification criteria has shown that only 59 % of the patients meeting the 1999 APS Sapporo classification criteria met the revised criteria [27]. Therefore, it is expected that these revised criteria will have positive implications in APS research by means of limiting the inclusion of a heterogeneous group of patients and also by providing a risk-stratified approach. Furthermore,

Table 14.5 Revised classification criteria for the APS [25]

Clinical criteria
1. Vascular thrombosis[a]
One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall
2. Pregnancy morbidity
(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus
(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of (a) eclampsia or severe preeclampsia defined according to standard definitions or (b) recognized features of placental insufficiency[b]
(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
In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above
Laboratory criteria[c]
1. 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 > the 99th percentile or > mean + 3SD of 40 healthy controls), on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay
2. 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 Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies)
3. Anti-β_2-glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma, present on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay, according to recommended procedures
Definite APS is present if at least one of the clinical criteria and one[c] of the laboratory criteria are met, with the first measurement of the laboratory test performed at least 12 weeks from the clinical manifestation[d]

[a]Coexisting inherited or acquired factors for thrombosis are *not* a reason for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to (a) the *presence* and (b) the *absence* of additional risk factors for thrombosis. Indicative (but not exhaustive) cases include age (>55 in men and >65 in women) and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg/m^2, microalbuminuria, estimated GFR <60 mL/min), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis

[b]Generally accepted features of placental insufficiency include: (1) abnormal or non-reassuring fetal surveillance test(s), e.g., a nonreactive non-stress test, suggestive of fetal hypoxemia; (2) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery; (3) oligohydramnios, e.g., an amniotic fluid index of 5 cm or less; or (4) a postnatal birth weight less than the 10th percentile for the gestational age

Table 14.5 (continued)

[c]Investigators are strongly advised to classify APS patients in studies into one of the following categories:
I: More than one laboratory criteria present (any combination)
IIa: Anticardiolipin antibody present alone
IIb: Lupus anticoagulant present alone
IIc: Anti-β_2-glycoprotein I antibody present alone
[d]Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation

Table 14.6 Preliminary criteria for the classification of catastrophic APS [26]

1. Evidence of involvement of three or more organs, systems, and/or tissues[a]
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]

Definite catastrophic APS: All four criteria
Probable catastrophic APS:
All four criteria, except for only two organs, systems, and/or tissues involvement
All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS
1, 2, and 4
1, 3, and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation
[a]Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50 % rise in serum creatinine, severe systemic hypertension (>180/100 mmHg), and/or proteinuria (>500 mg/24 h)
[b]For histopathologic confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally
[c]If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS (9)

although the APS classification criteria are not meant for clinical purposes, they are the best available tool to avoid overdiagnosis of APS in clinical practice.

Regarding the classification criteria for the catastrophic APS, a validation study showed that they have a sensitivity of 90.3 %, a specificity of 99.4 %, a positive predictive value of 99.4 %, and a negative predictive value of 91.1 % [28].

14.8 Assessment of Thrombosis Risk in APS Patients

Several attempts have been made in order to identify the individual risk of thrombosis in patients positive for aPL [29–31]. A study of pregnant women with APS reported that patients with triple aPL positivity (i.e., positivity for LA, aCL, and anti-β_2GPI) and/or previous thromboembolism had an increased likelihood of poor

neonatal outcomes than patients with double or single aPL positivity and no thrombosis history. More recently, a global APS score (GAPSS) was developed in a cohort of 211 SLE from a single center [31]. GAPSS is derived from the combination of independent risk for both thrombosis and loss of pregnancy, taking into account a panel of seven different aPL, conventional cardiovascular risk factors, the autoimmune antibody profile (i.e., antinuclear, anti-dsDNA, or anti-ENA antibodies), and the use of thromboprophylactic drugs. The authors assigned the risk factors identified by multivariate analysis-weighted points proportional to the ß-regression coefficient values. Finally, six factors were included in the model, and they included IgG/IgM aCL (5 points), IgG/IgM anti-β_2GPI antibodies (4 points), LA (4 points), IgG/IgM anti-phosphatidylserine-prothrombin complex antibodies (3 points), hyperlipidemia (3 points), and arterial hypertension (1 point). A GAPSS cutoff value of $\geq$10 points appears to have the best diagnostic yield.

14.9 Therapy

Treatment decisions in APS fall into four main areas: prophylaxis, prevention of further thromboses of large vessels, management of pregnancy in association with aPL, and treatment of acute thrombotic microangiopathy, mainly catastrophic APS.

Elimination of aPL may be accomplished by several therapeutic regimens, including high-dose steroid administration, immunosuppression (e.g., cyclophosphamide), or plasma exchange. The decrease or elimination is, however, temporary, and antibodies rapidly return (within 1–3 weeks) on cessation of therapy. Therefore, therapy should not primarily be directed at effectively reducing the aPL levels, and the use of immunotherapy is generally not indicated, unless required for the treatment of the underlying condition, e.g., SLE, or in acute life-threatening situations, such as the catastrophic APS. The risk of recurrence of thrombosis is markedly increased in the first 6 months after discontinuation therapy, suggesting a "rebound" phenomenon. Therefore, for patients who have already experienced thrombotic events, lifelong treatment with anticoagulants is essential [32].

In cases of first venous event, low-risk aPL profile or a known transient precipitating factor (e.g., oral contraceptives), anticoagulation could be limited to 3–6 months and antiaggregants, as well as avoidance of the triggering factors, may indeed be sufficiently effective for future thromboprophylaxis [33].

Patients with definite APS with a first venous thrombosis event should receive oral anticoagulant therapy to a target INR 2.0–3.0. Patients with definite APS and arterial thrombosis should receive oral anticoagulant therapy to a target around 3.0 or receive a combined therapy with antiaggregant plus anticoagulation with a INR target between 2.0 and 3.0 [34].

Long-term anticoagulation with oral vitamin K antagonists such as warfarin is the cornerstone treatment in APS. However, novel oral anticoagulation therapies have been developed during the last years; these therapies are direct anti-Xa inhibitors and included rivaroxaban, apixaban, and edoxaban as well as a direct thrombin inhibitor named dabigatran etexilate. Although these are promising therapies for

patients with arterial or venous thrombosis, data in APS is scare but prospective clinical trials are ongoing. However, a recent report described three cases who developed new APS features (i.e., cerebral emboli, stroke, and porto-mesenteric venous thrombosis) in patients who were switched from oral warfarin to new anticoagulants (one case dabigatran and two cases rivaroxaban) [35].

The thrombocytopenia occurring during the course of the APS is usually mild and does not require any active intervention. However, in a minority of cases, it can be severe and refractory to prednisone therapy. In these cases, immunosuppressive therapy (e.g., azathioprine), intravenous immunoglobulins, or rituximab may be effective.

A recently published non-randomized prospective pilot study has shown the efficacy and safety *of* rituximab for the treatment of non-criteria aPL manifestations in patients with classic APS [36]. According to the results, rituximab may be effective in controlling some non-criteria aPL manifestations, such as thrombocytopenia and skin ulcers.

It is important to consider that the presence of moderate to severe thrombocytopenia in patients with ongoing thromboses is not a contraindication for anticoagulation.

Management of the catastrophic APS includes an aggressive approach with a combined treatment that includes anticoagulation with heparin, high-dose steroids, plasma exchange, and/or intravenous immunoglobulins [26]. For patients with refractory catastrophic APS, rituximab and eculizumab are good alternatives. A recent publication [37] demonstrated that 75 % of patients with refractory catastrophic APS treated with rituximab recovered from the acute catastrophic APS episode; however, 20 % of them died at the time of the event. Eculizumab, a humanized monoclonal antibody against complement protein C5, is currently approved for the treatment of paroxysmal nocturnal hemoglobinuria and is a promising therapy in catastrophic APS [38]. Eculizumab treatment benefits patients with microangiopathies, reducing intravascular hemolysis and blocking complement-mediated pathogenic effects. Recently, a few case reports have described the benefits of eculizumab therapy in catastrophic APS patients who were refractory to conventional therapy or for the prevention of recurrent catastrophic APS after renal transplantation [39].

14.10 Prevention

In patients with aPL who have never suffered from a thrombotic event (primary thromboprophylaxis), energetic attempts must be made to avoid or to treat any associated risk factors – e.g., antihypertensives, cholesterol-lowering agents, treatment of active nephritis, avoidance of smoking, or sedentarism.

Individual decisions should be made based on several aspects, including the aPL profile (type of antibodies, level, and persistence), the coexistence of other prothrombotic factors, the presence of an underlying autoimmune disease (specially SLE) [34], and, potentially, the GAPSS score.

Care should be also taken with the administration of oral contraceptives. There may be a case for the prophylactic treatment of individuals with high levels of IgG

aCL or persistent LA activity with antiaggregants (aspirin, 75–150 mg daily), specially in those with added risk factors [40], although a recently published trial has not confirmed the benefits of aspirin in the APS primary thromboprophylaxis [41]. For higher-risk patients (patients with SLE and persistently positive LA), primary thromboprophylaxis with hydroxychloroquine and low-dose aspirin is recommended [34].

On the other hand, prophylaxis of venous thrombosis is required for patients undergoing surgical procedures (particularly, hip surgery), those requiring long stays in bed, or during the puerperium. The use of low-molecular-weight subcutaneous heparin is recommended in those circumstances.

Low-dose aspirin (50–100 mg daily) administered from the beginning of pregnancy until just prior to delivery is the accepted standard therapy for the prevention of fetal loss today. This may be combined with daily subcutaneous heparin in the face of previous fetal losses using aspirin [42, 43]. In cases of ongoing anticoagulation, warfarin administration should be discontinued as soon as pregnancy is diagnosed, since it is teratogenic, and switched to heparin plus low-dose aspirin. In addition, close monitoring of pregnancy with Doppler techniques, in order to detect early placental vascular insufficiency, and delivery with the first signs of fetal distress are mandatory [44].

Some potential alternatives for the treatment of refractory obstetric APS include double antiaggregant therapy, intravenous immunoglobulins, and biologic therapies, especially antitumor necrosis factor alpha agents and plasma exchange sessions [45].

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