Antiphospholipid Antibodies and Autoimmune Diseases

Graciela Remondino* and Alberto Allievi

Autoimmune Diseases Group, Internal Medicine, Hospital Juan A. Fernández, Buenos Aires, Argentina

Abstract: Antiphospholipid Syndrome (APS) is a common autoimmune disorder in constant evolution. During the last 30 years the clinical and immunological features were established and numerous investigators and clinical practitioners established consensus definition of the diagnostic criteria. The last international experts meeting in Sydney 2006 modified the previous Sapporo criteria. In the autoimmunity field, the association of APS with systemic lupus erythematosus (SLE) is the strongest. However, as we learnt more about APS, multiple associations and clinical varieties have been defined. It is very important to be aware of the different clinical manifestations of APS in patients with SLE and also in other autoimmune diseases (AD) different from SLE. In that way, we present a series of a number of patients with AD in association with APS and or positive antiphospholipid antibodies (aPL) assisted by us in the last twenty years. Finally, according to our own experience and in agreement with published data, we consider that the opportunity to look for aPL in other AD different from SLE, is after the thrombotic event has occurred.

Keywords: Antiphospholipid antibodies, systemic lupus erythematosus, antiphospholipid syndrome, autoimmune disease.

INTRODUCTION

Since its recognition as a separate entity in the early 1980s, APS has increasingly gained the interest of hematologists, obstetricians, rheumatologists and immunologists. APS is an autoimmune disorder in continuous evolution and our knowledge has greatly improved in recent years. APS features venous and/or arterial thrombosis and obstetric morbidity.

Adaptive immune response against self-PL-binding proteins ends in the production of specific antiphospholipid autoantibodies (aPL) and in particular anti-β_2 glycoprotein I antibodies (anti-β_2GPI). These are formal diagnostic markers and pathogenic autoantibodies.

Although APS is considered an autoimmune-mediated disease, new evidence supports that aPL are necessary but not sufficient to trigger some of the clinical manifestations of this syndrome. It has been recognized that additional factors, such as mediators of the innate immunity, play a key role as a second hit able to induce thrombotic events in the presence of aPL. Environmental agents, mainly infections, trigger the production of autoantibodies cross-reacting with PL-binding proteins enhancing the aPL thrombogenic effect. These findings do support the concept of a mosaic of factors involved in the pathogenesis of APS [1].

The APS multifactorial pathogenic model resembles the pathogenic model of systemic lupus erythematosus (SLE), an autoimmune disease closely related to it, and which used to be taken for it in the 80s. All systems or tissue may be involved in APS. This has made the definition of APS complex. However, in recent times the consensus classification has clarified its definition. In 1999, as there weren't enough uniform criteria for diagnosis, a board of experts held a meeting in Sapporo, Japan, establishing the APS preliminary classification criteria [2]. The clinical criteria were defined by the presence of arterial or venous thrombosis and/or fetal loss or 3 or more >10 week-miscarriages which can not be related to genetic causes. The presence of lupus anticoagulant (LAC), IgG or IgM anticardiolipin (aCL) in medium or high titre confirmed 2 or more times, with a six-week window between them were established as laboratory criteria [2].

Later in 2004 in Sydney, Australia, some modifications were proposed. Among them, the laboratory criterion of the presence of anti-β_2GPI and the increase to 12 weeks to the window between the two laboratory determinations. In that meeting, the experts also provided definitions on features of APS that were not included in the updated criteria (cardiac valvular involvement, thrombocytopenia, livedo reticularis, APS nephropathy and the non-thrombotic manifestations of the central nervous system) [3].

ANTIPHOSPHOLIPID ANTIBODIES ASSOCIATED WITH OTHER AUTOIMMUNE DISEASES DIFFERENT FROM APS: HISTORICAL REVIEW

Antiphospholipid antibodies were firstly identified in SLE patients. It was later found to be associated to a large number of AD. According to different authors, aPL were present in 12-44% of SLE patients [4-7]. Even though the aPL prevalence differs in SLE depending on the authors considered, it is agreed that SLE is the disease which is more frequently associated to APS.

In a meta-analysis, Wahl *et al.* could observe that the presence of LAC in SLE patients represented a six-fold risk of developing thrombotic events, whereas aCL increased this risk only twice [8]. aPL can also be found in healthy people. In a cohort of 552 healthy blood donors, aPL were found in 9.4% and in a higher percentage in the elderly [9].

*Address correspondence to this author at the Hospital Juan A. Fernández, Buenos Aires, Argentina; Tel: +54 11 4813 8370; Fax: +54 11 4816 1054; E-mail: graremon@fibertel.com.ar

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aPL have been found in a wide range of other ADs. To date, there is agreement that aPLs are found in other ADs less frequently than in the SLE. In some cases, aPL remain as spectators of the disease, whereas in a lower rate of cases, aPL are associated to thrombotic events and/or obstetric morbidity.

Nabriski *et al.* found aPL in 43% of their autoimmune thyroiditis patients. None of them evidenced APS [10]. In the study of Rees *et al.* 17% of positive aPL in 144 patients with systemic vasculitis were found. Only 9 of them met the Sapporo criteria for APS, whereas other 4 patients had some APS clinical and serological findings but did not meet the Sapporo criteria [11]. Sherer *et al.* described 3 patients with APS associated to dermatomyositis and polymyositis: one of them having transverse myelitis, the second one pulmonary thromboembolism, and the third recurrent miscarriage, stroke, livedo reticularis and mitral regurgitation [12]. In Behcet's disease (BD), aPL are found in a highly variable percentage according to different authors [13, 14]. A study suggests that the aPL presence in BD may indicate a more severe disease [15]. According to Tokay *et al.* aPL would not have a pathogenic role in the disease [16]. In a series of 74 patients with primary Sjögren´s syndrome, the presence of aPL reached 30%. The authors concluded that the aCL low titration associated with hypergammaglobulinemia in patients with primary Sjögren´s syndrome may be framed within the natural repertoire of antibodies of the syndrome characterized by being B-cell hyperresponsive [17]. Ramos-Casals *et al.* evaluated 82 primary Sjögren´s syndrome patients, and found that 13% of them had aPL. Only 4 of them developed definite APS whereas other 2 had probable APS and 7 had APS-related features not included in the current classification criteria of APS [18].

A prospective study on aCL prevalence including 98 patients with newly diagnosed polymyalgia rheumatica and/or giant cell arteritis (GCA) found positive aCL in 20 of them. They suggest aCL may identify a subset of patients at risk of developing GCA or other vascular involvements [19].

In an aCL prospective study of early rheumatic diseases, Merkel *et al.* found that aCL were present in the 16% of rheumatoid arthritis and SLE but were less frequent in other rheumatoid diseases where the prevalence was close to that found in a healthy cohort represented by blood donors [20].

The "Euro-Phospholipid" project started in 1999 with a multicentre, consecutive and prospective design allowed the identification of the prevalence and characteristics of the main clinical and immunological manifestations at the onset and during the evolution of APS and demonstrated that it is possible to recognize more homogeneous APS subsets of clinical significance [21]. These authors found that patients with APS associated with SLE had more episodes of arthritis, livedo reticularis and more frequently exhibited thrombocytopenia and leukopenia. Arthritis and livedo reticularis was more common among women, while myocardial infarction, epilepsy and lower limb arterial thrombosis was more common among men, whereas older onset patients were more frequently male and had more strokes and angina pectoris, but less frequently livedo reticularis [22].

APS CLASSIFICATION

APS can be classified as Primary, Secondary or Catastrophic Antiphospholipid Syndrome (CAPS)

Primary APS

APS not associated with other diseases is called primary APS. In 1988, Asherson described the serologic characteristics of these patients as follows: low titres of antinuclear antibodies (ANA), absence of double strand DNA antibodies (dsDNA), and presence of mitochondrial antibodies (M5) which are also direct against phospholipids in mitochondrial membranes. Primary APS clinical occurrences were grouped in three subsets: 1- patients having idiopathic deep vein thromboses (DVT), pulmonary embolism and pulmonary hypertension in the absence of any autoimmune disease; 2- patients with stroke, transient ischemic attacks and other large vessel occlusions, including myocardial infarction or peripheral vessel thrombosis, particularly under the age of 45, and 3-patients with recurrent miscarriages [23].

Later on, in 1992, Piette *et al.* suggested that a 5-year follow-up or longer was necessary after the first clinical occurrence of APS to rule out SLE progression [24].

Secondary APS

When APS is associated or occurs with other AD or infectious, neoplastic or drug-induced diseases, it is called secondary APS. In the autoimmunity field, the association of APS with SLE is the strongest. However, as we learnt more about antiphospholipid syndrome, multiple associations and clinical varieties have been defined.

Catastrophic APS

Asherson described catastrophic APS (CAPS) as a multiorgan failure due to multiple small vessel occlusions. The vascular-occlusive phenomena occur sequentially and in a narrow days or weeks interval. aPL are present usually in high titres. Less than 1% of APS patients develop CAPS. CAPS is a life-threatening disorder in approximately half of the patients. It may be triggered by different factors: infections and surgical traumas are the most important triggers [25].

SOME CLINICAL MANIFESTATIONS OF THE APS

The following brief presentations of clinical cases illustrate the wide spectrum of clinical manifestations of APS. They were observed by the authors during their clinical practice in a public health hospital in Buenos Aires, Argentina.

Probable APS Associated with SLE or SLE-Like Disease

Since APS started to be documented, it has been described in SLE patients or either in women with limited clinical criteria for SLE (SLE-like). Here, we report a 16-year-old girl with SLE and renal involvement (type II glomerulonephritis) associated with myocarditis and pneumonitis. She improved with corticosteroids and cyclophosphamide. Five years after the initial diagnosis, she developed her second episode of pneumonitis with a proven mild decreased glomerular filtration rate. Between the ages of 25 and 26, she was admitted to the intensive care unit seven times with

episodes of tonic-clonic seizures. Her kidney disease was progressing to sclerosing glomerulonephritis. At the age of 26 years, she became pregnant. At that time, her proteinuria level was 8g/24h, urea 134mg/dl, creatinine 3.8mg%, hematocrit 22%, positive intense ANA, positive DNA, diminished C3 and C4, negative anti-Sm, anti-RNP, anti-La/SSB Ro/SSA and aCL and strong positive LAC. She received meprednisone, azathioprine, low molecular weight heparin (LMWH), intravenous immunoglobulins (IVIG), anticonvulsive agents, erythropoietin and atenolol. At week 32 of gestation, she presented a spontaneous rupture of the membranes. A girl was born by caesarean section weighing 1490g, with a favourable outcome. Fourteen months later she underwent dialysis for kidney failure. At present she is 27 years old and is in the renal transplant waiting list. The diagnosis was SLE associated with features of APS (probable APS).

Sneddon's Syndrome

A 52-year-old male with a 15-day history of focal neurological deficit in his left hemibody with gradual onset is presented. The patient evidences amnesia, impregnation syndrome and depressive syndrome. On examination the patient was awake, had a mild left hemiparesis, mild pyramidal syndrome, livedo reticularis, neurocognitive deficit, and unsteady walk. Brain CT scan showed bilateral paraventricular lacunar hypodense images and bilateral parietal atrophy. Severe hypertension was diagnosed. Laboratory tests revealed positive LAC, IgG aCL 200GPL, IgA aCL >100 APL, ANA 1:1200, and C3 and C4 levels within normal range. With the diagnosis of Sneddon's syndrome and multiple cerebral infarcts, the patient was treated with oral anticoagulation therapy. During the following 8 years no episodes of stroke were registered; however, his cognitive impairment became worse.

Catastrophic APS in a Patient with Kikuchi-Fuyimoto Disease

We described a 30-year-old man with a diagnosis of Kikuchi- Fuyimoto disease (KFD) and CAPS who was admitted to our hospital with a two-month history of febrile syndrome, rash, arthralgia, pharyngotonsillitis and weight loss (more than 10kg). He exhibited hepatosplenomegaly, cervical and submaxillary lymphadenopathy, elevated erythrocyte sedimentation rate (ESR), anemia and IgM positive for cytomegalovirus (CMV) infection. While he was empirically treated with tuberculostatic drugs, he suddenly developed systemic inflammatory response syndrome, multiple organ failure and distal necrosis. Severe sepsis was suspected and antibiotics, corticoids and recombinant human activated protein C was administrated. Exhaustive laboratory testing for sepsis was negative. Histopathological examinations of lymph node confirmed KFD. The patient was discharged after two months in hospital. Laboratory tests showed the presence of aPL. This case exhibits a KFD complicated by definite CAPS. The CMV infection could be a triggering factor for CAPS in this patient [26].

APS and Behcet's Disease

BD is a chronic, inflammatory vasculitis characterized by arthritis, mucocutaneous, ocular, vascular and neurological involvement. A 37-year-old male had a history of sinusitis, otitis media and chronic mastoiditis. Before admission in our institution, he was hospitalized 6 times in a year due to aseptic meningoencephalitis. The patient was bradypsychic and had a history of an episode of DVT involving his lower limbs. His relatives described previous episodes of oral ulcers. During hospitalization he sequentially manifested jugular, retinal, portal vein and inferior cava vein thromboses. The patient had hypertransaminemia associated with positive hepatitis C virus (HCV), lower-limb purple and erythema nodosum, impaired visual capacity and fundus oculi compatible with retinal vasculitis. Microscopic urinary smears showed microhematuria with 80% dysmorphic erythrocytes. Serum creatinine and C3 and C4 levels were in normal range. Assays for ANCA, cryoglobulins, human immunodeficiency virus (HIV) and venereal disease research laboratory (VDRL) were negative. HLA B51 was positive. LAC test was strongly positive while aCL were negative, in two opportunities. Neuro-BD associated with APS was diagnosed. He was treated with corticosteroids, cyclophosphamide and acenocumarol (INR: 3.0). The patient had complete neurological recovery, with no repetition of meningoencephalic episodes, remission of the lower limbs and upper right limb edema, recanalization of portal and cava veins. Skin pathergy test was negative, and otitis media persisted. Meprednisone was gradually reduced until discontinuance in a year. He continued his treatment with cyclophosphamide during two years and indefinite anticoagulation. He has achieved a 7-years neurological remission and no thrombosis occurred during the last five years. In our patient Neuro-BD and APS were present at the same time[1].

APS in Association with Autoimmune Thyroiditis and Sjögren's Syndrome

A woman had a DVT episode involving her lower limbs at the age of 28 years. Six years later, she complained of phosphenes, headache, photophobia, polyarthralgias and dry eyes. Then she is treated with hydroxychloroquine and artificial tears. Laboratory tests for ANA, dsDNA and Ro/SSA antibodies were negative. C3 and C4 levels were in normal range. At 35 years, saphenous vein thrombosis was developed. Persistent positive LAC determinations with negative aCL were detected during 6 months. She began indefinite oral anticoagulation treatment. Six years later, she is diagnosed with autoimmune thyroiditis. Levothyroxine substitutive treatment was installed and she continues with acenocumarol treatment at INR 2-3 with a good clinical evolution. She didn't present new thrombotic episodes.

APS and Progressive Systemic Scleroderma

In 1983 we studied a 38-year-old woman with Raynaud phenomenon, sclerodactylia, severe chest skin thickening, external retromalleolar ulcer, and subsequent dysphagia and soft tissues calcifications. Scl-70 and centromere antibodies were negative. A diagnosis of progressive systemic scleroderma was made. Her sixth pregnancy was in 1986. A normal boy was born weighting 2.350g. Laboratory abnormalities in the mother changed during pregnancy (intense positive ANA and dsDNA and hypocomplementemia). In 1988 she had severe depression and cerebellar hemiataxia

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associated with sudden vision loss in the left eye. After one year she spontaneuosly recovered. A diagnosis of APS was made in 1992. LAC and high levels of IgG aCL were detected in two opportunities; 100mg/day aspirin and acenocumarol were started. Years later, when she was 48-years-old a monoclonal IgA kappa-type protein is detected and a bone marrow biopsy (BMB) revealed only 5% of plasmatic cells. At present she is 58 years and her illness is stable and she did not developed an IgA Multiple Myeloma.

APS in Association with CREST

A 53-year-old female was hospitalized in the coronary unit with symptoms compatible with pulmonary thromboembolism. It is confirmed by V/Q scintigraphy and then, acenocumarol therapy was initiated. She had a history of Raynaud´s disease and relapsing malleolar ulcers in both lower limbs since the age of 30 years; recent dysphagia for solids and mild sclerodactylia. She also had two normal term newborns, an intrauterine fetal death (14 weeks) and another normal newborn but with intrauterine developmental delay with neurological and madurative deficit. At the age of 27 years she developed DVT in her lower limbs, and APS was confirmed. The esophageal manometry confirms the esophageal hypomotility. Positive nuclear antibodies of centromeric pattern (Hep2), and LAC, negative aCL, and nRNP antibodies. Normal C3 and C4 levels were found. CREST variant of Systemic Scleroderma associated with APS is confirmed. She has been on anticoagulants since then. At present she is 61 years old and her illness is stable.

APS with Cardiac Valvular Manifestations

A female patient of 14 year-old developed diffuse alopecia, febrile syndrome, poly arthralgia. Laboratory data revealed a positive ANA 1:1000, negative dsDNA and anti-Sm, and C3 and C4 levels within normal values. Two years later, she exhibited significant proteinuria with a decreased glomerular filtration rate. She had focal proliferative glomerulonephritis and was treated with intravenous cyclophosphamide for 3 months. At the age of 18 years she presented a meningeal syndrome with negative cultures, associated with a left brachiocrural hemiparesis. Superior longitudinal sinus thrombosis was found, and she was treated with corticosteroids. The VDRL assay was weak positive with negative treponemic tests and normal complement. In 1996, aPL investigation revealed high titres IgG aCL (103GPL). Antiaggregation with aspirin 100mg/day was installed. At the age of 22 years she evidenced a mild mitral disease with an enlarged left atrium. The following year, she had a miscarriage. At 25 years, she got pregnant again and received meprednisone 8mg/day and aspirin 100mg/day. Her pregnancy was unremarkable. At week 38th a girl was born by caesarean section weighing 2840g with a 1 min-Apgar score of 9/10, and presenting facial acrocyanosis for 5 days which was interpreted as possible neonatal APS. During puerperium she was administered prophylactic heparin.

At the age of 33 , she became pregnant with her third child and treated with aspirin 100mg/day. A caesarean section with no complications was performed at week 39th of gestation. A boy was born weighing 3200g. LAC remained negative and aCL IgG were positive with a titre of 40GPL. Since then, the remission persisted with hydroxychloroquine and aspirin 100mg/day. After a 19 years follow-up, she presented a mild mitral stenosis with slightly enlarged left atrium and normal doppler. We concluded that it was a juvenile SLE-like disease associated with APS with remarkable mitral valve disease. She was treated only with aspirin and having a very good clinical outcome.

Primary APS with Severe Thrombocytopenia

A female 25-year-old patient had her first pregnancy loss at week 30, with intrauterine growth retardation. During puerperium she presented cardiac insufficiency consecutive to acute and severe arterial hypertension.anemia and low platelet count. Two consecutive LAC and aCL were tested, with six weeks interval and both determinations were positive. At the age of 26, a second pregnancy treated with LMWH in anticoagulant doses had a satisfactory evolution until the 29th week. At that time she developed severe thrombocytopenia from 180x109/l to 35x109/l. Intravenous immunoglobulins were administered and platelet count increased to 65x109/l. At the 30th week, a caesarean intervention was practiced and a baby weighing 2600g was born alive.

Primary APS is Characterized by Recurrent Fetal Loss Associated with C4 Deficiency (C4AQ0) or Low C4 Levels

Low levels C4 state or C4 genetic deficiencies (C4AQ0) may be related with APS.

A 30-year-old otherwise healthy woman visits the doctor due to a history of two fetal losses at 16th and 23rd weeks respectively. In the second placenta there were proved infarction areas. In 1998, she was diagnosed with APS due to positive LAC and IgM aCL in repeated occasions. A chronic false biological positive reaction for syphilis is also detected. During her third pregnancy she was receiving aspirin and LMWH. There was evidence of pathological doppler at week 26th. Therefore, an elective caesarean section was induced. The newborn weighing 500g dies 72 hours later. She is re-evaluated post-partum evidencing thyroiditis with subclinical hypothyroidism, persistently low C4 levels with normal C3, negative ANA and positive 52-kd SSA/RO antibodies.

APS Associated with Eclampsia and Posterior Leukoencephalopahy Syndrome

A 32-year-old female patient with a personal history of livedo reticularis in her lower limbs and an episode of palpebral ptosis associated to positive LAC and positive IgG and IgM aCL, was admitted on the 22nd week of her first pregnancy.

She presented acute onset of complete bilateral blindness associated with headaches, altered mental functioning, seizures, severe hypertension and left hemiplegia. Two days after admission, her fetus died. Computed axial tomography (CAT scan) and magnetic resonance imaging (MRI) studies showed extensive multifocal, bilateral white matter abnormalities in the parietal and occipital cerebral hemispheres, indicating a posterior leukoencephalopathy syndrome (RPLS). She had a remarkable low platelet count, proteinuria, impaired renal function; negative ANA, normal C3 and persistent low C4 level. She was treated with corticoids and regular dialysis. Three months after admission, she was completely recovered. Clinical follow up and neuroimaging

studies showed almost complete resolution of abnormalities suggesting that RPLS was associated with cerebral edema without concomitant infarction. At present she is 34-year-old and she is completely recovered.

Primary APS Leading to SLE

Several studies have suggested that a few patients with primary APS may go on to develop SLE features [27-31]. Progression from primary APS to classical SLE is rare. The transition period may be long, and regular follow-up is essential in patients with primary APS [32]. We describe a 26-year-old woman with polyarthralgia, erythema nodosum, and two times positive test for aCL and LAC. During her first pregnancy she developed severe pre-eclampsia and a fetal loss. She became pregnant again at the age of 29 years. Her baby presented fetal growth retardation. At the age of 35 years, she developed a 20 minutes episode of focal seizures. No alterations were found on EKG, brain CAT or MRI scans. One year later, she developed moderate hypertension with no other clinical signs or laboratory abnormalities. A spiral CAT scan showed bilateral renal stenosis. Anticoagulation with acenocumarol was started. Five months later, a spiral CAT showed recanalization of both renal arteries. Blood pressure normalization was detected [33]. At the age of 41 years the patient complained of hypertension. Nephrotic syndrome with proteinuria >3g/24 hours, granular and blood cylinders were present. The kidney biopsy evidenced diffuse proliferative glomerulonephritis with intensive immune deposits revealed by immunofluorescence.

In brief, the patient presented a SLE-like disease, associated to APS. APS was the dominant condition for 8 years. Later a diffuse proliferative glomerulonephritis and antibodies indicative of SLE (positive dsDNA and anti-Sm) with low levels of C3 and C4 let us consider an evolution from primary APS to SLE. This patient shows the progression of APS-related syndrome evolving into defined serological and clinical SLE. Progression of the disease was evidenced 15 years later from the beginning of her APS related symptoms.

Positive aPL in a SLE- Like Patient in Association with Autoimmune Thyroid Disease who Goes on to Definite APS

A 25-year-old female with polyarthralgia had ANA 1:800, C3 and C4 levels within normal limits and positive M5 antibodies. Amaurosis fugax episodes with normal brain CAT scan was observed. Biologically false positive VDRL test, positive LAC and negative aCL were found. A diagnosis of subclinical Autoimmune Thyroid disease was made simultaneously. In 1988, at the age of 27 years, she gets pregnant for the first time, while on aspirin 100mg/day. On week 42nd, she undergoes a caesarean section with no complications and a healthy 3000g baby was born. Two years later, and after a normal pregnancy, a 4021g normal baby was born on week 40. Until the age of 44 years, the evolution had no remarkable complications but then she developed an ischemic cerebrovascular accident (CVA), featuring expressive aphasia and facio-hemicrural hemiparesia. She experienced full recovery, and since then she has been on oral anticoagulants. At present she is 48 year-old, and has not had any other ischemic CVA. Anti-M5 became negative and aPL are still positive. This is a patient with SLE like-disease, autoimmune thyroid disease and positive aPL who after 23 years of follow up, developed an ischemic CVA associated to persistent positive aPL.

False-Positive Reactions in the VDRL Test and in the Fluorescent Treponemal Antibody Absorption Assay in Positive aPL healthy Women

A 58-year-old woman presented with a reactive VDRL for the first time when she was donating blood donor in 1996. She was examined in the infectious disease department. The Fluorescent Treponemal Antibody Absorption Assay (FTA-ABS) proved to be reactive. The patient received treatment with penicillin although she had no evidence of clinical symptoms of syphilis or evidence of autoimmune manifestations. Her husband's serological studies for syphilis were negative. Despite having denied any possible risky behavior, the diagnosis of syphilis was maintained, which resulted in considerable conflict in her family environment. Over the following 6 years her VDRL remained positive, with values between 2 and 16 dilutions and the FTA-ABS was alternatively read as reactive and non-reactive. She continued receiving treatment. In view of these discrepancies in the diagnostic tests over those 6 years, complementary studies were performed. Microhemagglutination Assay (MHA-TP), FTA-ABS, rheumatoid factor, Rose-Ragan test and HIV test were all negative, whereas LAC, IgG aCL and IgM 130MPL and type 2 mitochondrial antibodies (AMA) were strong positive. We present a healthy woman mistakenly diagnosed as syphilis because of a false-positive VDRL and FTA-ABS related to aPL. We believe that the woman never had syphilis and the positive FTA-ABS resulted from cross reactions between the two recognized autoantibodies (AMA and aPL) [34].

Women with Primary APS, False Positive VDRL Test and M5 Anti-Mitochondrial Antibodies

A healthy 25-year-old woman with a chronic biological false positive reaction for syphilis had a history of two intrauterine deaths at week 22nd and week 24th of her pregnancies. aPL investigation evidenced positive LAC and aCL Ig G >100GPL, negative ANA ; strong positive M5 antibodies; and C3 and C4 levels within normal limits. This is a case of primary APS with a history of intrauterine death and positive aPL and M5 antibodies and a chronic biological false positive reaction for syphilis.

APS or Positive aPL in Solid Organ Transplant

A 57-year-old woman underwent orthotopic liver transplantation (OLT) for primary sclerosing cholangitis, associated with Crohn's disease and on the 5th post-transplant day she evidenced signs of CAPS. She had a history of two transient ischemic attacks six months before transplantation. A CNS CAT scan was normal and a doppler ultrasound of the carotid arteries showed 15% occlusion of the left internal carotid artery. A LA was diagnosed, so she was treated with aspirin. The transplant procedure was uneventful. Antithrombotic prophylaxis was started intraoperatively with aspirin and LMWH, and was sustained postoperatively. The patient had a favourable outcome until day 7, when she developed right hemiparesia. An MRI demonstrated an ischemic lesion in the pons. A doppler ultrasound evidenced 90% vascular occlusion of the left internal carotid artery. She started intravenous anticoagulation with heparin. On day 10,

the patient suddenly developed intense dyspnea, tachycardia, right bundle branch block, profuse sweating, abdominal bloating with generalized pain, arterial hypotension, marked acrocyanosis and livedo reticularis of the four extremities, with worsening of her neurological deficits.

A CAT scan of the abdomen showed marked bowel dilatation, and a large, uncomplicated subhepatic hematoma. She progressively developed encephalopathy, oligoanuria, and hyperthermia and hyperdynamic circulation. A laparotomy showed extensive, patchy ischemia of both small and large intestine associated to a hemoperitoneum of approximately one litre, with no evident bleeding source. All blood, urine and abdominal fluid cultures were negative. No biochemical evidences were suggestive of diffuse intravascular coagulation. The platelet count remained stable. She had a diffuse alveolar infiltrate in the right base and was placed on mechanical ventilation and hemodynamic support. Respiratory support was withdrawn five days later, after her hemodynamic, renal and respiratory functions improved**.** A brain MRI showed an extensive ischemic lesion of the left hemisphere, with marked edema, and middle line herniation. Her neurological status slowly improved, but a right hemiparesis and severe expressive aphasia persisted. The graft function remained optimal until she developed steroid resistant acute rejection on day 41 post-OLT which was controlled after switching her from cyclosporin to tacrolimus. On day 64 post-transplantation the patient was sent to a neurology centre for her rehabilitation.

We think aPL are a risk factor for CAPS or allograft failure. The association of aPL or APS, with autoimmune diseases involving the liver, as well as the ever increasing indications for liver transplantation demand a greater awareness of this severe complication when other causes of multiorgan failure have been ruled out [35].

Positive aPL in a Pregnant Woman with Severe Arteriopathy Related to Takayasu´s Arteritis

Takayasu arteritis (TA) is a rare chronic large-vessel vasculitis that affects most Asian young women. TA patients usually present fever and lack of radial/cubital pulses due to arterial occlusion of aortic branches ("pulseless disease"). Stenosis, aneurysms and hypertension are also common manifestations of the inflammatory compromise. Several neurological symptoms are secondary to vascular damage.

At the age of 21 years a patient developed fever, anemia and high blood pressure, class III–IV dyspnea and difficulty to raise both upper limbs. She had no radial pulses and presented severe aortic insufficiency associated with signs of heart failure. ESR remained elevated and aPL were positive. She had an aneurysmatic dilatation of the descending aorta; a complete occlusion of the left subclavian vein; a 50% blockage of right aorta with a mild dilatation of the primitive left carotid and aneurysmatic distal dilatation. Also a 50% of the right iliac artery was damaged. She received meprednisone and enalapril. Total aortic valve replacement due to severe aortic insufficiency plus a replacement of the descending aorta with a re-implantation of the coronary ostium was performed without complications. The patient was discharged from hospital with acenocumarol with a INR of 3.0. Seven years after, steroids were withdrawn; but methotrextate, folic acid, enalapril and carvedilol were sustained. At the age of 31 years she got pregnant when was not on steroids. ESR and PCR were normal. Lupus anticoagulant was positive while aCL IgG/IgM were negative. She had a complete spontaneous abortion at 6 weeks.

The following year, she got pregnant for the second time. No antihypertensive medication was needed. She received azathioprine 50 mg/day, carvedilol 625 mg/day and LMWH (enoxaparin 80mg) until week 12th. Then, treatment was shifted to acenocumarol and at week 33rd, LMWH was reinstalled. At week 34th, while she was normotensive, presented tachycardia, shortness of breath on exertion and orthopnea. ECG and echocardiogram remained unchanged. Twenty for hours later she had an uneventful elective cesarean section under epidural anesthesia. She had a 2480g boy presenting a 1 min-Apgar score of 9/10. After 30 and 60 days both the mother and the neonate were healthy. This woman with a diagnosis of TA and aPL had a pregnancy without complications. She was treated with anticoagulants since she had a mechanical valve associated to the large vessel vasculitis. In our opinion, aPL present in the TA woman´s blood did not play any role in the vascular occlusion or in the obstetric morbidity observed during the first pregnancy[2].

CONCLUSIONS

Both aPL and APS are more commonly associated to SLE. However, and to a lesser extent, APS may be associated to a very large and yet not well defined AD spectrum.

In our experience, not frequent examples of APS in overlap with other AD appeared in patients who presented CAPS and Kikuchi-Fuyimoto Disease and APS with NeuroBehcet Disease.

Several serological manifestations, such as false positive reactions for syphilis or M5 antibodies or primary C4 deficit may accompany aPL. The presence of aPL in the normal population together with the limited association between overlap APS with other AD different from SLE, discourages the systematic search of aPL in AD not evidencing thromboembolic disease or obstetric morbility. In our experience, women with primary APS have a more remarkable history of obstetric morbility than women with APS secondary to SLE. Future data will reveal whether the pathogenesis and/or the prognosis of patients with APS associated to other AD is different from that of patients with primary APS. Whether the diverse APS presentations delineate clinical subsets with a different prognostic profile needs to be elucidated.

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