Antiphospholipid syndrome*
*Síndrome antifosfolípide**

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Abstract: Antiphospholipid syndrome is an acquired multisystem disorder characterized by recurrent thromboses in the arterial system, venous system, or both. Antiphospholipid syndrome is classified into 2 groups: primary and secondary. Secondary antiphospholipid syndrome is often associated with systemic lupus erythematosus and less frequently with infections, drugs and other diseases. Serologic markers are antiphospholipid antibodies, lupus anticoagulant and anticardiolipin. The primary diagnostic criteria include arterial thrombosis or venous thrombosis and recurrent fetal loss. About 41% of patients with lupus anticoagulant have skin lesions as the first sign of antiphospholipid syndrome. Cutaneous manifestations include livedo reticularis, cutaneous ulceration and livedo vasculitis. The mainstays of prophylaxis and treatment of thrombosis are anticoagulant and antiplatelet agents.
Keywords: Skin manifestations; Antiphospholipid syndrome; Thrombosis

Resumo: *Condição adquirida, sistêmica, caracterizada por tromboses recorrentes no sistema arterial, venoso ou ambos, a síndrome antifosfolípide pode ser primária ou secundária, esta última mais associada ao lúpus eritematoso sistêmico e menos freqüentemente a infecções, fármacos e outras doenças. São marcadores sorológicos da síndrome antifosfolípide os anticorpos antifosfolípides anticoagulante lúpico e anticardiolipina. O critério diagnóstico primário inclui trombose arterial ou venosa e morte fetal recorrente. Cerca de 41% dos pacientes apresentam lesões cutâneas como primeiro sinal da síndrome, que também pode provocar livedo reticular, ulcerações cutâneas, vasculite livedóide, entre outras manifestações. Seu controle consiste principalmente no tratamento e profilaxia da trombose com anticoagulantes e antiagregantes plaquetários.*
Palavras-chave: Manifestações cutâneas; Síndrome antifosfolipídica; Trombose

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial and/or venous thrombosis, fetal death and recurrent miscarriages, and thrombocitopenia, along with elevated titles of atiphospholipid antibodies (APA): lupic anticoagulant and/or cardiolipin. Antiphospholipid syndrome was originally described in patients suffering from systemic lupus erythematosus, and in the past 20 years the involvement of many organs has been described. Cutaneous manifestations are frequent and in 41% of patients they may represent the first manifestation of the syndrome.[1] Livedo reticularis and cutaneous ulcerations are the most prevailing dermatological manifestations. Treatment is based on antiplatelet aggregating or aticoagulant drugs.[2]

The goal of this review is to make readers familiar with historical, epidemiological and etiopathogenic aspects, clinical manifestations, laboratorial diagnosis, differential diagnosis, treatment and prognosis of antiphospholipid syndrome.

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HISTORY

The first antiphospholipid antibody (APA), which reacts with bovine heart antigens, was detected in patients with syphilis back in 1906.[3] It was later identified as cardiolipin, a mithocondrial phospholipid.[4]

Conley and Hartmann were the first to describe, in 1952, the presence of circulating anticoagulant in patients with systemic lupus erythematosus (SLE).[5]

In 1963, Bowie et al.[6] noted the relation between systemic anticoagulants in patients with SLE and thromboembolic events.

Feinstein, Rapaport, in 1972[7] ssuggested the name of "lupic anticoagulant" for this circulating anticoagulant, and Nilsson et al.,[8] in 1975, associated it to recurrent spontaneous abortions.

In 1983 Hughes[9] described the association between antiphospholipid antibodies and venous and arterial thrombosis.

In 1987 Harris et al.[10] Proposed the name antiphospholipid syndrome.

In the beginning of the 1990s, two groups discovered that some anticardiolipin antibodies required the presence of a plasma phospholipid-bound protein (antiβ2-glucoprotein I) to bind to cardiolipin.[11,12]

EPIDEMIOLOGY

Frequency

Frequency in the general population is unknown. APAs can be found in 50% of systemic lupus erythematosus (SLE) patients, and in percentages ranging from 1 to 5% of the healthy population, tending to occur more often in the elderly. Recent studies suggest that the occurrence of antiphospholipid syndrome in SLE patients is between 34% and 42%.[13] In a study with 100 patients with venous thrombosis and no SLE history, 24% had anticardiolipin antibody, and 4%, lupic anticoagulant.[14]

Mortality/morbidity

Antiphospholipid syndrome can contribute to a increase in the frequency of strokes, especially in young individuals,[15] as well as that of myocardial infarction. Valvular cardiac disease can be more aggressive, requiring valve change.[16] Recurrent lung embolus or thrombosis may lead to pulmonary hypertension.[15]

Catastrophic antiphpospholipid syndrome is the most serious manifestation, and is commonly fatal (mortality index of roughly 50%), and is characterized by infarctions in many organs within a period that can vary from days to weeks.[17,18]

Even though spontaneous fetal loss usually occurs in the second or third trimester of pregnancy, it can occur at any time.[19]

Race

There is no race predominance in APS.[20]

Gender

There is predominance in females, especially in secondary APS. This is in accordance with the association between APS and SLE and other connective tissue diseases, where there is predominance in females.[20]

Age

APS commonly occurs in young individuals and middle-aged adults, although it can manifest in children and elderly. There are reports of its occurrence in infants of less than eight months of age.[20]

ETIOLOGY

Causes

Antiphospholipid syndrome is an autoimmune disorder of unknown cause. Association between antiphospholipid antibodies and autoimmune or rheumatic diseases, malignancies, hematological diseases, infections, neurological diseases and drugs has been reported (Chart 1).[21]

Genetic predisposition

Familial association: APAs are found more often in relatives of individuals with APS. A study showed an incidence of 33%.[22]

Association with HLA: recent studies have revealed na association between APA and groups of individuals bearing certain HLA genes, including DRw53, DR7 (mainly individuals of hispanic origin) and DR4 (mainly in white individuals).[23]

PATHOPHYSIOLOGY

An alteration occurs in the homeostasis of blood coagulation. Mechanisms by which APAs interact with the coagulation cascade, thereby producing clinical events, are speculative and have not been totally elucidated yet. Presence of an endothelial lesion, associated to the presence of an APA is a requirement for thrombotic complication.

Possible mechanisms by which APAs induce thrombotic events:[24,25]

1. APAs can bind to platelet membrane phospholipids, resulting in an increase of its adhesion and aggregation.

2. APAs can combine with endothelial cells membrane phospholipids together with antiβ2-glucoprotein I (β2-GP I) and induce activation of the endothelial cell, thus leading to alteration of expression of adhesion molecules, citocin secretion and prostaciclins metabolism, enhancing platelet adhesion and aggregation.

3. Lesion of the endothelial cell can also lead to

CHART 1: Conditions associated with antiphospholipid syndrome

Immune diseases	Systemic lupus erythematosus (25-50%), idiopathic thrombocitopenic purpura (30%), rheumatoid arthritis (33%), psoriatic arthritis (28%), Sjögren's syndrome (42%), giant cell arteritis/ rheumatic polimyalgia (20%), mixed connective tissue disease (22%), systemic sclerosis (25%), Behçet's disease (20%), poliarteritis nodosa, dermatomyositis/polimyositis, autoimmune hemolytic anemia, active chronic hepatitis *Percentages in parenthesis represent patients with APA and not necessarily presence of APS clinical manifestations.
Malignancy	Solid tumors, leukemia, lymphoproliferative disorders/Hodgkin's disease, multiple myeloma, fungoid mycosis
Hematologic diseases	Myelofibrosis, von Willebrand's disease, paraproteinemias
Infectious diseases	Syphilis, hanseniasis, tuberculosis, micoplasma, Lyme's disease, malaria, HIV infection, hepatitis A, hepatitis C, HTLV-1, mononucleosis, adenovirus infection, parvovirus infection, measles, varicella, mumps, bacterial infections (endo carditis and sepsis)
Neurologic diseases	Sneddon's syndrome, miastenia gravis, multiple sclerosis, migraine (hemicrania)
Medication	Clorpromazine, phenytoin, hidralazine, procainamid, quinidine, clozapine, streptomicin, fenothiazines

Source: Nahass GT.[21]

a decrease in endothelium-derived relaxing factor, thus enhancing vasospasm and ischemia.

4. In secondary antiphospholipid syndrome, vascular endothelial lesion has already occurred, increasing occlusion/spasm, ischemia/infarction of vessels and alteration in reperfusion.

5. APAs can interfere in the interaction between coagulation proteins C and S, consequently affecting the formation of the coagulation control complex (activated protein C, protein S and factor V).

Possible mechanisms by which APAs can be produced:[26-28]

1. Autoimmunity.

2. APAS represent a response to internal membrane antigens (e.g. phosphoserin), which are exposed by cells not cleared from circulation due to overload or clearence system defect.

3. APAs may also be crossed reaction antibodies induced by exogenous antigens of infeccious microorganisms (e.g. viral or bacterial).

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Diagnosis depends on high clinical suspicion and confirmation by laboratory findings. When arterial or venous thrombosis occurs in patients who do not have obvious risk factors for thrombosis, or when thrombotic events are recurrent, APS should be considered.[29] However, diagnosis can be difficult owing to a plethora of clinical manifestations and laboratorial difficulties related to detection techniques and result standardization. Moreover, antiphospholipid antibody levels can increase, diminish or occasionally disappear in the course of the disease.[30]

Due to diagnostic difficulties, classification criteria for the antiphospholipid syndrome have been formulated in a recent consensus (Chart 2).[29]

Definite diagnosis of APS requires the presence of at least one clinical and one laboratorial criterion, with no interval limits between clinical event and laboratorial finding. Due to lack of worldwide agreement to differentiate low from moderate or high anticardiolipin antibody levels, three definitions are accepted: a) 15 to 20 phospholipid units separate low from moderate anticardiolipin antibody levels; b) two or 2.5 times the average level of anticardiolipin antibody; c) ninety-ninth percentile of anticardiolipin levels of normal population.[29]

Antiphospholipid syndrome can be classified as primary or secondary. The primary form occurs in the absence of related or base diseases, being more common than the secondary,[2] which is characterized by the association with a large spectrum of ilnesses.[21]

In systemic lupus erythematosus (SLE), antiphospholipid antibodies are present in over one third of patients, although not all of them present the clinical syndrome.[2] Clinical features

CHART 2: International guidelines for preliminary criteria of antiphospholipid syndrome classification

A. Clinical criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous or small vessel thrombosis, occurring in any tissue or organ and confirmed by Doppler or histopathological examination. Histopathology should exclude vasculiditis.

2. Gestational morbidity

a) One or more deaths of morphologically normal fetuses with over 10 gestational weeks

b) One or more births of morphologically normal fetuses with 34 or less gestational weeks by virtue of pre-eclampsia, eclampsia or delayed uterine growth.

c) Three or more spontaneous abortions before 10 weeks of gestational age, excluding chromossomal or maternal causes.

B. Laboratorial criteria

1. Anticardiolipin antibody: IgG or IgM anticardiolipin antibody in moderate to high titles (>20 units) in two or more occasions with a minimal interval of six weeks. Assay must be standardized ELISA.

2. Lupic anticoagulant antibody: lupic anticoagulant antibody in plasma, detected according to the International Society of Thrombosis and Hemostasis.

Source: Gezer S.[29]

and specific antibodies are similar in both primary and secondary APS, and the clinical course of secondary APS is independent on activity or severity of SLE.[31]

CLINICAL MANIFESTATIONS

The most common clinical manifestation of antiphospholipid syndrome is thrombosis, which can affect arterial or venous vessels in any organ. Venous thrombosis, particularly in the lower limbs - probably one of the most common forms of venous thrombosis[25] occurs in over 55% of APS patients.[32] Other affected sites include renal, retinal and hepatic veins.[25] Arterial thrombosis involves the brain in over 50% of the cases, causing transient ischemic attacks (TIA) and strokes; approximately 90% of patients less than 50 years old with TIA are positive for antiphospholipid antibodies.[33] Other sites of arterial thrombosis include heart, eyes, kidneys and peripheral arteries.[32] In APS, thrombosis episodes can occur in vascular beds infrequently affected by other pro-thrombotic states.

Various obstetrical complications can be associated to APS, including miscarriage (mainly in the end of the first trimester), fetal death (in the second and third trimesters of pregnancy), pre-eclampsia, delayed intrauterine growth and Hellp's syndrome.[21] Fetal loss after 10 gestational weeks is a feature of APS bearers, contrary to what is observed in general population, in which miscarriages are more often within the first nine gestational weeks[32] and associated to various causes.[33]

The spectrum of APS clinical manifestations is large; it being able to affect various organs, being characterized by a predominance of thrombotic microangiopathy or ischemia secondary to thromboembolic events[34] (Chart 3).

Cutaneous manifestations

Cutaneous manifestations are generally explained by vascular occlusion and represent a landmark for diagnosis and for the need for extensive systemic investigation, since in 41% of patients suffering from APS they constitute the first sign of the disease.[2,35]

Livedo reticularis (Figure 1) and cutaneous ulcerations are the most frequent dermatological lesions,[30] the former being characterized by purpuric and mottled vascular lesions, with location, extension, infiltration and regularity of different patterns, and which can be physiological or related to numerous conditions, such as SLE and other immunological conditions, infectious diseases and cholesterol embolization.[2] The association between APS and moderate to severe livedo reticularis is significant,[2] and lesions are usually disseminated, infiltrated and have irregular pattern.[30]

Sneddon's syndrome, characterized by extensive livedo reticularis and strokes,[30,36,37] can be associated to APS, and the state of hypercoagulability justifies these features;[30] nevertheless, the absence of antiphospholipid antibodies has been described.[2]

Cutaneous ulcerations normally appear in the extremities, even though they can occur in other areas, leaving atrophic scars.[30] There are four distinct types of ulcerations: 1. small, painful leg ulcerations, of livedoid vasculitis; 2. large ulcera-

CHART 3: Clinical manifestations of antiphospholipid syndrome

Organ system	Primary pathogenic process*	
	Large vessel thromboembolism♦	**Thrombotic microangiopathy**
Arterial	Aorta or carotid, axilar, hepatic, ileofemoral, mesenteric, pancreatic, poplitean, splenic or suclavian arteries thrombosis	
Cardiac	Angina, myocardial infarction, vegetation of cardiac valves, valvular abnormalities, intracardiac thrombus, non-bacterial thrombotic endocarditis (Libman-Sacks), peripheric embolus or artherosclerosis	Myocardial infarction, myocarditis or valvular abnormalities
Cutaneous	Superficial Thromboflebitis, splinter hemorrhage, leg ulcers, distal cutaneous ischemia,skin infarctions, blue finger syndrome or acrocianosis	Livedo reticularis, superficial gangrene, purpura, echimoses or subcutaneous nodules
Endocrin or reproductive	Adrenal failure or infarction, testicular infarction, prostate infarction or necrosis, pituitary gland failure	
Gastrointestinal	Budd-Chiari'syndrome, hepatic, intestinal or splenic infarction, esophageal perforation, ischemic colitis, gallbladder infarction not attributable to stones, pancreatitis or ascitis	Bowel, liver, pancreas or spleen gangrene or infarction
Hematologic	Trombocitopenia, hemolytic anemia, hemolytic-uremic syndrome or thrombotic thrombocitopenic purpura	Disseminated intravascular coagulation
Neurologic	Transitory ischemic attack, stroke (thrombotic or embolic), multiple infarction dementia, transverse myelitis, corea, seizures, encefalopathies, migraine cerebral pseudotumor, cerebral venous thrombosis, amaurosis fugax or multiple mononeuritis	Microthrombi or microinfarctions
Obstetric	Abortion or fetal death, delayed intrauterine growth, Hellp's syndrome, oligohydramnious, pre-eclampsia or uteroplacentary failure	
Ophtalmological	Retinian artery or vein thrombosis, amaurosis fugax	Retinitis
Pulmonary	Pulmonary embolus, pulmonary hypertension, alveolar hemorrhage or pulmonary arterial thrombosis	Alveolar hemorrhage or acute respiratory distress syndrome
Renal	Renal artery or vein thrombosis, renal infarction, hypertension, acute or chronic renal failure, proteinuria, hematuria or nephrotic syndrome	Acute renal failure, thrombotic microangiopathy or hypertension
Venous	Deep venous thrombosis, adrenal, hepatic, mesenteric potal, splenic or inferior cava vein thrombosis	
Miscelaneous	sal septum perforation, avascular bone necrosis	

Source: Levine JS et al.[34]
* Many clinical manifestations of the antiphospholipid syndrome can be a result of large vessel thromboembolism, thrombotic microangiopathy, or both. For the sake of covenience, only manifestations that result exclusively from thrombotic microangipathy or that have it as main characteristic are listed on the "thrombotic microangopathy" column.
♦ Manifestations of antiphospholipid syndrome, the pathogeny of which is uncertain (e.g. thrombocitopenia), are listed in the "large vessel thromboembolism" column.

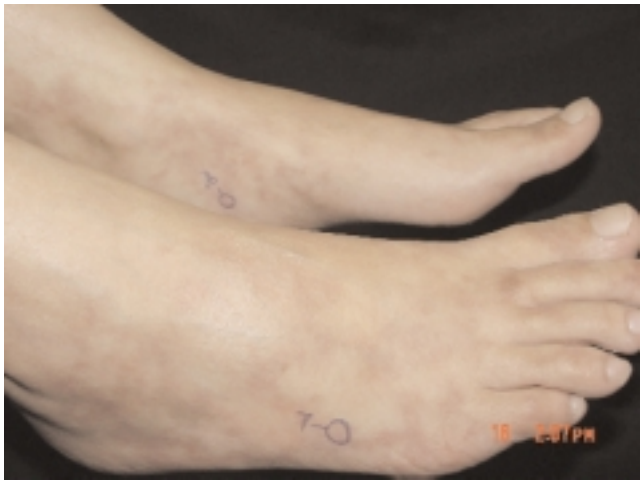

FIGURE 1: Livedo reticularis. One of the cutaneous signs most commonly associated with the antiphospholipid syndrome.

tions similar to those of gangrenous pioderma; 3. Delos type ulcerations; 4. periungueal ulcerations.[38]

Other cutaneous manifestations of APS are thrombophlebites, more common in patients with primary APS when compared to controls,[21] sharpned subungueal hemorrhages (multiple lesions in different fingers warn the occurrence of thrombotic events) and a variety of lesions resembling vasculitis, including purpuras, echimoses, painful nodules and erythematous maculae.[30] Cutaneous gangrene has been reported in 19% of APS patients,[2] and disseminated superficial cutaneous necrosis occurs in 3% of the patients, being the latter characterized by sudden onset painful purpuric lesions in the limbs, head and buttocks.[30]

The association between Degos' disease (malignant atrophic papulosis), anetodermia, progressive systemic sclerosis (PSS), discoid lupus erythematosus (DLE) and T-cell lymphoma and antiphosholipid syndrome is debated. Patients with apparent Degos' disease and positive for antiphospholipid antibodies are speculated to have APS with livedoid vasculitic lesions, resembling malignant atrophic papulosis. Anetodermia could develop due to dermal ischemia and a consequent degeneration of elastic fibers. In PSS, elevated titles of anticardiolipin antibody are found in 33% of patients. These antibodies are proposed to modulate platelet function, resulting in tissue fibrosis and vascular injury. Rarely, DLE lesions can be associated with APS, with no clinical or laboratorial evidence of SLE. In T-cell lymphoma, neoplastic clones are suggested to be able to induce B-cell proliferation with the production of antiphospholipid antibodies.[2]

LABORATORIAL DIAGNOSIS

Antiphospholipid antibodies

Antiphospholipid antibodies form a familily of autoantibodies that exhibit a great spectrum of specific targets, all of them recognizing various combinations of phospholipids, phospholipid-bound plasmatic proteins or both.[34] They can be IgG, and/or IgM, or, less often, IgA.[39] Even though these antibodies have not yet been conclusively evidenced as a cause of thrombosis and abortions, they are useful laboratorial markers of APS.[40] The most common antiphospholipid antibodies subgroups are lupic anticoagulant antibody, anticardiolipin antibody and antiβ2-glucoprotein I antibody. Recent works have described antibodies such as antiprothrombin; however, furher work is still needed for the establishment of its clinical relevance.[41]

Anticardiolipin antibodies are currently detected by an ELISA-type standardized test, which measures immunological reactivity to phospholipids or to β2-glucoprotein phospholipids-bound proteins.[42] Results are expressed quantitatively:[33]

a. weakly positive if IgG varies between 5 and 15 GPL (IgG phospholipid) or if IgM is lower than 6 MPL (IgM phospholipid);

b. moderately positive if IgG varies between 15 and 80 GPL, and IgM between 6 and 50 MPL; and

c. strongly positive if IgG is over 80 GPL and IgM ove 50 MPL.

High IgG levels are seemingly more clinically relevant in terms of predicting the occurrence of thromboses, thrombocitopenia and recurrent miscarriages. Many cases of low or moderate levels of anticardiolipin antibodies have proven to be transient, able to result in occasional interoccurring infections. This is why it is important to repeat the test after six or eight weeks after an initial positive result. Persistence of anticardiolipin antibody in he serum is a necessary criterion for establishing APS.[2]

Antiβ2-glucoprotein antibodies are also detected by immunoassay technique (ELISA).[43,44] Presence of antiβ2-glucoprotein IgG has a high specificity for APS; however, it has low sensitivity, thus its detection should be associated to that of antiardiolipin antibodies.[29] Although its positivity is not currently included in the criteria for APS, antiβ2-glucoprotein antibodies are also related to thromboses and other APS manifestations.[34]

Lupic anticoagulant antibodies are directed against phospholipid-bound proteins, such as β2-glucoprotein I or prothrombin, and are detected by tests that assess phospholipid-dependent coagulation.[45] Due to their heterogenous nature, performing more than one assay becomes necessary for a correct diagnosis. There are different methods to

detect a lengthening of clotting time (Chart 4).[34] The most frequently used are aPTT (activated partial thromboplastin time), KCT (Kaolin clotting time) and dRVVT (dilute Russel's Viper Venom Time). aPTT was previously used as a screening test for lupic anticoagulant antibody,[2] but its sensitivity in APS patients is approximately 30% to 40%. Therefore, many patients with APS have a normal aPTT. KCT is a good screening test for lupic anticoagulant, though the technique is difficult and has complicating factors. dRVVT (based on snake poison) is the most sensitive,[29] thus being the prefered method for the detection of lupic anticoagulant antibody. A more complete screening demands a combination of all of these tests.[2]

In spite of the frequent concordance between lupic anticoagulant antibody and anticardiolipin or antiβ2-glucoprotein, these antibodies are not identical. Some lupic anticoagulant antibodies react with phospholipids other than cardiolipin and with other proteins besides antiβ2-glucoprotein, whereas some anticardiolipins and antiβ2-glucoprotein antibody do not have activity against lupic anticoagulant.[34] Cooccurrence of both anticardiolipin and lupic anticoagulant antibodies in a same patient ranges between 50% and 75%.[21] Several antiposphospholipid antibodies assays should be used for laboratorial diagnosis of APS, since the patient can be negative according to one test and positive according to another.[34]

Generally, lupic anticoagulant antibodies are more specific for APS, albeit anticardiolipin antibodies are more sensitive. APS specificity of anticardiolipin antibody increases with title increase and is higher for IgG than for the IgM isotype.[34]

In studies of the association between the presence of antiphospholipid antibodies and the risk for thrombosis, lupic anticoagulant was concluded to be a clear risk factor for thrombosis, regardeless of type or site of affection, presence of SLE or of the methods used for detection. Conversely, anticardiolipin antibody and antiβ2-glucoprotein antibody are possible risk factors for thrombosis in a few selected situations. Measurement of antiprothrombin antibodies, on the other hand, have not been, to date, helpful in the definition of thrombosis risk, due to the lack of data proving their clinical association with APS.[39]

Histopathology

Skin biopsy is usually necessary for a differential diagnosis. Absence of vasculitis and the finding of non-inflammatory thrombosis of small dermal and hipodermal arteries and veins are the characteristic cutaneous lesions of antiphospholipid syndrome.[34]

CHART 4: Classification and detection of antiphospholipid antibodies

Antibody	Method of detection
Lupic anticoagulant antibody	*First stage*: prolonging of clotting in at least one *in vitro* phospholipid-dependent clotting test with the use of platelet-poor plasma. Tests can be subdivided according to coagulation cascad. Extrinsic pathway (diluted prothrombin time), intrinsic pathway (aPTT, diluted aPTT, silica-coloidal clotting time and kaolim clotting time), common on final pathway (dilute Russel's viper venom time, Taipan venom time, and textarine and ecarine time) *Second stage*: failure in correcting prolonged clotting time by mixing normal patient plasma *Third stage*: confirmation of presence of lupic anticoagulant antibody by shortening or correction of prolonging of clotting time after the addition of excess phos pholipids or platelets. *Fourth stage*: exclusion of coagulopathies by using assays for specific factors if confirming tests are negative or if a specific factor is suspected.
Anticardiolipin antibody	Solid-phase Immunoassay (generally ELISA) is formed by cardiolipin attached to wheels, generally in the presence of bovine seric β2-glucoprotein. Anticardiolipin antibodies of patients with APS are β2-glucoprotein I-dependent; antibodies of patients with infectious diseases are β2-glucoprotein I-independent.
Antiβ2-glucoprotein I antibody	Solid-phase Immunoassay (generally ELISA) is formed by human β2-glucoprotein attached to wheels.

Source: Levine JS et al.[34]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of the antiphospholipid syndrome should be made with patients presenting thromboembolic disorders, infections, vasculidites and increased KPTT (Kaolim partial thromboplastin time).[29]

Thromboembolic Disorder

Antiphospholipid syndrome is one of the many disorders that present a hypercoagulable state, in which thromboembolic phenomena can happen in both arterial and venous territory.[46] Differential diagnosis should be made with diseases and predisposing factors for thromboembolism, such as clotting factors deffects, clot lysis, metabolic defects, platelet alterations, stasis (immobilization, surgery), hyperviscosity, vessel wall defect, use of oral contraceptives, estrogen therapy, pregnancy, puerperium, neoplasia, diabetes, hypertension, cigarrette smoking, hyperlipidemia.[34]

Contrary to other predisposing diseases, which can be identified by means of laboratory exams, APS can display as single alteration the presence of antiphospholipid antibodies. Diagnosis may not be suspected in patients that present symptoms of slow and gradual evolution, potentially leading to idle ischemia and progressive functional loss of an organ.[34]

Infections

When high levels of antiphospholipid antibodies are detected, the possibility of an infectious cause should be considered. These antibodies are frequently seen in patients with syphilis, Lyme's disease, HIV-1, *Micoplasma* infections, malaria and viral infections such as hepatites C, adenovirus, rubella, varicella and mumps.[29] Diagnosis will be made clear with specific tests for the suspected infection.

Vasculiditis

The majority of APS patients has altered clotting screening tests, arterial or venous thrombosis and recurrent abortions. When vascular occlusion occurs in the presence of a known autoimmune disease, e.g. SLE, the possibility of vasculiditis should be considered.[47] Particularly in patients with catastrophic APS, multisystem vascular occlusion can simulate a disseminated vasculiditis, such as thrombotic thrombocitopenic purpura (TTP) and disseminated intravascular coagulation (DIVC).[48] In TTP, the finding of microangiopathic hemolytic anemia (squizocytes) associated with fever, neural and renal alterations, albeit with normal coagulation tests is common. On the other hand, in DIVC, the patient usually has a base disease, which evolves with complex coagulopathy and with formation of fibrin degradation products and increased KPTT.

Increased KPTT

Increased KPTT as an isolated laboratory finding can occur in acquired or hereditary deficiencies of clotting factors VIII, IX, XI and XII. It can also occur secondarily to the presence of an inhibiting factor, which can be a specific factor itself (e.g. an antibody against factor VIII) or a non-specific one (e.g. heparin or lupic anticoagulant). For this reason, KPTT is considered as a good screening test to assess inhibitors such as lupic anticoagulant.[49] In order to differentiate between deficiency of a factor and presence of an inhibitor, normal plasma should be used. In APA, there is a failure in the correction of KPTT even after the infusion of normal plasma. The finding of antiphospholipid antibodies help to confirm the diagnosis. In the presence of specific inhibiting factors, such as antifactor VIII antibody, KPTT is increased due to a reduction of the clotting factor's levels. After mixing normal plasma in the proportion of 1:1, an immediate correction of its values occurs; however, KPTT might increase again within one or two hours under a temperature of 37°C.[29] Inhibitory effects of fibrin degradation products in DIVC can also prolong KPTT. Moreover, depending on the reactant system used, heparin effects (therapeutic or contamination) can also be detected through KPTT prolonging, even in concentrations which are considered low, like 0,05U/ml.[29]

Livedo reticularis

A very frequent skin color alteration found in patients with APS can occur phisiologically (*cutis marmorata*), idiopathically, congenitally or being part of collagen disases (PAN, dermatomiositis, SLE), chronic infections (syphilis, tuberculosis), intravascular obstruction (embolus, thrombocitemia, crioglobulinemia), vessel wall disease (artherosclerosis), lymphomas and by drugs (amantadine, quinine).

Cutaneous ulcerations

Within common APS dermatological manifestations, cutaneous ulcerations should be dicerned from ulcers of vascular origin (artirial, venous, small, medium and large-caliber vasculiditis and lymphatic), neuropathic origin (diabetes, hansebiasis, t*abes dorsalis* and syringomielia), metabolic origin (goou, Gaucher's disease), hematological origin (sickle cell anemia, spherocitosis, talassemia, leukemia), traumatic (pressure), cold, radiodermitis, burns, factitious, neoplastic origin (basocellular and scamocellular carcinomas, sarcomas, lymphomas and metastasis), infectious (bacterial, fungic and protozoan), paniculitis and gangrenous pioderma.

In cutaneous gangrene and necrosis which occur in APS, antiphospholipid antibodies can be

associated with other pathogenic circulating factors, such as crioglobulins, hepatitis antibodies or antiendothelial antibodies.[2]

Patients with SLA and antilupic antibodies may present ulcerations that leave scars with china-like atrophic centers when involute, mimmicking Degos' disease. This latter syndrome is a rare entity, with leality of 50%, and in which antiphospolipid antibodies are negative.[2]

TREATMENT

Primary profilaxis, prevention of recurrent thrombosis, treatment of acute thrombosis and handling during pregnancy should all be considered for the treatment of APS.

Profilaxis

Patients who are positive for antibodies but have no history of thrombosis are not candidates for profilatic treatment with drugs.[2] Nevertheless, risk factors for thrombosis, e.g. hypertension, smoking, hypercholesterolemia, contraceptive use and prolonged immobilization should be eliminated.[50]

Profilatic use of aspirin in low doses is useful for prevention of thrombosis in women with recurrent miscarriages, but it does not prevent deep venous thrombosis in men with APS.[29,34,50] In SLE and secondary APS, hydroxicloroquine has shown protecting effect against thromboses, not to mention reduction of cholesterol levels and glicemia.[2,29,34]

Patients who undergo surgery and need to be immobilized for long periods of time require profilatic heparinization, and in APS sometimes doses should be higher than usual, namely, 25,000 to 40,000U/day, due to resistance to anticoagulants effects.[2]

Treatment of obstetrical complications

Presence of antiphospholipid antibodies increases risk of miscarriages during the fetal period (over 10 gestational weeks) and of premature labor due to uteroplacentary failure.[2,34] Treatment has evolved, thus decreasing the number of these complications (Chart 5).

Use of prednisone, at the daily dose of 40mg, has decreased incidence of spontaneous abortion, but increased the number of preterm labors and maternal morbidity,[32,51,52] including diabetes, hypertension and sepsis.[32] Although intravenous immunoglobulins can be used for the treatment of a few autoimmune diseases during pregnancy, randomized studies have not demonstrated benefit in comparison to heparin treatment in APS.[34,51,52]

Many prospective studies have demonstrated that treatment with a combination of heparin and low-dose aspirin are more effective in preventing spontaneous abortions in patients with APS than aspirin alone,[2,29,32,34,40,51,52] hence, this should be initiated as soon as pregnancy is confirmed.[34,40] AAspirin dose should be of 81mg/day; however, heparin dosing is still a controversial issue.[2,29,32,34,51,52] Some authors recommend doses of 5,000 SC every 12 hours, in the absence of a history of previous thromboses,[32,52] while others recommend doses which vary according to pregnancy stage and previous history of thrombosis.[32,51]

Non-fractioned heparin can be replaced by low molecular weight heparin, with the advantage of daily administration, in addition to reducing the risks of low platelet counts and osteoporosis induced by non-fractioned heparin.[29,32,34,40] The low molecular weight heparins used in pregnancy are enoxaparin 40mg/day and dalteparin 5,000U/day.[29]

Incidental finding of antiphospholipid antibodies during pregnancy with no previous clinical history of its complications does not require treatment.[29]

Patients using warfarin for previous thrombosis should have their treatments substituted with heparin in the course of pregnancy, due to the latter's teratogenic effects.[2,32]

Catastrophic antiphospholipid syndrome

This rare manifestation of APS, characterized by generalized vascular occlusion, often resulting in death, might not respond to isolated anticoagulant therapy. Treatment is made with a combination of anticoagulation, steroids, and plasmapheresis or intravenous immunoglobulin.[2,29,32,34,50] The use of fibrinolytic agents has no proven benefit.

Treatment after primary thrombotic event

There is no evidence that acute treatment of thrombosis secondary to APS should be any different from treatment of acute thrombosis due to other causes.[20] Initial therapy is made with non-fractioned or low molecular weight heparin, followed by warfarin.[32,51] Since patients with APS and thrombosis are at high risk for recurrent thromboembolism episodes, prolonged, perhaps life-long oral anticoagulation therapy is a guarantee for the prevention of new episodes.[29] The most widely used oral anticoagulant is warfarin. Studies show still variable resultes concerning intensity of anticoagulant treatment.[32,40,50,51] Whereas some indicate a lower risk for new episodes of thrombosis with an intensive warfarin treatment, maitaining INR > 3,[2,29,53,54] eother studies, including a prospective one,[55] show that INR can be maintained between 2 and 3 in control, with recurrence indices similar to patients with INR > 3, albeit with lower bleeding risk.[34,55,56]

Cutaneous manifestations in general respond to the treatment of base disease. There are studies

CHART 5: Obstetrical treatment of APS with subcutaneous heparin

Recurrent embrionary period abortions and preeclampsia with no history of thrombotic events

A. Non-fractioned heparin 5.000-7.500U 12/12 hours in the first trimester; 5.000-10.000U 12/ 12 hours in the second and third trimesters

B. Low molecular weight heparin:
1) enoxaparin 40mg/day or dalteparin 5.000U/day or
2) enoxaparin 30mg 12/12 hours or dalteparin 5.000U 12/12 hours

Fetal death or early pre-eclampsia or severe placentary failure

A. Non-fractioned heparin 7.500-10.000U 12/12 hours in the first trimester; 10.000U 12/12 hours in the second and third trimesters

B. Low molecular weight heparin:
1) enoxaparin 40mg/day or dalteparin 5.000U/day or
2) enoxaparin 30mg 12/12 hours or dalteparin 5.000U 12/12 hours

Anticoagulation in women with previous thrombotic events

A. Non-fractioned heparin 7.500U every 8-12 hours

B. Low molecular weight heparin
1) weight-adjusted (enoxaparin 1mg/kg 12/12 hours or dalteparin 200U/kg 12/12 hours) or
2) intermediate doses (enoxaparin 40mg/day or dalteparin 5.000U/day in the first 16 gestational weeks and every 12 hours from 16th week on)

Source: Luzzana C et al.[51]

which report cure of chronic ulcerations caused by livedoid vasculiditis after the use of fibrinolytic agents.[2]

EVOLUTION, PROGNOSIS AND COMPLICATIONS

Clinical manifestations of APS are quite heterogenous, which determines a highly variable evolution.[57,58]

Even though the association between clinical manifestations and presence of antiphospholipid antibody is more evident in primary APS, there is no difference in evolution of primary or secondary forms.[34]

There is little consistent data in the literature concerning prognosis and clinical evolution of patients. A few recent studies suggest three forms of evolution:[59]

1. isolated or associated clinical manifestation in a single episode (e.g. livedo reticularis and livedo reticularis + cerebral ischemia);

2. recurrent episodes: APS frequently occurs with recurrence of its clinical manifestations, mainly thrombotic events.[57,60,61] Anticardiolipin antibodies titles greater than 40, associated with a previous thrombosis episode, are independent risk factors for a new thrombosis episode. Patients with SLE and who are positive for anticardiolipin antibodies have a higher predisposition to recurrent thrombotic events. Average time between the first and the second event is three years. The severity of the initial clinical manifestation and the presence of antiβ2-GPI antibody in the first episode of the disease suggest a worse prognosis, since average time for the second event is reduced to less than 12 months;[57,62]

3. catastrophic antiphospholipid syndrome (CAS) or Asherson's syndrome: is an uncommon variant of APS, predominantly characterized by small vessel obstructive disease, affecting at least three different organs in a period varying from days to weeks. It manifests clinically as three distinct forms:[48]

a. einitial event of APS;

b. primary evolution of APS: most common form;

c. secondary evolution of APS (commonly associated with SLE).

The reason why some patients develop thromboembolic events in large vessels and others in small vessels is still unknown. Notwithstanding the fact that 45% of the patients do not have a well defined triggering factor, it is postulated that infections, trauma, coagulopathies, use of medication, neoplasias, pregnancy and acutization of SLE might be involved as triggers of this syndrome.[48]

The kidney is the most affected organ, followed by the lung, CNS, heart and skin (55% to 66%). The most commom dermatological manifestations are livedo reticularis, skin necrosis and purpura.[34]

The mortality rate is 50% and death is due to

multiple organ dysfunction.[34,48,59]

Prognosis of patients suffering from APS is quite variable and depends on different factors:

1. severity of initial clinical manifestation: the kind of initial clinical manifestatin affects both the frequency and type of a subsequent event. If the clinical picture is associated with high anticardiolipin antibody titles (over 40); if there are two associated clinical manifestation (e.g. livedo reticularis and venous thrombosis) or hemolytic anemia as the initial manifestation, prognosis is worse;[57,59]

2. previous disease history: A previous thrombotic episode increases the probability of a new event;[60]

3. high antibody levels: presence of antiβ2-GPI in the initial picture increases the probability of complications in over 50%;

4. proper therapy: the use of anticoagulants decreases the probability of serious events by about 78 to 91%;[34,57,60]

5. neoplasias: neoplasia prevalence during APS evolution ranges from 17 to 20%.[60]

COMMENTS

The Antiphospholipid Syndrome is a multisystem disorder associated with a variety of circulating antibodies, the targets of which are different phospholipid complexes. The main clinical manifestations are fetal loss and arterial and/or venous thrombotic complications, which may manifest as cutaneous lesions. It is important for the dermatologist to recognize cutaneous signs associated to this syndrome, thus collaborating for its early diagnosis and treatment. ❑

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Questões e resultados das questões

1. Quanto aos mecanismos de indução de trombose pelos anticorpos antifosfolípide (AAF), assinale a resposta correta:
   a) a presença de lesão vascular associada à presença de um AAF é requisito para complicação trombótica
   b) AAFs ligam-se a fosfolípides de membrana das plaquetas, resultando em diminuição de sua adesão e agregação
   c) AAFs não interferem na formação do complexo de controle da coagulação
   d) vasoespasmo e isquemia não estão associados à lesão da célula endotelial

2. Sobre a epidemiologia da SAF, podemos fazer várias afirmações, exceto:
   a) AAFs podem ser encontrados em proporção que varia até de um a 5% da população saudável
   b) AAFs podem ser encontrados em 50% dos pacientes com LES
   c) SAF pode contribuir para aumento na freqüência de acidentes cerebrovasculares
   d) há predominância de SAF em pacientes caucasianos

3. Anticorpos antifosfolípides são dirigidos contra:
   a) fosfolípides e proteínas plasmáticas ligadas a fosfolípides
   b) proteínas do complexo MHC classe III
   c) proteínas plasmáticas ligadas a carboidratos
   d) antígenos nucleares

4. Anticorpos antifosfolípides podem ser encontrados nas infecções relacionadas abaixo, exceto:
   a) HIV
   b) Hepatite C
   c) impetigo
   d) rubéola

5. Estas manifestações são características clínicas da síndrome antifosfolípide, exceto:
   a) trombocitose
   b) trombose arterial
   c) vegetações de válvulas cardíacas
   d) aborto ou morte fetal

6. Qual a percentagem aproximada de pacientes que manifestam lesões cutâneas como primeiro sinal da síndrome antifosfolípide?
   a) 5%
   b) 20%
   c) 40%
   d) 80%

7. As úlceras cutâneas são uma das manifestações clínicas mais freqüentes da síndrome antifosfolípide (SAF), podendo causar cicatrizes atróficas. São típicas da SAF:
   a) úlceras de vasculite livedóide, úlceras orais, úlceras lembrando doença de Degos
   b) úlceras de vasculite livedóide, úlceras lembran do pioderma gangrenoso, úlceras neurotróficas
   c) úlceras de vasculite livedóide, úlceras orais, úlceras neurotróficas
   d) úlceras de vasculite livedóide, úlceras lembran do pioderma gangrenoso, úlceras periungueais

8. A síndrome de Sneddon caracteriza-se por:
   a) livedo reticular + síndrome antifosfolípide
   b) livedo reticular + acidentes cerebrovasculares
   c) síndrome antifosfolípide + acidentes cerebrovasculares
   d) livedo reticular + presença de anticorpos antifosfolípides

9. Anticorpos anticardiolipina são detectados atualmente por:
   a) testes de coagulação
   b) imunofluorescência direta
   c) imunoensaio de fase sólida (Elisa padrão)
   d) fixação de complemento

10. Marque a resposta correta:
   a) o VDRL é um teste específico e sensível para SAF
   b) anticorpos anticardiolipina contra a β2-glico proteína I são mais específicos do que anticorpos contra fosfolípides
   c) anticorpos anticoagulante lúpico são direcionados principalmente contra β2-glicoproteína e fibrinogênio
   d) o PTTa é um teste altamente sensível para SAF

11. O diagnóstico diferencial da SAF deve ser realizado com as doenças relacionadas abaixo, exceto:
   a) vasculite
   b) tromboembolismo
   c) infecções
   d) psoríase

12. A SAF castastrófica caracteriza-se por oclusão multissistêmica e pode simular as seguintes doenças:
   a) púrpura trombocitopênica trombótica e coagulação intravascular disseminada
   b) hemofilia e púrpura trombocitopênica trombótica
   c) púrpura trombocitopênica idiopática e mielodisplasia
   d) coagulação intravascular disseminada e mieloma múltiplo

13. Quanto à profilaxia da SAF, as afirmações abaixo são corretas, exceto:
a) todos os pacientes com anticorpos positivos devem receber antiagregantes plaquetários
b) fatores associados a trombose, como hipertensão, devem ser controlados
c) a hidroxicloroquina pode ser usada em pacientes com LES e SAF secundária
d) pacientes com SAF e com necessidade de imobilização prolongada podem necessitar de altas doses de anticoagulantes.

14. Na SAF associada à gestação, qual o melhor tratamento?
a) aspirina
b) warfarin
c) aspirina e warfarin
d) aspirina e heparina

15. Quanto ao uso de anticoagulantes na gravidez:
a) o uso de warfarin é recomendado
b) as doses de heparina podem variar durante a gestação
c) aspirina isoladamente é útil
d) anticoagulantes orais podem ser usados sem restrição

16. No tratamento da trombose na SAF:
a) o tratamento prolongado com anticoagulação não é necessário
b) controle do RNI não é necessário
c) o tratamento inicia-se com heparina e continua com warfarin
d) o tratamento é diferente das tromboses originadas por outras causas

17. Quanto à evolução da SAF, pode-se afirmar:
a) é pior na forma primária
b) é pior na forma secundária
c) não existe diferença entre as duas formas
d) a SAF catastrófica é comum

18. Quanto ao prognóstico da forma recorrente da SAF, qual é o evento mais comum?
a) livedo reticular
b) isquemia cerebral
c) úlcera de perna
d) fenômenos trombóticos

19. Os fatores abaixo são de mau prognóstico na SAF, exceto:
a) títulos de anticardiolipina superiores a 40
b) episódio prévio de trombose
c) gravidade da manifestação clínica inicial
d) ausência de anticorpo antibeta 2-glicoproteína I

20. Quanto à síndrome antifosfolípide catastrófica, as afirmações abaixo são corretas, exceto:
a) pode ser evento inicial da SAF
b) pode ser evolução da SAF primária
c) pode ser evolução da SAF secundária
d) é a forma associada à oclusão predominante de grandes vasos

GABARITO

Lúpus eritematoso cutâneo - aspectos clínicos e laboratoriais. 2005;80(2):119-31.

1- d	11- a
2- c	12- c
3- b	13- c
4- a	14- s
5- d	15- b
6- d	16- a
7- d	17- a
8- a	18- d
9- c	19- a
10- b	20- d