

Polymorphism of skin involvement in Hughes (antiphospholipid) syndrome

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ABSTRACT

Hughes antiphospholipid syndrome (APS) is an autoimmune disorder, and moreover is an important cause of acquired thrombophilia. It is also known as Hughes' syndrome, after Dr Graham RV Hughes, who first described the condition in the British Medical Journal in 1983. Owing to diagnostic complexity, classification criteria for the antiphospholipid syndrome have been frequently renewed. Currently, it was applied the new revised classification criteria for the Hughes' syndrome. The actual classification advises against using the term "secondary" APS because cumulative data studies didn't find differences in the clinical consequences of antiphospholipid antibodies among primary APS and "APS associated with other autoimmune disorders". Cutaneous involvement in APS is diverse and heterogeneous, and may be the primary manifestation of the disease.

Keywords: Hughes' syndrome, antiphospholipid syndrome, antiphospholipid antibodies, cutaneous manifestations, autoimmune disorders

I. INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disorder with recurrent arterial and/or venous thrombosis, and pregnancy loss associated with positive results of

anticardiolipin antibodies, anti beta 2 glycoprotein I antibodies or positive lupus anticoagulant tests.

Currently, APS is foremost a thrombotic syndrome, with clinical consequences in almost

all aspects of medicine. Antiphospholipid syndrome is regarded as an autoimmune systemic disease. It is also known as Hughes' syndrome, after Dr Graham RV Hughes, who first described the condition in the British Medical Journal in 1983 (1). At present there are about 80 autoimmune diseases, and the most known are systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis, type I diabetes mellitus, and dermatomyositis. The statistics about autoimmune diseases prevalence is not precisely but last numbers show about 50 million people diagnosed with autoimmune disease. There is an influence of age, gender, hormonal factors and other factors on clinical manifestations of APS. These types of diseases affects generally women, consequently about 75% of cases are females between 15-44 years of age.

APS has now two classification forms. „Primary APS“ is the form with no other underlying disease or no associated autoimmune diseases (2). Secondary APS is also named „APS associated with another autoimmune disease“, and as the name suggests, this form is associated with other autoimmune diseases, most often with systemic lupus erythematosus (SLE) (3,4). Both forms of APS are similar, but in the „APS associated with autoimmune diseases“ endocarditis, valve diseases and hemolytic anemia appears more frequently (4).

The basis of Hughes' syndrome pathology is the non-inflammatory vascular thrombosis, which may affect vessels of all sizes. Practically, it may affect any organ but the clinical hallmarks of Hughes' syndrome are thrombosis and pregnancy morbidity which underline the systemic nature of the disease.

APS occurs most commonly in young to middle-aged adults and the first manifestation with the thrombosis typically are diagnosed in the fourth or fifth decades (5), and rarely later in life (6). The most presenting clinical manifestations of Hughes' syndrome are (7): deep venous thrombosis: 32%, thrombocytopenia (<100.000/mm³): 22%, livedo reticularis: 20%, stroke: 13%, pulmonary embolism: 13%, fetal loss: 8%, hemolytic anemia: 7%, myocardial infarction: 3%. Also, females have higher frequency of arthritis, livedo reticularis, and migraine; but males have higher frequency of myocardial infarction, epilepsy, and arterial thrombosis in the lower legs and feet. Conversely, diagnosis can be difficult owing

to a plethora of clinical manifestations and laboratory difficulties related to detection techniques and result standardization.

Antiphospholipid antibodies (aPL) are present in 2-5% of the general population, usually at low titre and without symptoms, and the lupus anticoagulant (LAC) and anticardiolipin antibodies (aCL) are the serological hallmarks of the APS.

APS are reported as titers, GPL units or borderline, positive or high positive (33). Laboratory criteria for defining the APS include only the most well-established tests for lupus anticoagulants (LAC) and anticardiolipin (aCL) antibodies. In theory, the laboratory criteria for APS seems easy: a positive test for LAC and/or a medium to high IgM and/or IgG titre for aPL. A positive test should always be repeated after six to eight weeks with a second sample to establish persistent positivity.

Lupus Anticoagulants (LAC) is detected by a complete coagulation screening that starts by the detection of the increased PT and/or APTT. Subsequently, a mixing laboratory test which does not correct the PT and/or APTT indicates the presence of a LAC, or less commonly an inhibitor of any of the coagulation factors. Because no single assay is 100% sensitive for LAC, at least two different tests should be used for screening. The usual route is to do both the kaolin clotting time (KCT) and the dilute Russell viper venom time (DRVVT) procedures. The KCT examines the clotting cascade including contact activation; while the DRVVT focuses on the prothrombinase reaction using limiting amounts of phospholipid and direct activation of factor X to Xa. It is recommended to check for other causes of assay prolongation such as specific antifactor antibodies, factor deficiencies, or inhibitory anticoagulants such as heparin and confirmation of correction with excess phospholipids are essential (8). The patient with APS should have on screening a prolonged APTT, that does not correct in a 80:20 mixture with normal human plasma (50:50 mixes with normal plasma are insensitive to all but the highest antibody levels). LAC are more specific for APS than anticardiolipin antibodies (8).

Anticardiolipin antibodies (aCL) are measured by enzyme linked immunoassay (ELISA). In general, aCL are considered to be more sensitive than lupus anticoagulants (LAC) for the detection of APS (9). The aCL test is positive in 80% to 90% of patients with APS being implicated in approximately five times more cases of APS than are LAC. aCL are also associated with infections, hepatitis C, malaria, lyme disease, syphilis, HIV; leukaemia and solid-organ malignancies; alcoholic cirrhosis; and increase with age. The specificity of aCL for APS increases with titre and is higher for the IgG than for the IgM isotype (10). Currently, anti-beta2 glycoprotein I antibodies are included in the new criteria of diagnosis for antiphospholipid syndrome (11).

Existing data indicate that the treatment for patients with thrombosis associated with the APS should be the same as for patients with thrombosis of other grounds. Anticoagulation with acenocoumarol to an international normalized ratio (INR) of 2 to 3, after an episode of spontaneous thromboembolism, seems not enough in APS; therefore it is appropriate to achieve a target INR level of 2.5 to 4.0 or 3. Prophylactic oral anticoagulant should be long-term after venous thrombosis, because patients with Hughes' syndrome are prone to recurrent thrombosis. The presence of thrombosis regardless of enough anticoagulation may require corticosteroids, plasmapheresis, or cyclophosphamide in addition to anticoagulation. These patients may also benefit from therapy with weight-adjusted doses of a low-molecular-weight heparin. □

II. DERMATOLOGICAL MANIFESTATIONS OF HUGHES' SYNDROME

Although skin lesions are not a criterion for the diagnosis of APS, various cutaneous abnormalities have been associated (2). Skin lesions are one of the first signs of the Hughes' syndrome and may be noticeable as livedo reticularis, livedo racemosa, livedoid vasculitis, or ischemic ulcerations (Figure 1) (12). Moreover, the frequency of cutaneous manifestations seems to be about 41% of cases (13). The

mechanism of skin lesions of APS is vascular occlusion which may be a marker for diagnosis (2,13,14).

The most described skin manifestations of APS are livedo reticularis, livedo vasculitis, cutaneous ulcers, digital gangrene, subungueal splinter hemorrhages, thrombophlebitis, thrombocytopenic purpura, pyoderma-like leg ulcers, necrotizing vasculitis, painful skin nodules, primary anetoderma, and extensive cutaneous necrosis (10,15,16). In addition, APS is mentioned as a causal factor in the progress of the livedo-type skin lesions (2). On the other hand, livedo reticularis or „blotchy skin“ and cutaneous ulcerations are the most frequent dermatological lesions (17).

Skin biopsy is necessary for the differential diagnosis of cutaneous involvement of APS. The characteristic skin lesions of Hughes' syndrome usually show the absence of vasculitis but with non-inflammatory thrombosis of small dermal and hypodermal arteries and veins (10). Specific findings in blood vessels determined by APS include endothelial cell injury, intramural lymphocytic infiltrate, and luminal thrombi. Although the luminal thrombi may be absent, it is also a regular element in patients with a primary collagen vascular disease (18). Proliferation of dilated capillaries in the deep and superficial dermis may be present (18).

Anticoagulation, usually with acenocoumarol, is the mainstay of therapy, although steroids, immunosuppressive agents, hydroxychloroquine sulfate, and plasmapheresis may all be beneficial adjunctive therapy. Therapy for skin manifestations of APS is long-term anticoagulation with an international normalized ratio (INR) of 3:4 (19). Also, it is recommended to treat risk factors, such as smoking, hypertension and hypercholesterolemia. Leg ulcers respond to coumadin or thrombolytic drugs plus local care of the ulcer. Immunosuppressive agents, e.g., cyclophosphamide, and plasma exchange seem to be efficacious in addition to anticoagulation. Long term use of low doses of aspirin 75mg/day may be effective in diminishing the risk of arterial thrombosis. Prophylaxis of venous thrombosis includes the administration of heparin by subcutaneous or intravenous way (19).

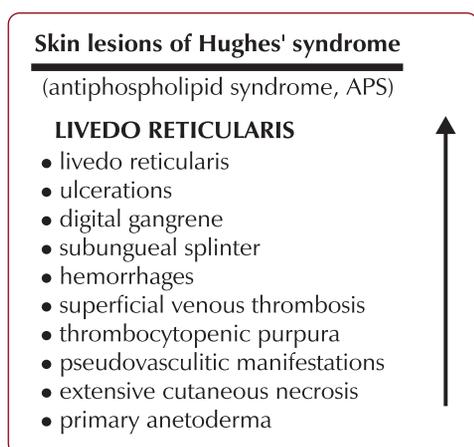


Figure 1. Asherson RA, Frances C, Iaccarino L, Khamashta MA, Malacarne F, Piette JC, Tincani A, Doria A – The antiphospholipid antibody syndrome: diagnosis, skin manifestations and current therapy. *Clin Exp Rheumatol* 2006 Jan-Feb; 2(1 Suppl 40):S46-51.

Livedo reticularis is the most frequent cutaneous manifestation of APS, and can be observed in about 55% of patients with this syndrome (20). Livedo reticularis is defined as

the painless reddish blue reticular skin lesion that does not blanch, and appears usually on members, buttocks, trunk, and face (17). Currently, the term "livedo reticularis" is used for all types of livedo, even with the Ehrmann classification from 1907, which classify livedo reticularis in two different forms:

1. the physiological form – livedo reticularis (cutis marmorata);
2. the pathological form – livedo racemosa.

Livedo reticularis has been frequently described in patients with APS and also reported in association with valvular heart pathology and strokes (i.e. Sneddon's syndrome). Sneddon's syndrome (or Ehrmann-Sneddon syndrome) (SS) is a neurodermatologic disorder of idiopathic livedo reticularis with systemic involvement. It is defined by the association of livedo racemosa with cerebral involvement. Moreover, livedo racemosa precedes the cerebrovascular events by years in more than 50% cases, and develops typically on the members, buttocks, trunk, and face (21). The cerebrovascular manifestations in SS are secondary to ischemic strokes (22). Practically, all cerebrovascular manifestations are determined by infarcts of the middle cerebral artery with hemiparesis, sensory disturbances and aphasia (23). Most authors suggest that 40–50% of SS patients are aPS – positive (24).

Livedo reticularis occurs in about 20% to 30% of patients with Hughes' syndrome and is found most often on the thighs and forearms (25). Furthermore, the recent data offered by Cervera et al., which studied one thousand patients with Hughes' syndrome, found livedo reticularis in about 20,4% of subjects (7). Characteristically, it is significantly associated with the arterial thrombosis from Hughes' syndrome (26). Recently, another study of Hughes et al., suggests that pregnancy loss may also be independently associated with widespread livedo reticularis in patients who are antiphospholipid antibodies negative, but a larger study is needed. Moreover, the association between APS and moderate to severe livedo reticularis seems to be significant (2) but it cannot be now considered specific to the Hughes' syndrome (7).

Livedoid vasculopathy, also known as "atrophie blanche" or "livedo vasculitis" is a rare idiopathic chronic disorder that appears firstly by painful, purpuric macules on the lower extremities that superficially ulcerate. In fact, the term "atrophie blanche" is used as a descriptive

term that represents the ivory-white stellate scars from the lower limbs. Livedoid vasculopathy was first reported to be associated with protein C deficiency in 1992. It is scarring in the form of asymmetrical, ivory-white, stellate plaques with peripheral telangiectasias and hyperpigmentation. The pathogenesis is unclear and usually appears to young patients. For many years, livedoid vasculopathy has been considered to be a primary vasculitic process but now is considered as an occlusive vasculopathy due to a hypercoagulable state. The histological examination shows dermal vessel occlusion without inflammatory cell infiltration. The absence of a sufficient perivascular infiltrate or leucocytoclasia argues against a vasculitis, being more in keeping with a thrombo-occlusive process. Treatment with acetylsalicylic acid, acenocoumarol or heparin as well as topical therapy with disinfectant and granulation-inducing agents may be a beneficial therapy for patients with livedoid vasculopathy. A future therapy may be the hyperbaric oxygen (HBO) treatment but the current data are furnished only by one successful trial applied on patients with livedoid vasculopathy.

Cutaneous ulcerations. Nonhealing skin ulceration is a cutaneous manifestation of the antiphospholipid syndrome and is associated with thrombosis of upper dermal blood vessels without vasculitis, consistent with antiphospholipid antibody-related skin necrosis. Furthermore, a high number of hereditary or acquired disorders are predisposing to thrombosis, such as the antiphospholipid syndrome, deficiency of antithrombin III, protein C or protein S, or abnormal clotting factors (factor V Leiden, factor II mutant). Ulcerations of APS are common, painful, necrotic, chronic, and recurrent, which typically occur on the lower extremities (19,25). Sometimes, they are leaving atrophic scars in evolution (17). Usually, wound healing is associated with a marked recovery in blood flow by scanning laser Doppler. The differential diagnosis of skin ulcerations from APS includes ulcers of vascular cause, neuropathic cause (diabetes mellitus, tabes dorsalis and syringomyelia), metabolic cause (Gaucher's disease), hematological cause (sickle cell anemia, thalassemia, leukemia, and spherocytosis), traumatic cause, cold, burns, radiodermatitis, neoplasm (basocellular and squamocellular carcinomas, lymphomas, sarcomas,

and metastasis), infectious origin, panniculitis and gangrenous pioderma.

A rare form of cutaneous necrosis from APS is **necrotizing purpura** and it often occurs on the legs, face, and ears, preceding the ulceration by years (27). The skin gangrene and necrosis associated with Hughes' syndrome may often be characterized by the association of the antiphospholipid antibodies with crioglobulins, hepatitis antibodies or antiendothelial antibodies (2). Superficial skin necrosis is emphasized by some reports (28,29), and also skin gangrene has been reported in 19% of APS patients (2). Moreover, some clinicians recommend that patients with cutaneous infarctions in the absence of atherosclerosis be evaluated for Hughes' syndrome. Consider fibrinolytic therapy if cutaneous infarction persists despite anticoagulant therapy.

Macules and nodules. Erythematous skin macules and painful skin nodules may be present with APS, and usually are located on the palms, soles, and fingers, but do not disappear on pressure (30-32). They are improving with salicylate therapy (33).

Multiple subungual splinter hemorrhages have been initially described as an important sign of subacute endocarditis. Multiple subungual splinter hemorrhages are not frequently in the Hughes' syndrome, however are reported in the absence of infective bacterial endocarditis, or secondary to warfarin withdrawal, with oral contraceptives, or during pregnancy (34). The mechanism of subungual splinter hemorrhages is most possibly thrombotic.

Anetoderma or „macular atrophy“ is defined by limited areas of flaccid skin caused by the loss of elastic tissue in the dermis. Anetoderma has firstly been reported in patients with HIV-1 disease. It may be primary, usually with autoimmune diseases, increased levels of antiphospholipid antibodies, prothrombotic abnormalities, and even with HIV-1 disease; or secondary to dermatoses. The etiology of anetoderma remains unknown. It seems that

immune deposits in the dermis or within the capillary walls may lead to ischaemia and subsequent degeneration of the elastic fibres, and therefore the antiphospholipid antibodies could participate in the elastolytic process, leading to anetoderma (35). Laboratory investigations will include the screening for prothrombotic abnormalities and for systemic lupus erythematosus. Patients with anetoderma should be evaluated for the possible presence of a prothrombotic state (36). It seems that anetoderma is more often associated with lupus and APS or lupus-like disease than with seronegative APS. □

III. CONCLUSION

The Hughes' syndrome is a multisystem disorder associated with a variety of circulating antibodies, the targets of which are different phospholipids complexes. Nowadays, APS is the foremost a thrombotic syndrome with clinical outcomes in all areas of medicine. This syndrome may potentially affect any organ/system including the skin. Dermatological complaints are often present in patients with APS and may be the first clue to the syndrome. Livedo reticularis is the most frequently reported cutaneous lesion of Hughes' syndrome; and also, other lesions, by order of frequency, are ulcerations, digital gangrene, subungual splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, extensive cutaneous necrosis and primary anetoderma. Noninflammatory vascular thrombosis is the most frequent histopathologic feature observed. Skin lesions are more associated in the catastrophic antiphospholipid syndrome, characterized by widespread microvascular occlusions involving multiple organs simultaneously. Therefore a careful history and detailed physical examination are essential to diagnose APS. All dermatologists should investigate the possibility of APS when facing cutaneous findings related to venous or arterial thrombosis or microthrombosis. Patients with Hughes' syndrome associated thrombosis should receive long-term oral anti-coagulants.

Knowledge of the skin manifestations of Hughes' syndrome is critical in the early identification and fast treatment of patients to prevent life-threatening complications of Hughes' syndrome (15). □

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